

# Index

'Note: Page numbers followed by "f" indicate figures and "t" indicate tables.'

## A

- A-EJ. *See* Alternative end joining (A-EJ)
- A-NHEJ. *See* Alternative NHEJ (A-NHEJ)
- A·T repeat sequence, 156
- AA. *See* Amino acid (AA); Aplastic anemia (AA)
- Abainsensitive-4* (*ABI4*), 189
- Abasic sites (AP sites), 635–636
- ABC. *See* ATP-binding cassette (ABC)
- Aberrations, 329–330
- ABI4*. *See* *Abainsensitive-4* (*ABI4*)
- Abiotic stress, 625
  - transgenerational changes in response to, 625–626
- Access model, 391–392, 397–398
- Acclimation, 625
- Accumulation
  - of large chromosomal aberrations, 512
  - of point mutations, insertions, and deletions, 512
- Acetolactate synthase* (ALS), 191–192
- Acetylation, 392–393
  - of H3K56, 458
- Acetyltransferase Rtt109, 501
- ACM. *See* Active chromatin marks (ACM)
- Actinobacteria*, 303
- Activation-induced deaminase (AID), 291, 327–328
- Active chromatin marks (ACM), 624f
- Acute lymphoblastoid leukemia. *See* Acute lymphocytic leukemia (ALL)
- Acute lymphocytic leukemia (ALL), 314, 346–347, 574
- Acute myelogenic leukemia (AML), 330, 473–474
- Acute myeloid leukemia. *See* Acute myelogenic leukemia (AML)
- Acute radiation sickness (ARS), 572
- AD. *See* Alzheimer's disease (AD); Automodification domain (AD)
- Ada protein, 57
- Adaptation, 92, 625
- Adaptor protein claspin, 375
- ADAR. *See* Adenosine deaminase acting on RNA (ADAR)
- Adenine/thymine (AT), 89
- Adenomatous polyposis coli gene (APC gene), 557
- Adenosine deaminase acting on RNA (ADAR), 27
- Adenosine triphosphate (ATP), 374, 393, 544
  - S-Adenosyl-L-methionine (SAM), 411
  - S-Adenosylhomocysteine (SAH), 411
- ADH1*. *See* *Alcohol Dehydrogenase-1* (*ADH1*)
- ADP-ribose hydrolase 3 (ARH3), 478
- Adult hermaphrodite reproductive system, 164
- Aerospace travel, 573–574
- AFM. *See* Atomic force microscopy (AFM)
- African swine fever virus (ASFV), 38
- Aging, 511
  - DNA-damage accumulation theory, 511–512
  - genomic instability
    - age-related accumulation of DNA damage, 512
    - causes of age-dependent accumulation, 512–518
    - effect on gene expression profile, 521
    - function of cells, 520–521
    - genomic regions with susceptibility, 518–520
    - physiological consequences, 521
  - somatic mutation accumulation theory, 511–512
- AGO3. *See* ARGONAUTE3 (AGO3)
- Agrobacterium*, 189–190
- AGTendoV protein, 58
- AGTs. *See* *O*<sup>6</sup>-alkylguanine alkyl transferases (AGTs)
- AH2. *See* Annealing Helicase two (AH2)
- AID. *See* Activation-induced deaminase (AID)
- Alcohol, 593
- Alcohol Dehydrogenase-1* (*ADH1*), 189, 191–192
- AlkB dioxygenase, 57–58
- Alkylated DNA base, 158–159
- Alkylating agents, 166
- Alkylation, 277
  - damage, 312–313
- Alkyltransferases, 58
- ALL. *See* Acute lymphocytic leukemia (ALL)
- Allium cepa* (*A. cepa*), 382
- ALS. *See* *Acetolactate synthase* (ALS); Amyotrophic lateral sclerosis (ALS)
- Altered gene-expression patterns, 587
- Alternaria brassicicola* (*A. brassicicola*), 623
- Alternative end joining (A-EJ), 62, 145, 174, 655
  - pathway, 337
  - telomere mechanism, 454–455
- Alternative NHEJ (A-NHEJ), 128–129, 234, 321, 328, 328f, 363. *See also* Classical NHEJ (C-NHEJ)
  - in chromosomal aberration, 329–330
  - components, 329
  - pathway, 571
- Alzheimer's disease (AD), 516, 533
- Amino acid (AA), 259–260
- Amitosis, 102
- AML. *See* Acute myelogenic leukemia (AML)
- AMP-activated protein kinase (AMPK), 478
- AMPK. *See* AMP-activated protein kinase (AMPK)
- Amyotrophic lateral sclerosis (ALS), 516
- Anaphase-promoting complex/cyclosome (APC/C), 176
- Animal flesh, accumulation of environmental pollutants in, 546
- Annealing Helicase two (AH2), 264
- Anti-silencing *function1* (ASF1), 205
- Anticancer strategies, 347
- Antigenomes, 27
- AP sites. *See* Abasic sites (AP sites)
- AP-site. *See* Apurinic/apryrimidinic sites (AP-site)
- APC gene. *See* Adenomatous polyposis coli gene (APC gene)
- APC/C. *See* Anaphase-promoting complex/cyclosome (APC/C)
- APE1. *See* Apurinic endonuclease 1 (APE1)
- Aplastic anemia (AA), 360–361
- APLF. *See* Aprataxin and PNKP-like factor (APLF)
- APOBEC family of enzymes, 28
  - APOBEC3-mediated editing, 42–43
- APOBEC3. *See* Apolipoprotein-B mRNA-editing catalytic polypeptide-like 3 (APOBEC3)
- Apolipoprotein-B mRNA-editing catalytic polypeptide-like 3 (APOBEC3), 42–43
  - family, 37–38
- Apoptosis, 377
- Aprataxin (APTX), 464
- Aprataxin and PNKP-like factor (APLF), 330
- APTX. *See* Aprataxin (APTX)
- Apurinic endonuclease 1 (APE1), 280, 464
  - APE1-independent BER, 282
- Apurinic/apryrimidinic sites (AP-site), 275–276, 280, 323, 464, 493–494
- Arabidopsis*, 14, 189, 204–205, 291, 437, 618–619, 623
  - A. thaliana*, 625
  - genome, 208

Archaea, genome instability in, 51–55. *See also*  
 DNA viruses; RNA viruses  
 DNA damage responses  
 archaeal UV response on DNA sharing,  
 56–57  
 SOS response, 55–56  
*Sulfolobus* copes, 56f  
 DNA repair homologs, 52t–55t  
 DNA repair pathways, 57  
 base excision repair and removal  
 of uracil, 58  
 correcting mismatched bases, 60–61  
 direct reversal of DNA damage, 57–58  
 lesions recognized and repaired by NER, 59t  
 nucleotide excision repair, 59–60  
 recombination repair, 61–62  
 restriction-modification systems, 62–64, 63f  
 Archaeal genomes, 88  
 Archaeal UV response on DNA sharing, 56–57  
 Arginine methyltransferases (PRMT), 393  
 Arginine residues, 393  
 ARGONAUTE3 (AGO3), 430  
 ARH3. *See* ADP-ribose hydrolase 3 (ARH3)  
 ARS. *See* Acute radiation sickness (ARS)  
 Arsenic, 559  
 Artemis, 325  
 Artificial mutagenesis, 204  
 Artificial RNA template molecules, 109  
 Asyclobutane pyrimidine dimers (CPD),  
 464–465  
 ASF1. *See* Anti-silencing function1 (ASF1)  
 ASFV. *See* African swine fever virus (ASFV)  
 AT. *See* Adenine/thymine (AT); Ataxia  
 telangiectasia (AT)  
 ATAC-seq, 395  
 Ataxia telangiectasia (AT), 169, 448, 450–453,  
 468, 472–473, 516–517  
 Ataxia telangiectasia mutated protein kinase  
 (ATM protein kinase), 40, 141, 175,  
 204–205, 227–228, 292, 324, 339, 375,  
 453, 468, 472–473, 516–517, 636–637  
*AtHDAC19* gene, 623  
 ATM protein kinase. *See* Ataxia telangiectasia  
 mutated protein kinase (ATM protein  
 kinase)  
 ATM–CHK2 pathway, 230–231  
 ATM/Rad3-related protein  
 (ATR protein), 40, 312,  
 324, 375, 437, 636–637  
 Atomic force microscopy (AFM), 308  
 ATP. *See* Adenosine triphosphate (ATP)  
 ATP-binding cassette (ABC), 305–306  
 ATR protein. *See* ATM/Rad3-related protein  
 (ATR protein)  
 ATR-interacting protein (ATRIP),  
 40, 312, 375  
 ATR-mediated S-phase checkpoint pathway,  
 266–267  
 ATRIP. *See* ATR-interacting protein (ATRIP)  
 AUB. *See* AUBERGINE (AUB)  
 AUBERGINE (AUB), 430  
 Aurora kinases, 177  
 inhibitors, 456  
 Automodification domain (AD), 478  
 5-Aza-2'-dC treatment, 419

## B

B-lymphocytes, 22–23, 399–400  
 Backtracking, 464–465  
 Backup NHEJ. *See* Alternative NHEJ  
 (A-NHEJ)  
 Bacteria, genome instability in, 51–55. *See also*  
 DNA viruses; RNA viruses  
 DNA damage responses  
 archaeal UV response on DNA sharing,  
 56–57  
 SOS response, 55–56  
*Sulfolobus* copes, 56f  
 DNA repair homologs, 52t–55t  
 DNA repair pathways, 57–62, 69  
 due to genetic exchange, 78–80  
 due to homologous and illegitimate  
 recombination, 74–76  
 recombination-mediated genome instability,  
 75f  
 restriction-modification systems, 62–64, 63f  
 due to specialized genetic elements, 77–78  
 due to stable mutator genotypes, 73–74  
 stress responses effects on genome instability,  
 69–72  
 Bacterial genomes, 88  
 Bacterial mating. *See* Conjugation  
 Bacteriophages, 87–88  
 diversity-generating retro-elements in, 41  
 BAF180, 395  
 Baler–Gerold syndrome (BGS), 452  
 BARD1. *See* BRCA1-associated ring domain 1  
 (BARD1)  
 Basal cell carcinoma (BCC), 470–471  
 Base excision repair (BER), 57, 163, 167,  
 169–170, 206, 208–209, 232–233,  
 246, 275, 304, 313, 410–411, 447, 463,  
 493, 516, 636, 651, 652f, 653. *See also*  
 Nucleotide Excision Repair (NER)  
 biological implications beyond DNA damage  
 and repair, 291  
 diversity of immune cells by AID, 291  
 DNA demethylation, 291  
 deficiency in, 469–470  
 gene knockout in mice and cells, 283  
 phenotypes of homozygous knockout mice  
 of NER genes and, 284t–285t  
 interplay between NER and BER  
 nuclear-mitochondria signaling network, 292  
 overlapping substrate specificity between  
 BER and NER, 291–292  
 mammalian  
 APE1, 280  
 DNA base excision repair, 279f  
 DNA glycosylases, 279  
 DNA polymerases and DNA ligases,  
 281–282  
 enzymes process DNA termini in BER,  
 280–281  
 history and overview of BER, 276  
 mechanism, 277–279  
 scaffolding proteins in BER, 282  
 types of DNA damage repaired by BER,  
 276–277  
 pathway, 464, 465f  
 and removal of uracil, 58  
 short and long-patch repair, 209f  
 12 Base pair spacer (12-RSS), 327  
 23 Base pair spacer (23-RSS), 327  
 Base pairs (bp), 487–488  
 BCC. *See* Basal cell carcinoma (BCC)  
 Bcl-2, 377  
 BCR/ABL expression, 330, 346–347  
*Bean yellow dwarf* virus, 192  
 Becquerels (Bq), 571  
 Benzimidazoles 1 (BUB1), 475  
 Benzo(a)pyrene (BP), 286  
 exposure, 561  
 Benzothiadiazole (BTH), 626–627  
 BER. *See* Base excision repair (BER)  
 Bfa1–Bub2 complex, 381  
 BGS. *See* Baler–Gerold syndrome (BGS)  
 Bioactive food components, 548–549  
 Biodosimetry assays,  $\gamma$ H2AX in, 643  
 Bioindicators, 608  
 Biomarkers, 608  
 Biosensors, 608  
 Biotic stress, 626–627  
 Bipartite recognition, 286  
 BIR. *See* Break-induced replication (BIR)  
 “Bird-like” face, 448  
 BLM. *See* Bloom Syndrome protein (BLM)  
*Blm* mutants, 145  
 Bloom syndrome (BS), 346–347, 448, 450–453,  
 514–515. *See also* Werner Syndrome  
 (WS)  
 Bloom Syndrome protein (BLM), 339,  
 402–403, 452  
 Bloom’s syndrome cells, 656  
 BORIS. *See* Brother of Regulator of Imprinted  
 Sites (BORIS)  
 bp. *See* Base pairs (bp)  
 BP. *See* Benzo(a)pyrene (BP)  
 BP-induced malignant transformation, 562  
 BP-induced upregulation, 562  
 53BP1. *See* P53-binding protein 1 (53BP1)  
 Bq. *See* Becquerels (Bq)  
*Brachypodium*, 192  
 Brain, rDNA instability in, 533–534  
*Brassica rapa* (*B. rapa*), 628–629  
 BRCA1 C-terminal (BRCT), 326  
 BRCA1-associated ring domain 1 (BARD1),  
 339, 476  
 BRCA1. *See* Breast cancer susceptibility gene  
 1 (BRCA1)  
 BRCA2. *See* Breast cancer susceptibility gene  
 2 (BRCA2)  
 BRCT. *See* BRCA1 C-terminal (BRCT)  
 Break-induced replication (BIR), 120, 341  
 Breakage-first model, 399–400  
 Breast cancer susceptibility gene 1 (BRCA1),  
 262, 339, 417, 549  
 Breast cancer susceptibility gene 2 (BRCA2),  
 339, 417, 549  
 Brother of Regulator of Imprinted Sites  
 (BORIS), 590  
 BS. *See* Bloom syndrome (BS)  
 BTH. *See* Benzothiadiazole (BTH)  
 BUB1. *See* Benzimidazoles 1 (BUB1)  
 “Bulky” DNA lesions, 232–233

1,3-Butadiene effects, 560–561  
 Bystander cells, 588  
 Bystander effects, 588, 603–604, 608f, 637

## C

c-Jun N-terminal kinase (JNK), 262, 645  
 c-Myc protein, 362, 476–477  
 C-NHEJ. *See* Canonical NHEJ (C-NHEJ);  
   Classical NHEJ (C-NHEJ); Core NHEJ  
   (C-NHEJ)  
 C-terminal domain (CTD), 57, 308–310, 323  
 C-terminal extension (CTE), 356  
 C10rph124, 261  
 CAB box. *See* Cajal body localization element  
   (CAB box)  
 5caC. *See* 5-Carboxylcytosine (5caC)  
 Cadmium, 558  
*Caenorhabditis elegans* (*C. elegans*), 7, 51,  
   147, 164, 169, 429, 558, 588  
   adult hermaphrodite reproductive system, 164  
   “*C. elegans* TransGeneome” project, 166  
   DNA-damage checkpoints, 175  
     ATM, 175  
     cytokinesis checkpoint, 176–177  
     effectors, 176  
     embryogenesis, 175  
     sensor proteins in telomere length  
       maintenance, 175–176  
     sensors of DNA damage response, 175  
   DSB in, 170–175  
     HR, 170–173  
     NHEJ, 174  
     other conserved DSB-repair mechanisms,  
       174–175  
   excision repair, 167  
     BER, 169–170  
     NER, 167–169  
   GDISR, 164  
   genetic tools to explore DDR dynamics,  
     164–166  
   genome stability, 163, 166  
   genotoxic agents for DNA damage induction,  
     166  
   IR, 164  
   methods for DNA damage detection,  
     166–167  
   MMR, 170  
   model, 164  
   as model organism to study DNA repair and  
     DDR mechanisms, 165f  
   piRNAs in, 432–434  
   securin, 176  
   transgenes, 166  
*Caenorhabditis* Genetics Center (CGC), 164  
 CAF-I. *See* Chromatin assembly factor 1  
   (CAF-I)  
 CAF1. *See* CCRF-associated factor (CAF1)  
 Cairns–Foster mutagenesis, 76  
 Cairns–Foster system, 71, 76  
 Cajal body localization element (CAB box),  
   357  
 CAK. *See* Cdk-activating kinase (CAK);  
   Cyclin-activated kinase (CAK)  
 Cambrian period, 7

Camptothecin (CPT), 265–266, 383–384, 528  
*CaMV* 35S promoter, 194  
 Cancer, 454, 463, 527, 555, 569, 571–574,  
   576–577. *See also* Tumors  
   alterations in cancer predisposition, 290  
   anticancer strategies, 347  
   “Cancer Hallmarks”, 456  
   cancer-related DNA mutations, 455f  
   cells, 267, 354, 358–359  
     and hallmarks, 373  
   CIN, 454–455  
   development, 456  
   DNA-repair gene mutations, 456  
   drivers, 468  
   epigenetic regulation of cell-cycle and DNA  
     repair, 456–458  
   future directions in research, 660–661  
   genomic aberrations in DNA-repair  
     pathways, 661f  
   genomic instability  
     in hereditary cancer, 468–474  
     in sporadic cancers, 474–478  
   genotoxic agents, 454  
   high-throughput sequencing studies on CIN,  
     475–476  
   misregulation of HR in tumors, 346–347  
   mutator phenotype, 456  
   telomerase activity, 362–363  
   therapy, 478–480  
   triggering excessive genomic instability,  
     478–480  
     PARP1, 479f  
     synthetic lethality, 479f  
 Canonical NHEJ (C-NHEJ), 337, 468  
 Canonical nucleosomes, 487–488  
 Caov-4 cells, 379  
 5-Carboxylcytosine (5caC), 291, 410–411  
 Carcinogenesis, 454  
   sunlight UV-induced carcinogenesis, 454  
 Caretaker genes, 456  
 Carotenoids, 547  
 Cas genes. *See* CRISPR-associated genes (Cas  
   genes)  
 Cas1–4 core genes, 89  
 Cas6e subunits, 91  
 Cas8 subunits, 91  
 CAS9. *See* CRISPR-associated protein 9  
   (CAS9)  
 CasA. *See* Cas6e subunits  
 Cascade complex, 93  
 Casein kinase II (CKII), 381  
 Catalytic domain (CD), 326, 478  
 Catastrophic consequences, 391–392  
 Catastrophism, 7  
*Caulobacter crescentus* (*C. crescentus*), 56  
 CBS. *See* Chromosome breakage site (CBS)  
 C–C chemokine receptor type 5  
   (CCR5), 662  
 CCR5. *See* C–C chemokine receptor type 5  
   (CCR5)  
 CCRF-associated factor (CAF1), 290  
 CD. *See* Catalytic domain (CD)  
 CDC25a. *See* Cell division control protein 25a  
   (CDC25a)  
 Cdc5, 381

CDCA7 mutations. *See* Cell division cycle  
   associated 7 mutations (CDCA7  
   mutations)  
 CDK inhibitors (CKIs), 238, 244, 248  
 Cdk-activating kinase (CAK), 374, 464–465  
 CDK-interacting protein 1 (CIP1), 248  
 CDK1–cyclin B activity, 228–229  
 CDKN1A. *See* Cyclin-dependent kinase  
   tumor-suppressor protein inhibitor 1A  
   (CDKN1A)  
 CDKN2A. *See* Cyclin-dependent kinase  
   inhibitor 2A (CDKN2A)  
*CDKN2A* gene, 250  
 CDKs. *See* Cyclin-dependent kinases (CDKs)  
 cDNA, 27  
 Cell cycle, 129, 374, 374f  
   arrest, 556  
   cell death, 376–377, 376f  
     dual modes by genotoxic agent, 379  
   checkpoints, 234, 375, 495  
     complex, 173  
   epigenetic regulation and DNA repair,  
     456–458  
   progression, 393  
   regulation, 345–346, 559  
 Cell death, 376–377, 376f  
   dual modes by genotoxic agent, 379  
 Cell division, 457  
 Cell division control protein 25a (CDC25a),  
   414  
 Cell division cycle associated 7 mutations  
   (CDCA7 mutations), 419  
 Cell growth, 457  
 Cell proliferation, 410–411  
 Cell-cycle control in mammals, 228  
   cell-cycle phases, 228  
   checkpoint control, 234–237  
     DNA-damage checkpoints and disease,  
       236–237  
     G1/S cell-cycle checkpoint, 235–236  
     G2/M cell-cycle checkpoint, 236  
     intra-S-phase cell-cycle checkpoint, 236  
     molecular regulation of, 228–230  
     regulation of mammalian cell cycle, 229f  
 Cellular degeneration, DNA-damage response  
   for prevention of  
   nuclear–mitochondria signaling network, 292  
   overlapping substrate specificity between  
     BER and NER, 291–292  
 Cellular DNA, 636  
 Cellular factors on virus mutation rate, 27–28  
 Cellular response mechanisms, 243  
 Cellular senescence, 337, 348  
 CEN2. *See* Centrin 2 (CEN2)  
 CenH3. *See* Centromere (CenH3)  
 CENP. *See* Centromere proteins (CENP)  
 CENP-A, 392  
 Central nervous system (CNS), 30  
 Centrin 2 (CEN2), 209–210, 286  
 Centromere (CenH3), 146, 398, 492  
   effect, 146  
 Centromere proteins (CENP), 418–419  
 Cerebro-oculo-facial-skeletal syndrome (COFS  
   syndrome), 448  
 Cesium 137, 572

- CF. *See* Cystic fibrosis (CF)
- CFIDS. *See* Chronic fatigue and immune deficiency syndrome (CFIDS)
- CFS. *See* Common fragile sites (CFS)
- CFTR. *See* Cystic fibrosis transmembrane conductance regulator (CFTR)
- CGC. *See* *Caenorhabditis* Genetics Center (CGC)
- CGH. *See* Comparative genomic hybridization (CGH)
- CHD4-depleted cells, 396
- Checkpoint
- adaptation, 383f
  - consequences, 384
  - history, 380–382
  - in human cells, 383–384
  - relationship with genomic instability, 384–385
  - control, 234–237
    - DNA-damage checkpoints and disease, 236–237
    - G1/S cell-cycle checkpoint, 235–236
    - G2/M cell-cycle checkpoint, 236
    - intra-S-phase cell-cycle checkpoint, 236
    - molecular players in DNA-damage cell-cycle checkpoints., 235f
  - signaling, 500–502
- Checkpoint kinase 1 (CHK1), 230–231, 262, 375, 414
- CHK1-like serine threonine protein kinase, 176
- Checkpoint kinase 2 (CHK2), 172–173, 176, 414
- Chemical carcinogens
- 1,3-butadiene effects, 560–561
  - epigenetic regulators, 556
    - DNA methylation, 556–557, 557f
    - histone modifications, 557–558
    - RNA-induced effects, 557–558
  - metal effects, 558–559
  - PAHs influence, 561–562
  - tamoxifen effects, 559–560
- Chemical mutagens, 592
- Chemotherapy, 247
- Chernobyl nuclear reactor, 572
- “Cherry-picking”, 601
- ChIP. *See* Chromatin immunoprecipitation (ChIP)
- CHK1. *See* Checkpoint kinase 1 (CHK1)
- 5-Chlorodeoxyuridine (CldU), 645
- Chloroplasts, 3–4
- Cho, 59
- Choline, 547
- Chromatin, 391, 487, 500–502
- architecture and DNA repair, 205
    - proteins involved in DNA damage sensing, 205t
  - condensation, 618
  - levels of chromatin organization, 394f
  - maturity, 492–493
  - nuclear organization, 398
  - remodelers, 395–396, 396t
  - remodeling, 129, 458
    - proteins, 382
  - structure, 290, 617–619
    - changes in response to stress, 618
    - chromatin-remodeling factors role, 618–619
- Chromatin assembly factor 1 (CAF-1), 205, 314, 488, 618
- Chromatin immunoprecipitation (ChIP), 124
- Chromatin modifications, 13–15, 495, 503
- activation of s-phase checkpoint, 498–502
  - cellular processes, 487
  - DDT, 498–502
  - in genome stability, 492
    - DNA replication, 492–493
    - DNA-damage response and repair, 493–498
  - histone modifications and chromatin remodelers, 488
    - HATs, 488–490, 490f
    - HDACs, 488–490, 490f
    - histone phosphorylation, 491
    - histone sumoylation, 491
    - histone ubiquitination, 491
    - histone variants, 492
  - HKDM, 490–491
  - HKMT, 490–491
  - nucleosome exchangers and remodelers, 491
    - PTMs to histones, 489f
  - interrelationship of DNA and chromatin, 487–488
  - relationship between chromatin and repair choice, 502–503
  - replication stress, 498–502
- Chromatin-modifying factors, 476
- Chromodomains, 395
- Chromosomal
- A-NHEJ in chromosomal aberration, 329–330
  - maintenance, 452
  - passengers, 177
  - rearrangement in nucleic acid sequences, 411–413
    - chromosomal recombination, 413, 414f
    - instability of repeat elements, 411–413
- Chromosomal instability (CIN), 454–455, 474
- hypothesis of mechanisms, 475
  - oncogenes inducing CIN, 476–477
  - in sporadic cancers, 474–475
- Chromosomal instability positive (CIN<sup>+</sup>), 379
- Chromosome breakage site (CBS), 103
- Chromosomes, 585
- territories, 399–400
- Chromothripsis, 380, 477
- Chronic fatigue and immune deficiency syndrome (CFIDS), 605
- Chronic lymphocytic leukemia (CLL), 363, 476–477, 660
- Chronic myelogenous leukemia (CML), 330, 346–347
- Chronic respiratory infections (CRIs), 73
- Ciliates, 101
- sexual life circle of, 102–103
- CIMP. *See* CpG island methylator phenotype (CIMP)
- CIN. *See* Chromosomal instability (CIN)
- CIN<sup>+</sup>. *See* Chromosomal instability positive (CIN<sup>+</sup>)
- CIP1. *See* CDK-interacting protein 1 (CIP1)
- “cis-” models. *See* Moving models
- cis-acting elements, 28
- Cisplatin, 265, 267, 313–314, 375–376
- Cit<sup>+</sup> cells, 13
- Cit<sup>−</sup> cells, 13
- Civilian nuclear disasters, 572–573
- CKB2, 381
- CKII. *See* Casein kinase II (CKII)
- CKIs. *See* CDK inhibitors (CKIs)
- Claspin, 346
- Class switch recombination (CSR), 291, 321, 327–328
- Classic nutrients, 546–548, 547t
- lipids, 546–547
  - vitamins, 546–547
- Classical NHEJ (C-NHEJ), 233–234, 321–322.
- See also* Alternative NHEJ (A-NHEJ); Core NHEJ (C-NHEJ)
- components
- DNA-PK complex, 323–325
  - LIG4 complex, 326
  - programmed double-strand breaks, 326–328
  - V(D)J recombination, 327f
- Classical p53-mediated DDR programs, 247
- Classical Sanger sequencing, 38
- Clastogenic factors, 588
- Clavata3* (*CLV3*), 192
- CldU. *See* 5-Chlorodeoxyuridine (CldU)
- Cleaving cohesion, 176
- Click-iT technology, 642
- Clinical assays,  $\gamma$ H2AX in, 643
- CLL. *See* Chronic lymphocytic leukemia (CLL)
- Clustered regularly interspaced short palindromic repeats (CRISPR), 188, 425–426
- adaptation, 92–94
  - cas operon and CRISPR array organization in *E. coli* K12, 89f
  - interference, 94
  - structure, 88–89
- CLV3*. *See* *Clavata3* (*CLV3*)
- CML. *See* Chronic myelogenous leukemia (CML)
- CMM. *See* Congenital mirror movements (CMM)
- CMMR-D. *See* Constitutional mismatch repair deficiency (CMMR-D)
- cmr1–6* genes, 89–90
- CNAs. *See* Copy number alterations (CNAs)
- CNS. *See* Central nervous system (CNS)
- CNVs. *See* Copy number variations (CNVs)
- CO. *See* Crossover (CO)
- Cockayne syndrome (CS), 167, 210, 447–450, 516
- Cockayne syndrome protein A (CSA), 167, 289, 426–428
- Cockayne syndrome protein B (CSB), 167, 289, 292, 401, 464–465
- COFS syndrome. *See* Cerebro-oculo-facial-skeletal syndrome (COFS syndrome)
- Coincident SNPs, 12
- Cold shock response, 72



- Colorectal cancer (CRC), 303, 412–413, 471, 477–478, 661
- Comet fluorescence in situ hybridization (Comet-FISH), 644
- Common fragile sites (CFS), 401, 402f
- Comparative genomic hybridization (CGH), 375–376
- Concerted evolution, 338, 347
- Congenital mirror movements (CMM), 338
- Conjugation, 79–80
- Conserved regions 4 (CR4), 357
- Conserved regions 5 (CR5), 357
- Conserved regions 7 (CR7), 357
- Conserved telomere-maintenance component 1 protein (CTC1 protein), 360
- CONSTANS* gene, 621
- Constitutional mismatch repair deficiency (CMMR-D), 471
- Constitutive class, 398
- Constitutive heterochromatin, 418
- Contact-first model, 399–400
- “Conversion-duplication” events, 144
- Copy number alterations (CNAs), 344
- Copy number variations (CNVs), 469
- Copy-choice recombination, 25–26
- Copy-paste process, 409–410
- Core histones, 392
- Core NHEJ (C-NHEJ), 126–128. *See also* Alternative NHEJ (A-NHEJ); Classical NHEJ (C-NHEJ)
- core proteins involved in, 127t
- end processing, 126–127
- ligation, 128
- repair pathway, 127f
- Coronaviruses, 25–26
- CPD. *See* Asyclobutane pyrimidine dimers (CPD)
- CPDs. *See* Cyclobutane pyrimidine dimers (CPDs)
- CpG. *See* Cytosine–phosphate–guanine context (CpG)
- CpG island methylator phenotype (CIMP), 477–478
- CPT. *See* Camptothecin (CPT)
- Cr (VI). *See* Hexavalent chromium (Cr (VI))
- CR4. *See* Conserved regions 4 (CR4)
- CRC. *See* Colorectal cancer (CRC)
- CRIs. *See* Chronic respiratory infections (CRIs)
- CRISPR. *See* Clustered regularly interspaced short palindromic repeats (CRISPR)
- CRISPR RNAs (crRNA), 91, 193
- “crRNA biogenesis” phase, 91
- tag, 92
- CRISPR-associated genes (Cas genes), 87–88
- CRISPR-associated protein 9 (CAS9), 188, 425–426
- CRISPR/Cas systems, 87
- classification, 89–90
- composition, 90
- discovery, 87–88
- immunity mechanisms, 91f
- molecular machines, 91–92
- roles, 94–95
- at work, 92–94
- CRISPR adaptation, 92–94
- CRISPR interference, 94
- expression stage, 94
- stages of CRISPR-Cas immunity, 93f
- CRISPR/CAS9 system, 117, 662
- application
- in crops, 195
- system in model plant species, 194–195
- crRNA, 193
- for genetic engineering of plants, 193
- gRNA, 194
- P. furiosus*, 194
- PAM, 193
- potential limitations, 195
- CRISPR–bacteria immune system, 87
- CRISPR loci structure, 88–89
- CRISPR/Cas systems, 92–94
- classification, 89–90
- composition, 90
- CRISPR adaptation, 92–94
- CRISPR interference, 94
- discovery, 87–88
- expression stage, 94
- molecular machines, 91–92
- roles, 94–95
- stages of CRISPR-Cas immunity, 93f
- genome-editing technology, 87
- RMS, 87
- Crossover (CO), 118, 139–140, 172, 338, 656
- formation, 147–148
- interference, 146
- crRNA. *See* CRISPR RNAs (crRNA)
- Crucial tumor-suppressor genes, 557
- Cryptic pointers, 109
- CS. *See* Cockayne syndrome (CS)
- CSA. *See* Cockayne syndrome protein A (CSA)
- CSB. *See* Cockayne syndrome protein B (CSB)
- Cse1. *See* Cas8 subunits
- CSR. *See* Class switch recombination (CSR)
- CST protein complex, 360
- CtBP-interacting protein (CtIP), 329
- CTC1 protein. *See* Conserved telomere-maintenance component 1 protein (CTC1 protein)
- CTD. *See* C-terminal domain (CTD)
- CTE. *See* C-terminal extension (CTE)
- CtIP. *See* CtBP-interacting protein (CtIP)
- Cultivated mammalian cells
- γH2AX in, 641–643
- DSB-repair kinetics in, 637
- Curcumin, 548
- Cyclin-activated kinase (CAK), 287–288
- Cyclin-dependent kinase inhibitor 2A (CDKN2A), 477
- Cyclin-dependent kinase tumor-suppressor protein inhibitor 1A (CDKN1A), 248
- Cyclin-dependent kinases (CDKs), 238, 244, 374
- Cyclobutane pyrimidine dimers (CPDs), 57, 163, 206, 313, 448, 470, 635
- photolyase, 207
- Cystic fibrosis (CF), 73–74
- Cystic fibrosis transmembrane conductance regulator (CFTR), 73
- Cytokinesis, 374, 455–456
- Cytosine–phosphate–guanine context (CpG), 411
- ## D
- D-loop. *See* Displacement loop (D-loop)
- Dadzein, 548
- DAF-16, 168
- Dam* methylase, 39–40
- dam*-replacing genes (*drg*), 73
- DAPI. *See* 4',6-Diamidino-2-phenylindole (DAPI)
- Dark repair pathways, 206
- DBD. *See* DNA-binding domain (DBD)
- DBF4/DRF1-dependent kinase (DDK), 262
- DC. *See* Dyskeratosis congenita (DC)
- DCL proteins. *See* Dicer-like proteins (DCL proteins)
- DDB. *See* DNA damage-binding (DDB)
- DDB2. *See* DNA damage-binding protein 2 complex (DDB2)
- DDK. *See* DBF4/DRF1-dependent kinase (DDK)
- DDM1 protein. *See* DECREASED DNA METHYLATION1 protein (DDM1 protein)
- ddm1*, 618–619
- DDR. *See* DNA damage repair (DDR); DNA-damage response (DDR)
- DdRP. *See* DNA-dependent RNA polymerase (DdRP)
- DDT. *See* Dichlorodiphenyltrichloroethane (DDT); DNA damage tolerance (DDT); DNA-damage tolerance (DDT)
- Deamination, 277, 513
- enzymes and reactions in BER pathway, 278t
- DECREASED DNA METHYLATION1 protein (DDM1 protein), 618–619
- DEE model. *See* Double-end engagement model (DEE model)
- Defective mitophagy, 169
- Dementia with Lewy bodies (DLB), 533
- Dendritic atrophy, 530
- deoxyribonucleotide triphosphate synthesis (dNTP synthesis), 125
- 5'-Deoxyribose phosphate (dRP), 277–280, 464
- deoxyuridine-triphosphatase (dUTPase), 25
- Depurination, 513
- Depyrimidination, 513
- Determinators, search for, 607. *See also* Low radiation-dose effects
- bioindicators, 608
- biomarkers, 608
- biosensors, 608
- bystander effect, 608f
- emergent effects, 609
- signals, 608–609
- system-level responses, 609
- Developmental reprogramming, 211–212
- DGRs. *See* Diversity-generating retro-elements (DGRs)
- DHA. *See* Docosahexaenoic acid (DHA)
- DHJ. *See* Double Holliday junction (DHJ)

- Di- and tri-methylation at lysine 9 of histone H3 (H3K9me2, 3), 103–105
- 4',6-Diamidino-2-phenylindole (DAPI), 639
- DICER complex, 426
- DICER1, 559
- Dicer-like proteins (DCL proteins), 628
- DCL1 protein, 426
- DCL1a*, 190
- Dichlorodiphenyltrichloroethane (DDT), 592–593
- 2,6-Dichloroisonicotinic acid (INA), 626–627
- Diet, 543
- Dietary
- excess, 544, 544f
  - protection against GI, 546–549
- Dietary factors, 411, 543
- causes of GI, 544–546
- accumulation of environmental pollutants in animal flesh, 546
  - alcohol, 544
  - excess, 544, 544f
  - mutagens formed during food processing, 545
  - mutagens formed during storage of foods, 545
  - natural pesticides in food plants, 546
  - red meats, 544–545, 545f
- protection against GI
- bioactive food components, 548–549
  - classic nutrients, 546–548, 547t
- 7,8-Dihydro-8-oxo-guanine (8-oxoG), 313
- Dimer splitting reaction, 206
- Direct reversal of DNA damage, 57–58, 651–653
- Direct reversal repair (DR), 416–417
- “Dirty ends”, 121–123
- Displacement loop (D-loop), 118–120, 144–145, 172, 265, 339, 468
- Diversity-generating retro-elements (DGRs), 37–38
- in bacteriophages, 41
  - organization and function, 41f
- DLB. *See* Dementia with Lewy bodies (DLB)
- Dmc1, 147
- DNA, 555, 657
- archaeal UV response on DNA sharing, 56–57
  - and chromatin interrelationship, 487–488
  - coliphages, 39–40
  - cross-links, 313–314
  - demethylases, 620
  - demethylation, 291
  - double helix, 174, 569–571
  - elimination in ciliates, 426
  - fragmentation, 63–64
  - glycosylases, 279
  - hypomethylation, 559, 589
  - injury, 163
  - loops, 303
  - N-glycosylase homolog NTH-1, 169–170
  - polymerases and DNA ligases in coordinated reactions, 281
  - APE1-independent BER, 282
  - long-patch BER, 282
  - SN filling-BER, 281–282
  - rearrangement process, 101
  - repeats, 520
  - replication, 375, 492–493
    - cleanup after, 60–61  - resection initiation, 339
  - sequence, 615
  - strand, 174
- DNA damage, 51, 243, 527, 543, 545, 547–549, 571–572, 575–577, 585, 635
- $\gamma$ H2AX in biodosimetry and clinical assays, 643
- accumulation, 636
- theory of aging, 511–512
- age-related accumulation and GI, 512
- Comet-FISH technique, 644
- detection methods, 166–167
- direct reversal, 57–58
- DNA damage-prevention system, telomeres as, 363–364, 364f
- DSB detection in cultivated mammalian cells and tissues
- DSB repair proteins imaging at chromatin sites, 641–643
- phosphorylated histone H2AX as DSB marker, 636–641
- induction, 166, 397–398
- genotoxic agents, 166
  - siRNAs in neurospora, 435–436
- IR-induced, 635
- misrepair, 379
- recognition, 286–288
- DNA nucleotide excision repair, 287f
  - enzymes and reactions in NER pathway, 288t
- reponses
- archaeal UV response on DNA sharing, 56–57
  - SOS response, 55–56
  - Sulfolobus* copes, 56f
- study methods after UV, 644–646
- visualization of UV damages, 645f
- theory of aging, 512
- DNA damage repair (DDR), 40, 232, 391, 396t, 413–414, 415t, 616
- base damage and DNA SSBs, 276
- alkylation, 277
  - deamination, 277
  - oxidation, 277
- BER, 233, 276
- biological implications beyond, 291
- diversity of immune cells by AID, 291
  - DNA demethylation, 291
- DSB repair, 233–234
- alternative DSB-repair mechanisms, 234
  - c-NHEJ, 233–234
  - HRR, 234
- ICL repair, 232
- MMR, 233
- NER, 232–233
- p21 in, 249
- p53 in, 246
- role of DNMT1 and DNA methylation, 413–417
- SSBs with tyrosyl-DNA covalent linkage, 277
- transcriptional regulation by DNA methylation, 417
- DNA damage tolerance (DDT), 498–502, 499f
- checkpoint signaling, 500–502
  - chromatin, 500–502
  - EF-DDT, 500
  - histone H3–K79me3 modification, 501f
  - model of NuA4, 502f
  - PCNA modification, 499
  - TLS–damage tolerance, 500
- DNA damage-binding (DDB), 205
- DNA damage-binding protein 2 complex (DDB2), 645–646
- proteo-probe, 645–646
- DNA double-strand break repair (DNA DSB repair), 212–214, 227–228
- HR, 214–216
- of DNA double-strand break repair, 215f
  - replication-associated HR, 216
- NHEJ, 217
- of DNA double-strand break repair, 217f
- pathway choice and consequences
- genome manipulation, 343–344
  - HR and end joining for DSB repair, 343
  - meiosis, 343
- pathway genome stability dependency, 616–617
- proteins involvement, 214t
- DNA DSB repair. *See* DNA double-strand break repair (DNA DSB repair)
- DNA methylation, 13–15, 410f, 414f, 556–557, 557f, 589–590
- cellular functions, 420
  - DNA damage–repair genes, 417
  - dynamics, 409–411, 410f
  - future direction, 419–420
  - and heterochromatin stability, 417–419
  - multifaceted regulation of genome stability, 411–419
    - changes in nucleic acid sequences, 411–413
    - chromosomal rearrangement in nucleic acid sequences, 411–413
    - DNA-damage repair, 413–417, 415t
    - heterochromatin stability, 417–419  - role in plant genome stability and responses to stress, 619–622
    - changes in transposon activity, 621–622
    - correlation between DNA methylation levels and genome stability, 620–621
    - transcriptional regulation, 411
    - transgenerational changes in, 626
- DNA methyltransferase (DNMT), 409–411
- DNMT-deficient mouse model, 419
  - DNMT1, 412–413, 416f, 456–457, 556, 560
    - DNA-damage repair, 414–417, 415t  - enzymes, 556
- DNA mismatch repair in mammals
- DNA loops, 303
- and DNA-damage response
- alkylation damage and thiopurines, 312–313
- Cisplatin, 313–314
- DNA cross-links, 313–314
- fluorouracil, 313

- oxidative damage and noncanonical MMR, 313
- UV, 313–314
- MMR proteins, 304
- post-replication mismatch repair
  - activation of MutS and MutL proteins, 304–305
  - cartoon scheme for MMR, 305f
  - formation of single-strand gapped DNA, 305
  - licensing targeted excision, 310–311
  - MMR, 304
  - MMR factors, 306t
  - MutL homologs, 308–310, 309f
  - MutS homologs, 305–308
  - strand discrimination, 311–312
- preserving genomic integrity, 303
- regulation of MMR, 314
- DNA polymerase beta, 560
- DNA polymerase iota (Poli), 259
- DNA polymerase kappa (Polk), 259, 288–289
- DNA repair, 167, 493, 544, 556, 576
  - epigenetic regulation of cell-cycle, 456–458
  - factors role, 628
  - genes, 558
  - genetic diseases, 447
    - AT, 453
    - CSB, 454
    - FA, 450
    - HGPS, 453–454
    - NER-related diseases, 448–450
    - phenotypes, 454
    - RECQ-related diseases, 450–453
  - micro-RNAs role in regulation, 426–429, 427f–428f
  - mutants, 213–214
  - ncRNAs involvement in, 623
  - in organelles, 218
  - proteins, 395, 397–398
    - systems, 636
- repair of DNA base damage, 493–495, 494f
- repair of DNA DSBs, 495
  - activity of chromatin modifiers, 496f
  - checkpoint activation and DNA resection, 495–497
  - histone modifications and remodelers, 497–498
  - homology search and repair, 497
  - NHEJ, 495
- synthesis, 124–125
- systems, 51, 586
- DNA repair pathways, 57, 463, 651–656
  - advances and future directions
    - remaining questions in DSBs repair, 658–660
    - remaining questions in MMR, 656–658
  - base excision repair and removal of uracil, 58
  - BER, 653
    - pathway, 464, 465f
  - correcting mismatched bases, 60–61
  - direct reversal of DNA damage, 57–58, 651–653
  - DSB repair, 654–656
  - functional overlaps, 662f
  - future directions in research, 660–661
  - future perspectives in DNA-editing technologies, 662–663
  - genomic aberrations in, 661f
  - lesions recognized and repaired by NER, 59t
  - mammalian DNA damage–repair pathways, 652f
  - MMR, 465–468, 467f, 654
  - NER, 653–654
    - pathway, 464–465, 466f
  - nucleotide excision repair, 59–60
  - recombination repair, 61–62
  - repair of DNA DSB, 468
    - triggering excessive GI by, 478–480
- DNA topoisomerase-2 (Topo2), 528
- DNA viruses, 37–38. *See also* RNA viruses
  - APOBEC3 proteins, 42–43
  - benefits of high-fidelity NGS, 39f
  - diversity-generating retro-elements in bacteriophages, 41
  - DNA coliphages and MMR system, 39–40
  - genome instability, 42–43
  - inhibition of ATM and ATR
    - pathways, 42f
  - interaction between DNA viruses and eukaryotic DNA damage response, 40
  - mutator phenotypes, 38–39
  - organization and function of DGRs, 41f
  - rates of spontaneous mutation and genetic diversity, 38
  - recombination-driven genome instability in, 41–42
  - relationship between genome size and rate of spontaneous mutation in, 38f
- DNA-binding domain (DBD), 326, 478
- DNA-damage checkpoints, 175, 234
  - ATM, 175
  - cytokinesis checkpoint, 176–177
  - and disease, 236–237
  - effectors, 176
  - embryogenesis, 175
  - sensor proteins in telomere length maintenance, 175–176
  - sensors of DNA damage response, 175
- DNA-damage response (DDR), 163–164, 170, 227–228, 257, 276, 339, 354, 359, 363, 364f, 391–393, 493, 528, 571, 636
  - apoptosis, 244
  - CDK activity, 244
  - CHK1, 245
  - DDR kinase signaling, 245
  - G1/S cell-cycle arrest, 244–245
  - genetic tools to explore dynamics, 164–166
  - p21 in, 248–249
    - p21/p16 tumor suppressors, 245f
  - p53 in, 244
    - in tumor suppression and, 246–247
  - p53/p21 in control of G2/M cell-cycle checkpoint, 246f
  - for prevention of cellular degeneration
    - nuclear–mitochondria signaling network, 292
    - overlapping substrate specificity between BER and NER, 291–292
  - proteins, 659
  - repair of DNA base damage, 493–495, 494f
  - repair of DNA DSBs, 495
    - activity of chromatin modifiers, 496f
    - checkpoint activation and DNA resection at DSB, 495–497
    - histone modifications and remodelers with DSBs, 497–498
    - homology search and repair, 497
    - NHEJ, 495
    - transcription factor, 244
    - UV light, 244
- DNA-damage signaling, 230–231, 231f, 392
  - checkpoint control, 234–237
    - DNA-damage checkpoints and disease, 236–237
    - G1/S cell-cycle checkpoint, 235–236
    - G2/M cell-cycle checkpoint, 236
    - intra-S-phase cell-cycle checkpoint, 236
- DNA-damage repair, 232–234
  - BER, 233
  - DSB repair, 233–234
  - MMR, 233
  - NER, 232–233
  - KAP1, 232
  - MMR, 232, 657–658
  - RING finger 8, 231
  - SMC1, 232
  - transcription factor p53, 232
- DNA-damage tolerance (DDT), 487
  - identification of RAD18–RAD6 as mediator, 258–259
- DNA-damaging agents, 128, 203–204, 228
- DNA-dependent protein kinase (DNA-PK), 230, 458, 495
  - complex
    - Artemis, 325
    - DNA-PKcs, 324–325, 325f
    - Ku70/80 heterodimer, 323–324
  - kinases, 393
- DNA-dependent RNA polymerase (DdRP), 435
- DNA-ligase 4 (Lig4), 323
- DNA-ligase 4/Xrcc4/XLF complex (LIG4 complex), 326
- DNA-PK. *See* DNA-dependent protein kinase (DNA-PK)
- DNA-PKcs. *See* DNA-protein kinase catalytic subunit (DNA-PKcs)
- DNA-protein kinase catalytic subunit (DNA-PKcs), 323–325, 325f, 450, 468
- DNA-repair synthesis (DRS), 283, 645
- DNMT. *See* DNA methyltransferase (DNMT)
- DNMT3B* gene, 3915
- dNTP synthesis. *See* deoxyribonucleotide triphosphate synthesis (dNTP synthesis)
- Docosahexaenoic acid (DHA), 546–547

- Double Holliday junction (DHJ), 118–120, 143–146, 172, 341, 450, 656
- Double-end engagement model (DEE model), 149–150
- intermediate, 150
- Double-strand break repair (DSBR), 117–120, 174–175, 233, 321–322, 425–426, 468, 516, 654
- alternative mechanisms, 234
- c-NHEJ, 233–234
- chromatin structure, 233
- DNA strand break–induced small RNAs, 436–439
- DNA-PK signaling, 233
- hereditary cancers with defects of DNA
- DSBR, 472–474
- HR, 517, 655–656, 659–660
- HRR, 234
- immunofluorescence microscopy protocol
- discriminate S-phase cells, 642–643
- discriminating cells in G0, G1, S, and G2 phases, 643
- immunofluorescent detection of  $\gamma$ H2AX, 643
- kinetics in cultivated mammalian cells, 637
- microscopy and image acquisition, 643
- NHEJ, 517, 655, 659
- pathways, 40
- process, 167
- proteins imaging at chromatin sites, 641–643
- remaining questions in, 658–660
- sensing and chromatin remodeling, 339
- Double-strand breaks (DSBs), 61–62, 71, 117, 139, 157, 163, 170, 187, 204–205, 246, 260, 277, 304, 321, 337, 363, 379, 413–414, 447, 468, 493, 512, 528, 569–571, 587, 616, 635, 652f. *See also* Nonhomologous End Joining (NHEJ); Single-strand breaks (SSBs)
- checkpoint activation and DNA resection, 495–497
- DDR, 170
- detection in cultivated mammalian cells and tissues
- DSB repair proteins imaging at chromatin sites, 641–643
- phosphorylated histone H2AX as DSB marker, 636–641
- error-free method, 170
- histone modifications and remodelers with, 497–498
- HR, 170–173
- DNA DSB–repair pathway choice and consequences, 343–344
- fork stability/restart, 341–342
- in replication fork reactivation, 343f
- NHEJ, 174
- visualization by double-immunostaining, 641f
- double-stranded DNA (dsDNA), 121–123, 166, 172, 354, 393–394, 434
- dsRNA-binding proteins, 426
- molecules, 106–107
- Double-stranded ends (DSEs), 337
- DR. *See* Direct reversal repair (DR)
- Drake's rule, 37–38
- DRD1, 619
- drg*. *See* *dam*-replacing genes (*drg*)
- Drosophila*, 429, 591
- D. melanogaster*, 139–140
- EJ in, 145
- genes, 148
- genome stability in, 155
- Kc* cells, 155–156
- mei-9* mutant, 155–156
- MMR
- activity, 155–156
- genes, 156
- in meiotic recombination, 157
- and MSI, 156–157
- and somatic cell mutation, 157–159
- model organism, 140
- Msh6* mutant, 157
- nucleus, 140
- piRNAs in, 430–432
- recombination in, 139–140
- strain, 157
- dRP. *See* 5'-Deoxyribose phosphate (dRP)
- DRS. *See* DNA-repair synthesis (DRS)
- DRS-dependent incorporation, 645
- DSBR. *See* Double-strand break repair (DSBR)
- DSBs. *See* Double-strand breaks (DSBs)
- dsDNA. *See* double-stranded DNA (dsDNA)
- DSEs. *See* Double-stranded ends (DSEs)
- dUTPase. *See* deoxyuridine-triphosphatase (dUTPase)
- Dyskeratosis congenita (DC), 360–361, 519
- E**
- E-twenty-six (ETS), 362–363
- E2F. *See* E2F transcription factor (E2F)
- E2F family member 3 (E2F3), 262
- E2F transcription factor (E2F), 456–457
- E2F3. *See* E2F family member 3 (E2F3)
- EAC. *See* Esophageal adenocarcinoma (EAC)
- ebgR* gene, 12
- EdU. *See* 5-Ethynyl-2'-deoxyuridine (EdU)
- EF method. *See* Error free method (EF method)
- EF-damage tolerance (EF-DDT), 500
- EF3. *See* Elongation factor 3 (EF3)
- Effective population size, 7–8
- Effector regulation, 429
- EGCG. *See* Epigallocatechin-3-gallate (EGCG)
- EGFR. *See* Epidermal growth factor receptor (EGFR)
- Eicosapentanoic acid (EPA), 546–547
- EJ. *See* End joining (EJ)
- Elegant studies, 30
- Elongating spermatids (ES), 432
- Elongation factor 3 (EF3), 324
- Embryogenesis, 356
- Embryos, 430
- Eme1. *See* Essential meiotic endonuclease 1 (Eme1)
- EMNs. *See* Endonucleases/meganucleases (EMNs)
- EMS. *See* Ethylmethane sulfonate (EMS)
- 5'-End cleaning enzymes, 280
- 3'-End cleaning, 280
- End joining (EJ), 141
- End resection, 121–123, 328f, 329–330
- End-replication problem, 353
- Endonucleases/meganucleases (EMNs), 188
- Endosymbiotic gene transfer, 4
- Engels' system, 143–144
- Environmental stimuli, 616
- Enzymes. *See also* Base excision repair (BER)
- 3'-end cleaning, 280
- 5'-end cleaning enzymes, 280
- TDP1, 280–281
- TDP2, 280–281
- EPA. *See* Eicosapentanoic acid (EPA)
- Epidermal growth factor receptor (EGFR), 314
- Epigallocatechin-3-gallate (EGCG), 548
- Epigenetic changes, 589–592
- Epigenetic erasers, 622–623, 622f
- Epigenetic mechanisms, 615
- Epigenetic memory, piRNAs as mediators of, 592
- Epigenetic readers, 622–623, 622f
- epigenetic Recombinant Inbred Lines (epiRILs), 14
- Epigenetic regulation
- of cell-cycle and DNA repair in cancer, 456–458
- of macronuclear development in *Stichotrichous* ciliates, 108–109
- artificial RNA template molecules, 109
- cryptic pointers, 109
- excision of IES, 110–112
- macronuclear development in stichotrichous ciliates, 111f
- macronuclear precursor sequence, 109–110
- MDSs, 109
- nanochromosomes, 109
- oligohymenophorean scanRNA model, 108–109
- Piwi-like proteins, 108–109
- proofreading mechanism, 109
- RNAi technique, 112
- template-guided model, 109, 110f
- of macronuclear development in *Tetrahymena*, 106
- IES sequence, 108
- micronuclear-specific sequences, 106–107
- ScanRNA model, 106–107, 107f
- selective transcription of dsRNAs, 108
- sRNA analysis, 108
- Epigenetic regulators, 556
- DNA methylation, 556–557, 557f
- histone modifications, 557–558
- RNA-induced effects, 557–558
- role, 628–629
- Epigenetic writers, 622–623, 622f
- Epigenetics, 458
- epiRILs. *See* epigenetic Recombinant Inbred Lines (epiRILs)
- ER. *See* Estrogen receptor (ER)
- ERCs. *See* Extrachromosomal rDNA circles (ERCs)
- ERR. *See* Excess relative risk (ERR)
- Errant strand, 60
- Error free method (EF method), 170, 498–499
- Error-free PRR, RAD18 functions in, 264–265



Error-prone double-strand break repair, 76  
 ES. *See* Elongating spermatids (ES)  
 Esa1, 489  
*Escherichia coli* (*E. coli*), 37–38, 69, 87, 164, 170, 193, 304–306  
*E. coli* K12, 94  
   cas operon and CRISPR array organization in, 89f  
   photolyase, 57  
 Esophageal adenocarcinoma (EAC), 476  
 Essential meiotic endonuclease 1 (Eme1), 341  
 ESTR. *See* Expanded simple tandem repeat (ESTR)  
 Estrogen receptor (ER), 473–474  
 Ethylmethane sulfonate (EMS), 146, 164, 204  
 5-Ethynyl-2'-deoxyuridine (EdU), 641–642  
   fluorescent labeling, 642  
   incorporation, 643  
 ETS. *See* E-twenty-six (ETS)  
 Euchromatin, 456  
 Eukaryotes, 147  
   symbiotic interactions between viruses, prokaryotes and, 5–6  
 Evolution theories, 2–3  
 “Evolve-and-resequence” experiments, 6  
 Excess relative risk (ERR), 572–573  
 Excision repair, 167  
   BER, 169–170  
   NER, 167–169  
 Exo1, 123  
 EXO1. *See* Exonuclease 1 (EXO1)  
 Exocyclic amino groups, 277  
 Exogenous agents, 117, 230  
 Exonuclease 1 (EXO1), 263, 339, 414–416  
 Exopolyphosphatase (Ppx), 72  
 Expanded simple tandem repeat (ESTR), 586–587  
*Exportin 1* (*XPO1*), 476  
 Extrachromosomal rDNA circles (ERCs), 531

## F

F-box and WD-40 domain containing 7 (FBXW7), 477  
 F1 offspring, 587–588  
 F2 offspring, 587  
 F3 offspring, 587  
 FA. *See* Fanconi anemia (FA)  
 FA/BRCA pathway, 473–474  
 Facultative class, 398  
 Facultative heterochromatin, 418  
 FAD. *See* Flavin adenine dinucleotide (FAD)  
 Familial adenomatous polyposis (FAP), 470  
 FAN1. *See* Fanconi-associated nuclease 1 (FAN1)  
 FANC genes, 265  
 FANCD2 protein, 453  
 Fanconi anemia (FA), 157, 174–175, 265, 447–448, 450, 468  
 Fanconi-associated nuclease 1 (FAN1), 473  
 FAP. *See* Familial adenomatous polyposis (FAP)  
 Fapy-Gua, 203–204  
 FAS1. *See* Fasciata 1 (FAS1)  
 Fasciata 1 (FAS1), 205  
 Fatty desaturase genes, 192  
 FBXW7. *See* F-box and WD-40 domain containing 7 (FBXW7)  
 5-fC. *See* 5-FormylC (5-fC)  
 Fe (II)/ $\alpha$ -ketoglutarate-dependent dioxygenases (FeKGDs), 416–417  
 FEN1. *See* Flap endonuclease 1 (FEN1)  
 Fenton reaction, 203–204  
*Ferropasma acidarmanus* (*F. acidarmanus*), 58  
 FHA domain. *See* Forkhead-associated domain (FHA domain)  
*fimA* gene, 75–76  
 FimB invertases, 75–76  
 FimE invertases, 75–76  
 FISH. *See* Fluorescence in situ hybridization (FISH)  
 Fixation  
   of tissue sections for  $\gamma$ H2AX detection, 639  
   of touch prints and tissue sections, 639  
 FLAG-HA-tagged DDB2 protein, 645–646  
 Flap endonuclease 1 (FEN1), 282, 464  
 Flavin adenine dinucleotide (FAD), 57, 206  
*Flavobacterium okeanokoites* (*F. okeanokoites*), 188  
 FLT3/ITD. *See* FMS-like tyrosine kinase/internal tandem duplication (FLT3/ITD)  
 Fluorescence in situ hybridization (FISH), 167, 384  
   FISH-based technique, 399  
 Fluorescence microscopy, 638  
   detection  
     fixation and permeabilization of touch prints and tissue sections, 639  
     immunohistochemical staining of touch prints and tissue sections, 639  
 Fluorescence resonance energy transfer (FRET), 417–418  
 Fluorescent Labeling of EdU, 642  
 Fluoropyrimidines, 313  
 Fluorouracil, 313  
 5-Fluorouracil (5-FU), 169–170, 313, 379  
 FMR1 gene. *See* Fragile X mental retardation 1 gene (FMR1 gene)  
 FMS-like tyrosine kinase/internal tandem duplication (FLT3/ITD), 330  
*FokI* protein, 188  
 Folate, 547  
 Forkhead-associated domain (FHA domain), 126, 330, 491  
 Formamidopyrimidine DNA glycosylase (FPG), 208  
 5-FormylC (5-fC), 410–411  
 FPG. *See* Formamidopyrimidine DNA glycosylase (FPG)  
 Fragile sites, 477  
 Fragile X mental retardation 1 gene (FMR1 gene), 412–413  
 Fragile X syndrome (FXS), 412–413  
*Francisella novicida* (*F. novicida*), 95  
 Freezing, 400  
 FRET. *See* Fluorescence resonance energy transfer (FRET)

Frozen tissue sections preparation, 638–639  
 Fruit fly, 531–532  
 5-FU. *See* 5-Fluorouracil (5-FU)  
 “Futile DNA-repair cycle” model, 657–658  
 Futile repair loop, 158–159  
 FXS. *See* Fragile X syndrome (FXS)

## G

G-quadruplex structures (GQ structures), 357, 358f  
 G-T repeat sequence, 156  
 G1/S checkpoints, 375  
   cell-cycle checkpoint, 235–236  
 G2/M checkpoints, 375  
   cell-cycle checkpoint, 236  
 Galactic cosmic rays (GCR), 573  
 GATC sites, 60  
 GBM. *See* Glioblastoma multiforme (GBM)  
 GC. *See* Gene conversions (GC)  
 GCR. *See* Galactic cosmic rays (GCR)  
 GDISR. *See* Germline DNA damage-induced systemic stress resistance (GDISR)  
 Gen endonuclease homolog 1 (GEN1), 341  
 Gene amplification, 37–38, 41–42  
 Gene conversions (GC), 74–75, 338  
 Gene expression profile, GI effect on, 521  
 Gene replacement, 143–144  
 Gene targeting (GT), 187, 343–344, 344f  
 Gene-regulatory functions, 411  
 Generation time hypothesis, 4  
 Generic stress responses, 605  
 Genetic and epigenetic mechanisms of evolution, 14t  
 Genetic diseases, 117, 447–448  
 Genetic diversity  
   of DNA viruses, 38  
   HR in equilibrium of genetic stability vs., 338–339  
 Genetic drift, 6  
 Genetic elements, GI due to specialized, 77  
   insertion sequences, 77–78  
   miniature inverted-repeat transposable elements, 78  
   mobile genetic elements, 77f  
   transposons, 78  
 Genetic engineering, 187  
   CRISPR/CAS9 system, 193–195  
     applications of CRISPR/Cas system, 194–195  
     potential limitations of CRISPR/Cas system, 195  
   future perspectives of genome-editing technology, 196  
   of plants, 187  
   strategies for genome editing in plants, 188f  
 TALENS, 191–193  
   application in crops, 192–193  
   application in model plant species, 191–192  
   potential limitations, 193  
 ZFNs, 188–191  
   potential limitations, 191  
   application in crops, 190–191  
   application in model plant species, 189–190

- Genetic exchange, GI due to  
 bacterial genomes, 78–79  
 conjugation, 79–80  
 transduction, 79  
 transformation, 80
- Genetic instability, 344–347  
 induced by HR, 345f
- Genetic polymorphisms, 549
- Genetic robustness in RNA viruses, 28–29
- Genetic stability, HR role in, 338–339
- Genetic variability, 347
- Genistein, 548
- Genome editing, 188, 190, 663  
 future perspectives, 196  
 in plants, 188f
- Genome evolution, 13–15  
 comparison of genetic and epigenetic  
 mechanisms of evolution, 14t  
 symbiosis in, 3  
 adaptive evolution, 4–5  
 changes in structure of organellar genome,  
 4  
 mutation rates in organellar genomes, 4–5  
 symbiotic interactions between viruses,  
 prokaryotes, and eukaryotes, 5–6
- Genome instability (GI), 11, 157, 228, 247,  
 454, 463, 474, 478, 543, 556, 562f,  
 602–603, 605, 619, 623, 626, 628. *See*  
*also* Genome stability
- age-related accumulation of DNA damage,  
 512
- bacteria  
 due to genetic exchange, 78–80  
 due to homologous and illegitimate recom-  
 bination, 74–76  
 recombination-mediated genome  
 instability, 75f  
 due to specialized genetic elements, 77–78  
 due to stable mutator genotypes, 73–74
- bias in mutations in genomic regions, 12–13
- cancer development, 456
- cancer-related DNA mutations, 455f
- causes of age-dependent accumulation, 512  
 altered nuclear architecture, 517–518  
 deamination, 513  
 depurination, 513  
 depyrimidination, 513  
 deterioration of genome-maintenance  
 mechanisms, 515–517  
 oxidative stress, 512–513  
 replication errors, 513–515  
 replication stress, 513–515  
 selection, 518
- chromothripsis, 380
- CIN, 454–455
- dietary causes of, 544–546
- dietary protection against, 546–549
- DNA viruses, 42–43
- DNA-repair gene mutations, 456
- effect on gene expression profile, 521
- function of cells, 520–521
- genomic regions with susceptibility, 518  
 mtDNA, 520  
 nuclear DNA, 518–520
- genotoxic agents, 454
- in hereditary cancer, 468  
 deficiency in BER, 469–470  
 deficiency in NER, 470–471  
 hereditary cancers with defects in DNA  
 MMR, 471–472  
 hereditary cancers with defects of DNA  
 DSBs, 472–474  
 LFS, 469  
 MYH-associated polyposis, 469–470  
 TP53, 469  
 XP, 470–471
- mechanisms contributing to, 522f
- mutator phenotype, 456
- physiological consequences, 521
- promotion, 344
- relationship  
 with checkpoint adaptation, 384–385  
 with entry into mitosis with damaged  
 DNA, 379–380
- in sporadic cancers, 474  
 chromothripsis, 477  
 CIN in sporadic cancers, 474–475  
 high-throughput sequencing studies on  
 CIN in cancers, 475–476  
 hypothesis of mechanisms of CIN, 475  
 MSI in sporadic cancer, 477–478  
 oncogenes induce CIN, 476–477
- Genome integrity, 425, 616
- Genome maintenance  
 TLS-independent roles in, 265–266  
 TS-independent roles in, 265–266
- Genome manipulation, 343–344
- Genome replication, 391
- Genome stability, 1, 303, 353, 391, 399, 401,  
 409, 586. *See also* Genome instability  
 (GI)  
 anticancer strategies, 347  
 chromatin modifiers in, 492  
 DNA replication, 492–493  
 DNA-damage response and repair,  
 493–498
- evolution  
 of mutation rates, 7–11  
 theories, 2–3
- fixation of mutant allele, 6–7
- future directions in research, 660–661
- micro-RNAs role in regulation of, 426–429,  
 427f–428f
- impact of miRNAs on, 426–428
- misregulation of HR in tumors, 346–347
- multifaceted regulation by DNA methylation,  
 411–419  
 changes in nucleic acid sequences,  
 411–413  
 chromosomal rearrangement in nucleic  
 acid sequences, 411–413  
 DNA-damage repair, 413–417, 415t  
 heterochromatin stability, 417–419
- radiation-induced genome stability, 586–588
- role of PIWI-interacting RNA in maintenance  
 in germline, 429–434
- role of siRNAs in maintenance in germline,  
 435–439
- symbiosis in genome evolution, 3  
 adaptive evolution, 4–5
- changes in structure of organellar  
 genome, 4  
 mutation rates in organellar genomes, 4–5  
 symbiotic interactions between viruses,  
 prokaryotes, and eukaryotes, 5–6
- transgenerational genome instability,  
 586–588
- Genome-maintenance mechanisms, 515  
 BER, 516  
 DSBs, 516–517  
 MMR, 515–516  
 NER, 516
- Genomic accordions, 41–42
- Genomic DNA, 163
- Genomic instability. *See* Genome instability  
 (GI)
- Genomic molecular evolution, HR in, 347
- Genomic regions with susceptibility to GI, 518  
 mtDNA, 520  
 nuclear DNA, 518–520
- Genotoxic  
 agents  
 as anticancer drugs, 375–376  
 dual modes of cell death, 379  
 carcinogen, 555  
 event, 384  
 mechanisms, 560
- Genotoxins, 203–204
- Geometric modes, 27
- Germ cells, 356
- Germline, 163, 166–167  
 mutations, 473–474  
 nuclei, 101
- Germline DNA damage–induced systemic  
 stress resistance (GDISR), 164
- Gestational alcohol exposure, 593
- GFP. *See* Green fluorescent  
 protein (GFP)
- GG-NER. *See* Global genome NER  
 (GG-NER)
- GGR. *See* Global genome NER (GG-NER);  
 Global genome repair (GGR)
- GHKL. *See* Gyrase b, Hsp90, Histidine kinases,  
 and MutL homologs (GHKL)
- GHR. *See* Growth hormone receptor (GHR)
- GI. *See* Genome instability (GI)
- Glioblastoma multiforme (GBM), 417
- Global gene, 560
- Global genome NER (GG-NER), 59, 163, 167,  
 232–233, 448, 464, 494, 652f
- Global genome repair (GGR), 209, 636, 651
- Global genomic-NER (GG-NER)
- Glutathione S-transferase (GST), 374
- Glycerophosphodiesterase-like protein  
 (NtGPDL), 621
- Glycine max*. *See* Soybean (*Glycine max*)
- P-Glycoprotein, 377
- Golden Gate platform, 193
- GQ structures. *See* G-quadruplex structures  
 (GQ structures)
- Gray (Gy), 571
- Green fluorescent protein (GFP), 189, 380
- gRNA. *See* guide RNA (gRNA)
- GroE protein, 72
- Growth hormone receptor (GHR), 168

GST. *See* Glutathione S-transferase (GST)  
 GT. *See* Gene targeting (GT)  
 Guanine, 576  
 guide RNA (gRNA), 194  
 Gyrase b, Hsp90, Histidine kinases, and MutL  
 homologs (GHKL), 308–309

## H

H/ACA. *See* Hairpin-hinge-hairpin-ACA (H/ACA)  
 H1 molecule, 392  
 H2A dimers, 392, 394  
 H2AX, 392, 569–571, 636–637  
   phosphorylation, 458, 637, 645  
 $\gamma$ H2AX. *See* Phosphorylated form of H2AX ( $\gamma$ H2AX)  
 $\gamma$ H2AX detection in tissues of living organisms, 637–641  
   fixation and permeabilization  
     of tissue sections for  $\gamma$ H2AX detection, 639  
     of touch prints and tissue sections, 639  
   frozen tissue sections preparation, 638–639  
   immunohistochemical staining  
     of tissue sections for light microscopy  
        $\gamma$ H2AX detection, 639–640  
     of touch prints and tissue sections, 639  
   tissue touch prints preparation, 638  
   western blotting of  $\gamma$ H2AX in animal tissues, 640–641  
 H2AZ variant, 396  
 H2B dimers, 392, 394  
 H3K27. *See* Methylated lysine 27 (H3K27)  
 H3K36. *See* Histone H3 on lysine 36 (H3K36)  
 H3K4me3. *See* Trimethylation of lysine 4 from histone H3 (H3K4me3)  
 H3K9. *See* Lysine 9 of histone H3 (H3K9)  
 H3K9me2,3. *See* Di- and tri-methylation at lysine 9 of histone H3 (H3K9me2,3)  
 H4K20 trimethylation, 560  
 HA. *See* Hyperthermophilic archaea (HA)  
 hABH1 protein, 653  
*Haemophilus influenzae* (*H. influenzae*), 74  
 Hairpin-hinge-hairpin-ACA (H/ACA), 357  
 Hard inheritance, 585, 624  
 HATs. *See* Histone acetyltransferases (HATs)  
 16HBE cells, 562  
 HBOC. *See* Hereditary breast and ovarian cancer (HBOC)  
 HBV. *See* Hepatitis B virus (HBV)  
 HCAs. *See* Heterocyclic amines (HCAs)  
 HCV. *See* Hepatitis C virus (HCV)  
 HDACs. *See* Histone deacetylases (HDACs)  
 8-HDF. *See* 8-Hydroxy-7,8-didemethyl-5-deazariboflavin (8-HDF)  
 hDNA. *See* heteroduplex DNA (hDNA)  
 HDR. *See* Homology-directed repair (HDR)  
 HDV. *See* Hepatitis delta virus (HDV)  
 Head and neck squamous cell carcinoma (HNSCC), 473–474  
 Heat shock response, 72  
 Heat-shock factor (HSF-1), 168–169

Helix-distorting lesions, 163  
 Helix-turn-helix (HTH), 308  
 HELLS mutations. *See* Lymphoid-specific helicase mutations (LSH mutations)  
 Hematopoietic stem cells (HSCs), 354  
*HEN1a*. *See* *HUA ENHANCER 1a* (*HEN1a*)  
 Heparanase (HPA), 557  
 Hepatitis B virus (HBV), 42–43  
 Hepatitis C virus (HCV), 23  
 Hepatitis delta virus (HDV), 27  
 Hereditary breast and ovarian cancer (HBOC), 473  
 Hereditary cancer, 473–474. *See also* Sporadic cancers  
   with defects in DNA MMR, 471–472  
   with defects of DNA DSB  
     A-T and ATM, 472–473  
     hereditary cancers and FA/BRCA pathway, 473–474  
   genomic instability, 468  
     deficiency in BER, 469–470  
     deficiency in NER, 470–471  
     LFS, 469  
     MYH-associated polyposis, 469–470  
     TP53, 469  
     XP, 470–471  
 Hereditary nonpolyposis colon cancer. *See* Hereditary nonpolyposis colorectal cancer (HNPCC)  
 Hereditary nonpolyposis colorectal cancer (HNPCC), 156, 303, 412–413, 456, 471, 477–478  
 Heritability of transgenerational changes, 624  
 Hermaphroditic adults, 164  
 Herpes simplex virus (HSV), 37–38  
 Heterochromatin, 143, 456, 534  
   decondensation, 618  
   instability, 418–419  
   stability, 417–419  
 Heterochromatin protein 1 (HP1), 105, 418, 456–457, 617–618  
   HP1a, 430  
 Heterocyclic amines (HCAs), 544–545  
 heteroduplex DNA (hDNA), 149, 341  
*Hevea brasiliensis* (*H. brasiliensis*), 619–620  
 Hexavalent chromium (Cr (VI)), 559  
 HGPS. *See* Hutchinson–Gilford progeria syndrome (HGPS)  
 HGT. *See* Horizontal gene transfer (HGT)  
 HH syndrome. *See* Hoyeraal–Hreidarsson syndrome (HH syndrome)  
 High atomic number and energy (HZE), 573  
 High mobility group protein 1 (Hmo1), 501  
 High-dose irradiation, 572  
 High-fidelity mutants, 30  
 High-frequency microsatellite instability (MSI-H), 471–472  
 High-LET IR, 571, 576–577  
 High-throughput microarray technology, 560  
 High-throughput sequencing studies on CIN in cancers, 475–476  
 Higher-order structures, 395

HIP116/HLTF RAD5 N-terminal domain (HIRAN domain), 265  
 HIRAN domain. *See* HIP116/HLTF RAD5 N-terminal domain (HIRAN domain)  
 Histone acetyltransferases (HATs), 392–393, 488–490, 490f, 623  
 Histone deacetylases (HDACs), 392–393, 418, 488–490, 490f, 622–623  
   HDAC1 and 2, 456–457  
   HDAC6, 314  
 Histone H3 on lysine 36 (H3K36), 129  
 Histone lysine demethylases (HKDM), 490–491  
 Histone lysine methyltransferases (HKMT), 393, 490–491  
 Histone methyltransferases (HMT), 456–457  
 Histone modifications, 557–558, 590  
   and chromatin remodelers, 488  
   HATs, 488–490, 490f  
   HDACs, 488–490, 490f  
   HKDM, 490–491  
   HKMT, 490–491  
   nucleosome exchangers and remodelers, 491  
   PTMs to histones, 489f  
   and remodelers with DSBs, 497–498  
   role in maintenance of genome stability, 622–623  
 Histone(s), 392–393, 488  
   chaperones, 392, 488  
   code, 488  
   “code writers”, 488  
   H3 acetylation, 314  
   H3–K79me3 modification, 501f  
   histone–DNA interactions, 392–393  
   modifications, 392–394  
   phosphorylation, 491  
   sumoylation, 491  
   ubiquitination, 491  
   variants, 392–394, 492  
 HJ. *See* Double Holliday junction (DHJ)  
 HJs. *See* Holliday Junctions (HJs)  
 HJURP, 392  
 HKDM. *See* Histone lysine demethylases (HKDM)  
 HKMT. *See* Histone lysine methyltransferases (HKMT)  
 5hmC. *See* 5-Hydroxymethyl cytosine (5hmC)  
 Hmo1. *See* High mobility group protein 1 (Hmo1)  
 HMT. *See* Histone methyltransferases (HMT)  
 5-hmU. *See* 5-Hydroxymethyluracil (5-hmU)  
 HNPCC. *See* Hereditary nonpolyposis colorectal cancer (HNPCC)  
 HNSCC. *See* Head and neck squamous cell carcinoma (HNSCC)  
 Holliday Junctions (HJs), 118, 264, 339, 402–403, 656  
   resolution, 341  
 Holliday model, 118  
 Homodimers, 358–359  
 Homolog as repair template, 147

- Homologous recombination (HR), 56–57, 73, 117–118, 163, 170–172, 187, 213–216, 321, 337, 339, 382, 396, 398, 411, 436, 447, 493, 513–514, 516–517, 531, 571, 587, 616–617, 626, 636, 651, 652f, 655–656, 659–660. *See also* Mitotic recombination; Meiotic recombination
- anticancer strategies, 347
- ATM-1, 173
- C. elegans* homologous recombination pathway, 171f
- cell cycle checkpoint complex, 173
- cell cycle regulation of NHEJ and, 129
- CHK-2, 172–173
- CKU-70, 172
- of DNA DSB repair, 215f
- dsDNA, 172
- in equilibrium of genetic stability vs. diversity, 338–339
- GEN1-mediated DSB repair, 173
- in genomic molecular evolution, 347
- HR-dependent repair of DSBs, 61
- in mammalian cells, 337, 338f
- misregulation in tumors, 346–347
- models, 118, 119f, 340f
- BIR model, 120
- DSBR model, 118–120
- Holliday model, 118
- SDSA model, 120
- SSA model, 120–121
- molecular mechanisms and regulation, 339
- DSB sensing and chromatin remodeling, 339
- initiation of DNA resection, 339
- loading of RAD51 and strand exchange, 339–341
- resolution of HJ and HR outcomes, 341
- MUS-81, 173
- “nick/counterneck” mechanism, 173
- outcomes, 341
- PIKK, 173
- promotion of genome instability, 344, 345f
- protection against excessive HR, 344–345
- cell-cycle regulation, 345–346
- protection against HR intermediate accumulation, 346
- repression of HR initiation, 346
- protein complex, 172
- RAD-51 protein monomers, 172
- in replication fork reactivation and DSB repair, 341–344
- replication-associated HR, 216
- RIP-1, 172
- RPA, 170–172
- SC, 170–172
- steps, 121
- DNA repair synthesis, 124–125
- end resection, 121–123
- homology search and strand invasion, 124
- nucleofilament formation, 124
- proteins involved in HR repair pathways, 122t–123t
- resolution and dissolution of recombination intermediates, 125–126
- strand annealing, 125
- TOP-3, 173
- WRN-1, 173
- ZTF-8, 173
- Homologous recombination repair (HRR), 141, 143, 144f, 234, 246
- Homology search and repair, 497
- and strand invasion, 124
- Homology-directed repair (HDR), 265, 359, 473
- pathways, 463
- Horizontal gene transfer (HGT), 71, 78–79
- Horizontal transfer (HT), 4–5
- Homeotic effects, 604–605
- Hoyeraal–Hreidarsson syndrome (HH syndrome), 363
- HP1. *See* Heterochromatin protein 1 (HP1)
- HPA. *See* Heparanase (HPA)
- HPRT. *See* Hypoxanthine phosphoribosyl transferase (HPRT)
- HPV. *See* Human papillomavirus (HPV)
- HR. *See* Homologous recombination (HR)
- hRAD18, 259–260
- domain structure, 260f
- HRR. *See* Homologous recombination repair (HRR)
- HSCs. *See* Hematopoietic stem cells (HSCs)
- HSF-1. *See* Heat-shock factor (HSF-1)
- HSV. *See* Herpes simplex virus (HSV)
- HSV proteins, 40
- HT. *See* Horizontal transfer (HT)
- HTH. *See* Helix-turn-helix (HTH)
- HU. *See* Hydroxyurea (HU)
- HUA ENHANCER 1a (HEN1a)*, 190
- Human cancers, 243–244, 246
- Human cells, checkpoint adaptation in, 383–384, 383f
- Human diseases associated with GI cancer and genome instability, 454–456
- epigenetic regulation of cell-cycle and DNA repair in cancer, 456–458, 457f
- nucleosome representation, 458f
- genetic diseases associated with DNA repair, 447
- AT, 453
- CSB, 454
- FA, 450
- HGPS, 453–454
- NER-related diseases, 448–450
- phenotypes, 454
- RECQ-related diseases, 450–453
- molecular aspects, 447
- Human FANCD, 174–175
- Human papillomavirus (HPV), 250
- Huntington’s disease, 412–413
- Hutchinson–Gilford progeria syndrome (HGPS), 398, 448, 453–454, 517
- Hyaloperonospora arabidopsidis (H. arabidopsidis)*, 627
- Hybrid dysgenesis, 141, 434
- 8-Hydroxy-7,8-didemethyl-5-deazariboflavin (8-HDF), 206
- Hydroxykynurenine, 574
- Hydroxyl radical (·OH), 203–204, 571
- 5-Hydroxymethyl cytosine (5hmC), 291, 410–411
- 5-Hydroxymethyluracil (5-hmU), 410–411
- Hydroxyurea (HU), 166, 263
- “Hyper-recombination” phenotype, 246
- Hypermethylation, 557
- Hypermutation phenotypes, 412–413
- Hyperthermophilic archaea (HA), 60
- Hypoxanthine phosphoribosyl transferase (HPRT), 512
- HZE. *See* High atomic number and energy (HZE)
- I**
- IAP. *See* Intracisternal A-particle (IAP)
- iap* gene, 88
- IARC. *See* International Agency for Research on Cancer (IARC)
- ICE. *See* Integrative conjugative element (ICE)
- ICF. *See* Immunodeficiency, centromeric instability, and facial anomalies (ICF)
- ICL. *See* Interstrand cross-link (ICL)
- ICLR. *See* Interstrand cross-link repair (ICLR)
- ICRF. *See* Ionizing radiation induced foci (ICRF)
- Idiopathic pulmonary fibrosis (IPF), 360–362
- IDLs. *See* Insertion/deletion loops (IDLs)
- IdU. *See* 5-Iododeoxyuridine (IdU)
- IESs. *See* Internal eliminated sequences (IESs)
- Ig. *See* Immunoglobulins (Ig)
- IGF-1R. *See* Insulin-like growth factor-1 receptor (IGF-1R)
- IGS. *See* Intergenic spacer (IGS)
- IIS. *See* Insulin/insulin-like growth factor signaling (IIS)
- Illudins, 166
- IMH. *See* Initiation of mutagenic homing (IMH)
- Immune cell diversity by AID, 291
- Immune system effects, 573
- Immunity mechanism, 88
- Immunodeficiency, centromeric instability, and facial anomalies (ICF), 395, 419
- Immunofluorescence microscopy protocol for simultaneous visualization of  $\gamma$ H2AX and pDNA-PK/pATM/53BP1 repair proteins discriminate S-phase cells, 642–643
- discriminating cells in G0, G1, S, and G2 phases, 643
- Immunofluorescent detection of  $\gamma$ H2AX, 643
- Immunoglobulins (Ig), 326–327
- Immunohistochemical staining of tissue sections for light microscopy  $\gamma$ H2AX detection, 639–640
- of touch prints and tissue sections, 639
- Immunological method, 167
- Immunostaining procedure, 642–643
- Imprecise excision, 143
- <sup>111</sup>In-anti- $\gamma$ H2AX-Tat, 637
- INA. *See* 2,6-Dichloroisonicotinic acid (INA)
- Incision, 288–289
- Indels. *See* Insertion/deletion loops (IDLs)
- Individual variation, 606
- Indole-3-carbinol, 548
- Inheritance, 585
- Inheritance of acquired characteristics, 2



Initial response, 141–143  
     orthologous repair genes in fly, human, and yeast, 142t–143t  
 Initiation of mutagenic homing (IMH), 41  
 INK4A. *See* p16 protein  
 INO80 remodeler, 396  
 Insertion sequences, 77–78  
 Insertion/deletion loops (IDLs), 233, 303, 471–472, 654  
 Insulin-like growth factor-1 receptor (IGF-1R), 168  
 Insulin/insulin-like growth factor signaling (IIS), 168  
 Integrative conjugative element (ICE), 71, 78  
 Interference, 92  
 Intergenic spacer (IGS), 532  
 Intermediate accumulation, protection against HR, 346  
 Internal eliminated sequences (IESs), 103–105  
 International Agency for Research on Cancer (IARC), 543, 559–560  
 Interphase, 228  
 Interplay between bacteria stress responses, 70f  
 Intersister HR, 174  
 Interstrand cross-link (ICL), 118, 174, 265, 313–314, 473, 569–571  
 Interstrand cross-link repair (ICLR), 232, 447, 660  
     pathway, 451f  
*intI* gene, 71  
 Intra-S-phase cell–cycle checkpoint, 236  
 Intracisternal A-particle (IAP), 412, 557  
 Intriguing hypothesis, 8  
 Invaders, protecting genome from, 62–64  
 Iodine 131, 572  
 5-Iododeoxyuridine (IdU), 645  
 Ionizing radiation (IR), 61–62, 117–118, 164, 166, 228, 244, 337, 426–428, 569, 570f, 570t, 586, 635  
     aerospace travel, 573–574  
     civilian nuclear disasters, 572–573  
     historical timeline of human exposure, 570f  
     IR-induced DNA damages, 635  
     linear energy transfer, 571–572  
     medical radiation, 574–575  
     nuclear military attacks, 572–573  
     radiation dosage, 571–572  
     radon gas, 575–577  
 Ionizing radiation induced foci (ICRF), 265  
 IPF. *See* Idiopathic pulmonary fibrosis (IPF)  
 IR. *See* Ionizing radiation (IR)  
 Iridocytes, 3  
 Irregular fiber model, 394  
 isomiRs. *See* miRNA isoforms (isomiRs)

## J

*Jatropha curcas* (*J. curcas*), 15  
 JNK. *See* c-Jun N-terminal kinase (JNK)  
 Jumonji domain demethylases, 393

## K

K164, 259  
 K170, 363  
 KAP-1. *See* KRAB-associated protein 1 (KAP-1)  
 Karyokinesis, 455–456  
 kbps. *See* kilobase pairs (kbps)  
 KD mice. *See* Knock-down mice (KD mice)  
 Kelch-like 6 (*KLHL6*), 476  
 Ki-67 staining, 641–643  
 kilobase pairs (kbps), 75–76  
*KLHL6*. *See* Kelch-like 6 (*KLHL6*)  
 Knock-down mice (KD mice), 266  
 KRAB. *See* Krüppel-associated box (KRAB)  
 KRAB-associated protein 1 (KAP-1), 232, 453  
 KRAS, 559  
 Krüppel-associated box (KRAB), 232  
 Ku70/Ku80, 323–325  
     complex, 329  
     heterodimer, 323–324  
 KU80 protein, 417  
 L1. *See* Linker region 1 (L1)  
 Lac-repressor proteins (LacR), 399–400  
 $\beta$ -Lactam antibiotics, 71

## L

*lacZ* gene, 12, 170  
 LADs. *See* Lamina-associated domains (LADs)  
 Lamin A (LMNA), 398, 517  
 Lamina-associated domains (LADs), 398, 532  
 Laminopathies, 398  
 Large chromosomal aberration accumulation, 512  
 Large-scale structures, 395  
 Leading strand, 492  
*Legionella pneumophila* (*L. pneumophila*), 95  
 LET. *See* Linear energy transfer (LET)  
 LeuO promoter, 94  
*lexA* gene, 55–56  
 LFS. *See* Li–Fraumeni syndrome (LFS)  
 Life Span Study (LSS), 572  
 Life-style factors, 593, 607  
 Li–Fraumeni syndrome (LFS), 236–237, 244, 469  
 LIG1. *See* Ligase 1 (LIG1)  
 LIG4 complex. *See* DNA-ligase 4/Xrcc4/XLF complex (LIG4 complex)  
 Lig4. *See* DNA-ligase 4 (Lig4)  
 Ligase 1 (LIG1), 464  
 Ligase 3 (LIG3), 464  
 Ligation, 288–289  
 Light reactions, 57  
 LINE. *See* Long interspersed nuclear elements (LINE)  
 Linear energy transfer (LET), 571–572  
 Linear nonthreshold relationship (LNT relationship), 601–602  
 Linker region 1 (L1), 492  
 Lipids, 546–547  
 Liver-metabolizing genes, 576  
 Living intermediates, 3  
 LMNA. *See* Lamin A (LMNA)  
 LNT relationship. *See* Linear nonthreshold relationship (LNT relationship)

LOH. *See* Loss of heterozygosity (LOH)  
 Long interspersed nuclear elements (LINE), 412, 557  
     LINE-1, 544, 588–590  
     methylation, 558  
 Long terminal repeat elements (LTR elements), 412  
 Long-patch BER pathway (LP-BER pathway), 282, 453  
 Long-patch repair (LP repair), 208  
 Long-term genetic effects, 588  
 Loss of heterozygosity (LOH), 117, 471  
 Louis–Bar syndrome, 472–473  
 Low radiation–dose effects. *See also* Determinators, search for  
     adaptive/hormetic effects, 604–605  
     background to controversy, 601  
     bystander effects, 603–604  
     end points, 604t  
     epidemiology, 601–602  
     generic stress responses, 605  
     GI, 603  
     outcomes in, 602f–603f  
     targeted effects and NTEs, 602  
 Low-dose irradiation, 572  
 Low-fidelity DNA virus polymerases, mutator phenotypes by, 38–39  
 Low-LET  
     IR, 571  
     radiation, 589  
 LP repair. *See* Long-patch repair (LP repair)  
 LP-BER pathway. *See* Long-patch BER pathway (LP-BER pathway)  
 LSD1. *See* Lysine-specific demethylase 1 (LSD1)  
 LSH. *See* Lymphoid-specific helicase (LSH)  
 LSS. *See* Life Span Study (LSS)  
 LTR elements. *See* Long terminal repeat elements (LTR elements)  
 Lung cancer, 476  
 Lymphoid-specific helicase (LSH), 591  
     mutations, 419  
 Lynch syndrome. *See also* Hereditary nonpolyposis colorectal cancer (HNPCC)  
 Lysine  
     acetylation, 456–457  
     residue, 392–393  
 Lysine 9 of histone H3 (H3K9), 458, 623  
     methylation, 418  
     trimethylation, 560  
 Lysine-specific demethylase 1 (LSD1), 393  
 Lysogenic phase, 79  
 Lytic stage, 79

## M

m/n/c. *See* Mutations per nucleotide per cell infection cycle (m/n/c)  
 M059K human glioma cells, 383–384  
 M2–2protein, 25  
 mac. *See* Macronucleus (mac)  
 Macronuclear anlage, 103  
 Macronuclear destined sequences (MDSs), 106

- Macronuclear differentiation, 103
- Macronucleus (mac), 101
- epigenetic regulation of macronuclear development
  - in *Stichotrichous* ciliates, 108–112
  - in *Tetrahymena*, 106–108
  - “germline” nuclei, 101
  - from micronucleus to, 101
  - nuclear dimorphism, 102f
  - organization of micronuclear genomes, 103–106
  - sexual life circle of ciliates, 102–103
  - somatic nuclei, 101–102
- MAINTENANCE OF METHYLATION 1 protein (MOM1 protein), 619
- Major tropism determinant (*mtl* gene), 41
- Male germline, 141
- Malignant cells, 555
- Mammalian cells, 586
- Mammalian genomes, 227–228, 230
- Mammalian methyl purine DNA glycosylase (MPG), 653
- Mammals, piRNAs in, 432
- Manifest stochastic effects, 572
- MAPK. *See* Mitogenactivated protein kinase (MAPK)
- Mastrevirus*, 192
- Mating-type switching, 118
- MBDs. *See* Methyl-CpG-binding domain proteins (MBDs)
- 5mC. *See* 5-Methylcytosine (5mC)
- MCI. *See* Mild cognitive impairment (MCI)
- MCR. *See* Mutagenic chain reaction (MCR)
- MDC1. *See* Mediator of DNA-damage checkpoint 1 (MDC1)
- MDM2 gene. *See* Murine double-minute 2 gene (MDM2 gene)
- MDR1. *See* Multidrug resistance protein 1 (MDR1)
- MDS. *See* Multiple damaged sites (MDS)
- MDSs. *See* Macronuclear destined sequences (MDSs)
- 1-meA. *See* 1-Methyladenine (1-meA)
- me-AFLP. *See* Methylation-sensitive amplification polymorphism (me-AFLP)
- Measles virus, 27
- 3-meC. *See* 3-Methylcytosine (3-meC)
- MeCP2. *See* Methyl CpG binding protein 2 (MeCP2)
- Mediator of DNA-damage checkpoint 1 (MDC1), 380
- Medical imaging, 574–575
- Medullary carcinomas, 572–573
- MEFs. *See* Mouse embryonic fibroblasts (MEFs)
- mei-9* gene, 148
- mei-MCM complex, 148
- Meiosis, 337, 343
- Meiotic recombination, 139–140, 146, 166–167, 174. *See also* Homologous recombination (HR)
- centromere, 146
  - effect, 146
  - CO interference, 146
  - DEE model, 149–150
- Drosophila*, 139–140, 150
- as model organism, 140
  - structure of *D. melanogaster* chromosomes, 140f
- EMS, 146
- homolog as repair template, 147
- initiation, 147
- mechanisms, 147
- MMR in, 157
- promoting CO formation, 148–149
- Meiotic resolvases, 148–149
- Meiotic silencing. *See* Meiotic silencing by unpaired DNA (MSUD)
- Meiotic silencing by unpaired DNA (MSUD), 435
- MEN. *See* Mitotic exit network (MEN)
- Mendelian inheritance. *See* Hard inheritance
- MES. *See* Modern evolutionary synthesis (MES)
- Mesembryanthemum crystallinum* (*M. crystallinum*), 621
- Mesenchymal stem cells (MSCs), 356
- Mesothermophilic archaea, 60–61
- Metabolic rate hypothesis, 4
- Metabolism, 615–616
- Metals, 166
- effects on carcinogens, 558–559
- Methenyltetrahydrofolate (MTHF), 206
- Methoxychlor (MXC), 592–593
- Methyl CpG binding protein 2 (MeCP2), 418
- Methyl methane sulfonate (MMS), 277, 619
- Methyl-CpG-binding domain proteins (MBDs), 618
- MBD4, 414–416
- Methyl-G-C pair, 158–159
- 1-Methyladenine (1-meA), 57–58, 416–417
- Methylated lysine 27 (H3K27), 623
- Methylation, 393
- Methylation-sensitive amplification polymorphism (me-AFLP), 14–15
- 3-Methylcytosine (3-meC), 57–58, 416–417
- 5-Methylcytosine (5mC), 277, 291, 410–411, 556, 589
- Methylmethane sulfonate (MMS), 500
- Methylnitrosoguanidine (MNNG), 277, 312
- Mfd protein, 59
- MGEs. *See* Mobile genetic elements (MGEs)
- MGMT. *See* O<sup>6</sup>-methylguanine-DNA methyltransferase (MGMT)
- MHEJ. *See* Microhomology-mediated end-joining (MMEJ)
- mic. *See* Micronucleus (mic)
- Microhomology-mediated end-joining (MMEJ), 128, 128f, 145, 174, 234, 328, 495
- Micronuclear-specific sequences, 106–107
- Micronucleus (mic), 101, 377, 379–380, 384–385
- epigenetic regulation of macronuclear development
  - in *Stichotrichous* ciliates, 108–112
  - in *Tetrahymena*, 106–108
  - “germline” nuclei, 101
  - to macronucleus, 101
  - nuclear dimorphism, 102f
- organization of macronuclear genomes and, 103–106
  - sexual life circle of ciliates, 102–103
  - somatic nuclei, 101–102
- microRNA ribonucleoprotein complex (miRNP), 590
- microRNAs (miRNAs), 314, 429, 558, 590
- DNA-damage sensors and effectors activity regulation, 428–429
  - regulation of effectors, 429
  - regulation of sensors, 428–429
  - role in regulation of DNA repair and genome stability, 426–429, 427f–428f
- Microsatellite instability (MSI), 74, 156–157, 303, 412–413, 454, 477
- in sporadic cancer, 477–478
- Microsatellites, 454, 477
- Microtubule components, 177
- Mild cognitive impairment (MCI), 531, 533
- Mildew resistance locus-A1 (*MLO-A1*), 195
- Mildew-resistance locus (MLO), 192
- MIM1* gene, 619
- Minerals, 548
- Miniature inverted-repeat transposable elements (MITEs), 77–78
- MIP. *See* Mlh1-interacting protein (MIP)
- miRNA isoforms (isomiRs), 426
- miRNAs. *See* microRNAs (miRNAs)
- miRNP. *See* microRNA ribonucleoprotein complex (miRNP)
- miRs. *See* microRNAs (miRNAs)
- Mismatch binding, 308
- Mismatch repair (MMR), 57, 148, 155, 163, 167, 170, 206, 211–212, 232–233, 246, 263–264, 303, 314, 412–413, 447, 463, 465–468, 493, 513, 515–516, 651, 654. *See also* Post-replication mismatch repair
- activity in *Drosophila*, 155–156
  - components, 212t
  - deficiency, 157
  - DNA damage and age-related changes, 515f
  - and DNA-damage response
    - alkylation damage and thiopurines, 312–313
    - Cisplatin, 313–314
    - DNA cross-links, 313–314
    - fluorouracil, 313
    - oxidative damage and noncanonical MMR, 313
    - UV, 313–314  - genes in *Drosophila*, 156
  - hereditary cancers with defects in DNA MMR, 471–472
  - in meiotic recombination, 157
  - methyl-directed, 37–38
  - models
    - for MMR-dependent DNA-damage signaling, 658f
    - for signaling downstream MMR events, 657f  - and MSI, 156–157
  - pathway, 71, 73
  - in plants, 213f
  - proteins, 157

- regulation, 314  
 remaining questions in, 656–658  
 role in DNA-damage signaling, 657–658  
 and somatic cell mutation, 157–159  
 strand-discrimination signal role, 656–657  
 system, 39–40
- Mismatched base correction, 60–61
- Missing heritability, 585
- MITEs. *See* Miniature inverted-repeat transposable elements (MITEs)
- Mitochondria, 3–4, 8–9, 169
- Mitochondria-specific superoxide dismutase (Mn-SOD), 277
- Mitochondrial diseases, deficiency in, 169
- mitochondrial DNA (mtDNA), 12, 169, 518, 520. *See also* Nuclear DNA (ncDNA)
- Mitochondrial dysfunction, 169, 544
- Mitochondrial genomes, 4, 88
- Mitochondrial respiratory chain, 277
- Mitochondrial unfolded protein response (UPR<sup>mt</sup>), 169
- Mitogenactivated protein kinase (MAPK), 166
- Mitomycin C (MMC), 265
- Mitophagy, 292
- Mitosis, 228, 374
- Mitotic  
   catastrophe, 377–379  
   treatments induce in cell lines, 378f  
   cell rounding, 374  
   CO, 145–146  
   processes, 418
- Mitotic exit network (MEN), 381
- Mitotic recombination, 139–141. *See also* Homologous recombination (HR)  
*Drosophila*, 139–140, 150  
   EJ in, 145  
   as model organism, 140  
   hybrid dysgenesis, 141  
   initial response and pathway choice, 141–143  
   mechanisms, 141  
   mitotic COs and dHJ model, 145–146  
   SDSA, 143–145
- Mitotic shake-off, 374, 374f
- MLH. *See* MutL homologs (MLH)
- Mlh1-interacting protein (MIP), 304–305
- MLH1, 303, 414–416
- MLO. *See* Mildew-resistance locus (MLO)
- MLO-A1. *See* Mildew resistance locus-A1 (MLO-A1)
- MMC. *See* Mitomycin C (MMC)
- MMEJ. *See* Microhomology-mediated end-joining (MMEJ)
- MMR. *See* Mismatch repair (MMR)
- MMS. *See* Methyl methane sulfonate (MMS); Methylmethane sulfonate (MMS)
- Mn-SOD. *See* Mitochondria-specific superoxide dismutase (Mn-SOD)
- MNNG. *See* Methylnitronitrosoguanidine (MNNG)
- Mobile elements, 77
- Mobile genetic elements (MGEs), 71, 77f
- Modern evolutionary synthesis (MES), 2
- Modern synthesis. *See* Modern evolutionary synthesis (MES)
- Molecular evolution studies, 37–38
- Molecular mechanisms and regulation, 339  
   DSB sensing and chromatin remodeling, 339  
   initiation of DNA resection, 339  
   loading of RAD51 and strand exchange, 339–341  
   resolution of HJ and HR outcomes, 341
- Molecular players in DNA-damage cell-cycle checkpoints., 235f
- “Molecular switch” model, 657
- MOM1 protein. *See* MAINTENANCE OF METHYLATION 1 protein (MOM1 protein)
- Monoubiquitinated FANCD2-FANCI, 265
- Monte Carlo simulation, 6
- Mouse embryonic fibroblasts (MEFs), 364, 477
- Moving models, 656–657
- MPG. *See* Mammalian methyl purine DNA glycosylase (MPG)
- Mre11, 121–123
- MRE11–RAD50–NBS1 complex (MRN complex), 217, 329, 398, 473, 636
- MRN complex. *See* MRE11–RAD50–NBS1 complex (MRN complex)
- MRX complex, 121–123, 495
- MSCs. *See* Mesenchymal stem cells (MSCs)
- MSH. *See* MutS homologs (MSH)
- MSH3 protein, 661
- Msh6 gene, 156
- MSI. *See* Microsatellite instability (MSI)
- MSI-H. *See* High-frequency microsatellite instability (MSI-H)
- MSI1. *See* Multicopy suppressor of IRA1 (MSI1)
- MSUD. *See* Meiotic silencing by unpaired DNA (MSUD)
- mtd gene. *See* Major tropism determinant (mtd gene)
- mtDNA. *See* mitochondrial DNA (mtDNA)
- MTHF. *See* Methenyltetrahydrofolate (MTHF)
- MTS1. *See* p16 protein
- Multicopy suppressor of IRA1 (MSI1), 205
- Multidrug resistance protein 1 (MDR1), 377
- Multiple damaged sites (MDS), 571
- Murine double-minute 2 gene (MDM2 gene), 469, 530
- MUS81, 341
- Mutagenesis, 70–71, 313
- Mutagenic chain reaction (MCR), 663
- Mutagenic chemicals, 164
- Mutagen formation  
   during food processing, 545  
   during storage of foods, 545
- Mutant allele fixation, 6–7
- Mutation, 468, 472, 475–476
- Mutation rate, 37–38, 43  
   evolution of, 7  
     intriguing hypothesis, 8  
     mutation rates per nucleotide, 10f  
     scaling of base substitution rate/nucleotide site/generation, 8f  
     somatic mutation rates, 9–11  
     tissue-specific frequencies of mutations, 11f  
   viral determinants, 25
- Mutations per nucleotide per cell infection cycle (m/n/c), 37–38
- Mutator  
   genotypes, 73–74  
   phenotypes, 38–39
- MutL homologs (MLH), 308–310, 309f, 498, 654  
   MLH1, 557
- MutLa, 654
- MutLβ, 654
- MutLγ, 654
- MutS, 306  
   MutS–DNA complex, 60  
   MutSβ, 654
- MutS homologs (MSH), 211, 304–306, 498, 654  
   domain I at N-terminus, 305–306  
   hMutSa–ADP–G:T mismatch complex, 307  
   mismatch binding, 308  
   MSH1 protein, 211–212  
   MSH2–MSH6 complex, 156  
   Phe39, 306  
   single molecule approaches, 308  
   structural models for, 307f  
   structure of hMutSβ, 308
- MXC. *See* Methoxychlor (MXC)
- Mycobacteria, 56
- MYD88. *See* Myeloid differentiation primary response gene 88 (MYD88)
- Myeloid differentiation primary response gene 88 (MYD88), 476
- MYH-associated polyposis, 469–470
- ## N
- N-terminal domain, 57, 309–310, 324
- N-terminal tails, 392, 557–558
- NAD. *See* Nucleolus-associated domain (NAD)
- NAHR. *See* Nonallelic HR (NAHR)
- National Bioresource Project–*C. elegans* (NBRP–*C. elegans*), 164
- Natural pesticides in food plants, 546
- NBDs. *See* Nucleotide-binding domains (NBDs)
- NBRP–*C. elegans*. *See* National Bioresource Project–*C. elegans* (NBRP–*C. elegans*)
- NBS1. *See* Nijmegen breakage syndrome 1 (NBS1)
- ncDNA. *See* Nuclear DNA (ncDNA)
- NCO. *See* Non-crossover (NCO)
- ncRNAs. *See* non-coding RNAs (ncRNAs)
- NDEA. *See* N-Nitrosodiethylamine (NDEA)
- NDMA. *See* N-Nitrosodimethylamine (NDMA)
- Negative-strand RNA viruses, 25–26
- NER. *See* Nucleotide excision repair (NER)
- Neurodegeneration  
   neurodegeneration-associated instability in rDNA, 531  
   in brain, 533–534  
   mechanisms in nonneuronal systems, 532–533  
   neurodegeneration-associated instability, 534–535, 535f  
   in nonneuronal systems, 531–532  
   nucleolar stress, 530–531

- Neuronal DNA damage, nucleolus as  
 DNA damage on, 528  
 DNA damage-induced nucleolar stress in  
 intact brain, 529  
 hypothetical model of nucleolar stress in, 529f  
 mediators of nucleolar stress response, 529–530  
 nucleolar stress-mediated responses to,  
 528–529  
 ribosomal deficiency and neurodegeneration,  
 530–531
- Neuronal system, 166
- Neurospora crassa* (*N. crassa*), 435  
 siRNAs in, 435–436  
 qiRNA, 435–436, 436f
- Next-generation sequencing (NGS), 38
- NFRs. *See* Nucleosome-free regions (NFRs)
- NGS. *See* Next-generation sequencing (NGS)
- NHEJ. *See* Nonhomologous end joining (NHEJ)
- “Nick/counternick” mechanism, 173
- Nickel exposure, 559
- Nijmegen breakage syndrome 1 (NBS1), 458  
 9–1-1 complex. *See* Rad9–Rad1–Hus1 complex  
 (9–1-1 complex)
- N*-Nitroso-*N*-methylurea (NMU), 277
- N*-Nitrosodiethylamine (NDEA), 158–159
- N*-Nitrosodimethylamine (NDMA), 158–159
- 30-NM fiber structure, 392  
 nucleosomes, 392, 394–395, 394f
- Nmeni. *See* *Streptococcus*-like system
- Nmp/B23 translocation, 528
- NMU. *See* *N*-Nitroso-*N*-methylurea (NMU)
- Nocodazole, 377
- non-coding RNAs (ncRNAs), 101, 425, 623  
 DNA elimination in ciliates, 426  
 in genome stability regulation and DNA  
 repair, 623  
 miRNAs in regulation of DNA repair and  
 genome stability, 427f–428f  
 DNA-damage sensors and effectors  
 activity regulation, 428–429  
 DNA-repair factors affecting miRNA  
 biogenesis, 428  
 indirect impact of miRNAs, 426–428  
 micro-RNA biogenesis, 426  
 piRNAs in maintenance of genome stability,  
 429–434  
 siRNAs in maintenance of genome stability,  
 435–439  
 targeting bacteriophage genomes by  
 CRISPRs/CAS9, 425–426  
 telomerase RNA, 426  
 telomere length, 426
- Non-crossover (NCO), 118, 139–140, 174
- Non-genotoxic carcinogen, 555
- Non- $\beta$  DNA structures, 569–571
- Nonallelic HR (NAHR), 344
- Noncanonical MMR, 313
- Nonclonal effects, 602f
- Nonhomologous end joining (NHEJ), 62,  
 117–118, 126–129, 145, 163, 170, 174,  
 187, 213–214, 217, 228, 233, 246,  
 263–264, 321, 337, 359, 398, 413–414,  
 436–437, 450, 463, 493, 513–514, 517,  
 571, 587, 616–617, 636, 651, 652f, 655,  
 658–659
- A-EJ, 128–129
- A-NHEJ, 328, 328f  
 in chromosomal aberration, 329–330  
 components, 329
- C-NHEJ, 126–128, 322  
 components, 323–326, 324f  
 end processing, 126–127  
 ligation, 128  
 NHEJ-mediated repair, 322f  
 programmed double-strand breaks, 326–328
- cell cycle regulation of HR, 129
- components, 659
- DNA double-strand break repair, 217f
- DNA in proximity, 659
- DNA-damage response proteins interaction,  
 659
- DNA-damaging agents, 330
- genomic DNA, 321
- models, 119f
- PNKP, 330
- protein, 396
- V(D)J recombination, 330–331
- Nonhomologous recombination, 25–26
- Nonneuronal systems, rDNA instability in,  
 531–533
- Nonsmall cell lung cancer (NSLC), 267
- Nonsteroidal anti-estrogen, 559–560
- Nonsteroidal anti-inflammatory drugs  
 (NSAIDs), 574
- Nontargeted effects (NTEs), 602, 602f
- NOR. *See* Nucleolus organizer region (NOR)
- NoRC. *See* Nucleolar repressive complex  
 (NoRC)
- Notch1* (*NOTCH1*), 476
- NSAIDs. *See* Nonsteroidal anti-inflammatory  
 drugs (NSAIDs)
- NSLC. *See* Nonsmall cell lung cancer  
 (NSLC)
- nt. *See* Nucleotide (nt)
- NTEs. *See* Nontargeted effects (NTEs)
- NtGPD. *See* Glycerophosphodiesterase-like  
 protein (NtGPD)
- NuA4 model, 502f
- NuB4 model, 493
- Nuclear  
 architecture, altered, 517–518  
 military attacks, 572–573  
 nuclear-mitochondria signaling network,  
 292, 293f  
 organization, 517–518  
 of chromatin, 398
- Nuclear DNA (ncDNA), 169, 518–519  
 DNA repeats, 520  
 rDNA, 519  
 telomeric DNA, 519
- Nucleic acid sequences, changes in, 411–413  
 chromosomal recombination, 413  
 instability of repeat elements, 411–413
- Nucleofilament formation, 124
- Nucleolar repressive complex (NoRC), 532
- Nucleolar stress, 527–528  
 DNA damage-induced, 529  
 hypothetical model of nucleolar stress in, 529f  
 mediators of nucleolar stress response,  
 529–530
- nucleolar stress-mediated responses to,  
 528–529
- ribosomal deficiency and neurodegeneration,  
 530–531
- Nucleolus, 527–528  
 neurodegeneration-associated instability of  
 rDNA, 531–535  
 as neuronal DNA damage  
 DNA damage on, 528  
 DNA damage-induced nucleolar stress in  
 intact brain, 529  
 hypothetical model of nucleolar stress in,  
 529f  
 mediators of nucleolar stress response,  
 529–530  
 nucleolar stress-mediated responses to,  
 528–529  
 ribosomal deficiency and neurodegen-  
 eration, 530–531
- Nucleolus organizer region  
 (NOR), 435–436
- Nucleolus-associated domain (NAD), 532
- Nucleoprotein, 25–26
- Nucleosome remodeling and deacetylase  
 complex (NuRD complex), 396
- Nucleosome-free regions (NFRs), 491
- Nucleosome(s), 392, 557–558  
 and 30-NM fiber, 394–395  
 exchangers and remodelers, 491  
 levels of chromatin organization, 394f  
 positioning and packaging, 417–418  
 “+1 nucleosome”, 492
- Nucleotide (nt), 7–8
- Nucleotide excision repair (NER), 59–60,  
 155–156, 163, 167, 206, 209–211,  
 232–233, 246, 263, 275, 283, 413–414,  
 447–448, 463, 493, 516, 636, 651, 652f,  
 653–654. *See also* Base excision repair  
 (BER); RECQ-related diseases
- complexes, 544
- CS, 167
- deficiency, 470–471  
 mitochondrial diseases, 169
- in development and aging, 168–169
- global genomic repair, 210f
- homozygous knockout mice of BER and  
 NER genes, 284t–285t
- interplay between NER and BER  
 nuclear-mitochondria signaling network,  
 292
- overlapping substrate specificity between  
 BER and NER, 291–292
- lesions recognized and repaired by, 59t
- mammalian  
 alterations in NER and cancer  
 predisposition, 290  
 and chromatin structure, 290  
 DNA-damage recognition, 286–288  
 incision, repair synthesis and ligation,  
 288–289  
 mechanisms, 286  
 TC-NER, 289–290  
 types of DNA damage repaired by, 286  
 unwinding of damaged DNA duplex,  
 286–288



NER-related diseases, 448–450  
 pathway, 55–56, 449f, 464–465, 466f  
 repair function, 168  
 XPA, 167  
 XPC, 167  
 Nucleotide-binding domains (NBDs), 304  
 Nucleus  
   replication, 400–403, 401f  
   transcription, 400–403  
 NuRD complex. *See* Nucleosome remodeling and deacetylase complex (NuRD complex)

**O**  
<sup>1</sup>O<sub>2</sub>. *See* Singlet oxygen (<sup>1</sup>O<sub>2</sub>)  
 O<sup>6</sup>-alkylguanine alkyl transferases (AGTs), 57, 651–653  
 O<sup>6</sup>-methylguanine (O<sup>6</sup>me-G), 57, 312, 413–414  
 O<sup>6</sup>-methylguanine-DNA methyltransferase (MGMT), 277, 312, 576, 653  
 O<sup>6</sup>me-G. *See* O<sup>6</sup>-methylguanine (O<sup>6</sup>me-G)  
 OB domains. *See* Oligonucleotide/oligosaccharide-binding domains (OB domains)  
 Off-target mutagenesis, 194–195  
 OGG1. *See* 8-OxoG DNA glycosylase/AP lyase (OGG1)  
 ·OH. *See* Hydroxyl radical (·OH)  
 Oil Seed rape mosaic virus (ORMV), 627  
 “Old radiobiology”, 607  
 Oligohymenophoreans, 101, 103  
 Oligonucleotide/oligosaccharide-binding domains (OB domains), 359–360  
 Oncogene  
   expression, 266–267  
   inducing CIN, 476–477  
   oncogene-induced senescence, 250  
*ONSEN* expression, 628  
 Open reading frames (ORFs), 435–436  
 “Opposite-sense resolution” pathway, 173  
 ORFs. *See* Open reading frames (ORFs)  
 ORMV. *See* Oil Seed rape mosaic virus (ORMV)  
 Overshoot synthesis, 216  
 Oxidation, 277  
 Oxidative damage, 313  
 Oxidative dealkylation, 653  
 Oxidative stress, 512–513  
 8-Oxo-7,8-dihydro-20-deoxyguanosine (8-oxodGuo), 203–204  
 8-Oxo-7,8-dihydroguanine (8-oxoGua), 203–204  
 8-OxoG DNA glycosylase/AP lyase (OGG1), 208  
 8-oxodGuo. *See* 8-Oxo-7,8-dihydro-20-deoxyguanosine (8-oxodGuo)  
 8-oxoG. *See* 7,8-Dihydro-8-oxo-guanine (8-oxoG)  
 8-oxoG products. *See* 8-Oxoguanine products (8-oxoG products)  
 8-oxoGua. *See* 8-Oxo-7,8-dihydroguanine (8-oxoGua)  
 8-Oxoguanine products (8-oxoG products), 469–470  
   formation, 166  
*Oxytricha*, 426  
*O. trifallax*, 103

## P

P-element–induced wimpy testis (PIWI), 426  
 PIWI-like proteins, 108–109  
 (p)ppGpp, 72  
 p16 protein, 250  
   in DNA-damage signaling and DNA repair, 243  
 P16<sup>INK4A</sup> tumor-suppressor protein, 250–251  
 p16–pRB pathway, 251  
 p53/p21 tumor suppressors, 245f  
 p21 protein, 587  
   in DNA-damage signaling and DNA repair, 243  
   p53/p16 tumor suppressors, 245f  
   p53/p21 in control of G2/M cell-cycle checkpoint, 246f  
   tumor-suppressor protein, 248  
     CDKN1A, 248  
     cell motility, 248  
     in DNA-damage repair, 249  
     in DNA-damage response, 248–249  
     E3 ubiquitin ligases, 248  
     G2/M cell-cycle progression, 248  
     and tumor suppression, 249–250  
 P491T, 363  
 p53 protein, 561, 587  
   in DNA-damage signaling and DNA repair, 243  
   p53-dependent apoptosis, 530  
   p53-mediated neuronal apoptosis, 529–530  
   p53-signaling, 559  
   p53–p21 pathway, 251  
   tumor-suppressor protein, 244–248  
     in DNA-damage repair, 246  
     in DNA-damage response, 244–245  
     and targeted DNA-damaging cancer therapy, 247–248  
   Tp53 gene, 244  
   in tumor suppression and DNA-damage response, 246–247  
 P53-binding protein 1 (53BP1), 380, 393, 458  
 PACT. *See* Protein activator of PKR (PACT)  
 pADPr. *See* Poly(ADP) ribose (pADPr)  
 PAH. *See* Polycyclic aromatic hydrocarbons (PAH)  
 PAIs. *See* Pathogenicity islands (PAIs)  
 PAM. *See* Protospacer adjacent motif (PAM)  
 PAP. *See* Peroxidase antiperoxidase (PAP)  
 PAP Complex Antibody, 639  
 Papillary cells, 572–573  
 PAR. *See* Poly-ADP-ribose (PAR)  
*Paramecium*, 3  
 Pararetroviruses, 37–38  
 PARG. *See* Poly(ADP-ribose) glycohydrolase (PARG)  
 Parkin–PINK1 protein degradation system, 292  
 Parkinson’s disease (PD), 292, 533  
 PARP. *See* Poly(ADP-ribose) polymerase (PARP)  
 Parvoviruses, 37–38  
 Pathogenicity islands (PAIs), 78–79  
 Pathway choice, 141–143  
 PcG protein binding. *See* Polycomb-group protein binding (PcG protein binding)

PCNA. *See* Proliferating cell nuclear antigen (PCNA)  
 PCNA-interacting peptide domain (PIP domain), 259, 307  
 PD. *See* Parkinson’s disease (PD)  
 PE. *See* Phosphoesterase (PE)  
*Pelomyxa*, 3  
 Pentatricopeptide repeat protein (PPR protein), 663  
 Penumbra region, 571–572  
 Permeabilization  
   of tissue sections for γH2AX detection, 639  
   of touch prints and tissue sections, 639  
 Peroxidase antiperoxidase (PAP), 638  
 Pesticides, 592–593  
*Petunia hybrida* (*P. hybrida*), 558  
 PGC-1α, 292  
 PH domain leucine-rich repeat protein phosphatase (PHLPP), 559  
 Phase variation, 74  
 PHD. *See* Plant homeodomains (PHD)  
 Phe39, 306  
 Philadelphia chromosome, 399–400  
 PHLPP. *See* PH domain leucine-rich repeat protein phosphatase (PHLPP)  
 Phosho-H2AX. *See* Phosphorylated form of H2AX (γH2AX)  
 3′-or 5′-Phosphodiesterase, 493–494  
 5′-Phosphate, 280  
 Phosphatidylinositol 3-kinase (PI3K), 168, 453, 636–637  
 Phosphatidylinositol-3 kinase-related kinases (PIKK), 173, 230, 324, 453, 495  
 Phosphatidylinositol-3,4,5-triphosphate (PIP3), 168  
 3′-Phospho-α, β-unsaturated aldehydes (3′-PUA), 279  
 Phosphoesterase (PE), 655  
 Phosphoinositide 3-kinase. *See* Phosphatidylinositol 3-kinase (PI3K)  
 Phosphorylated form of H2AX (γH2AX), 393, 571, 590, 608, 637  
   in biodosimetry and clinical assays, 643  
   in cultivated mammalian cells, 641–643  
   immunofluorescent detection, 643  
   immunohistochemical detection, 638f  
   visualization of DSBs by double-immunostaining, 641f  
 Phosphorylated histone H2AX as DSB marker, 636–641  
   DSB-repair kinetics in cultivated mammalian cells, 637  
   γH2AX detection in tissues of living organisms, 637–641  
 Phosphorylation, 393  
 Photolyases, 57, 653  
 6–4 photoproducts (6–4PP), 57, 163, 206, 448, 464–465, 470, 635  
 Photoreactivation, 206–208  
   CPD photolyase enzyme, 207f  
   proteins in photoreactivation and base excision repair pathways, 207t  
 Photosensitizers, 166  
*phr* gene, 57  
*Physcomitrella patens* (*P. patens*), 187

- Physiological consequences, 521  
 Phytochemicals, 548  
 pi-RISC. *See* piRNA induced-silencing complex (pi-RISC)  
 PI3K. *See* Phosphatidylinositol 3-kinase (PI3K)  
 PIKK. *See* Phosphatidylinositol-3 kinase-related kinases (PIKK)  
 “Ping-pong” amplification cycle, 591  
 PINK1, 292  
 PIP domain. *See* PCNA-interacting peptide domain (PIP domain)  
 PIP3. *See* Phosphatidylinositol-3,4,5-triphosphate (PIP3)  
 piRNA induced-silencing complex (pi-RISC), 430–432  
 piRNAs. *See* PIWI-interacting RNAs (piRNAs)  
 PIWI. *See* P-element-induced wimpy testis (PIWI)  
 PIWI-interacting RNAs (piRNAs), 426, 431f, 433f, 558, 590–591  
   biogenesis, 591–592  
   genome stability maintenance, 429–434  
     in *C. elegans*, 432–434  
     in *Drosophila*, 430–432  
     in mammals, 432  
   in transgenerational response, 434  
   as mediators of epigenetic memory, 592  
 PKR. *See* Protein kinase R (PKR)  
 Plant biotechnology, 187  
 Plant genome stability, 203. *See also* Transgenerational responses in plants  
   BER, 208–209  
   chromatin architecture and DNA repair, 205  
   dependency upon DSB DNA-repair pathway, 616–617  
   DNA double-strand break repair, 212–217  
     HR, 214–216  
     NHEJ, 217  
     proteins involved in, 214t  
   DNA repair in organelles, 218  
   DNA-damage signaling in plants, 204f  
   DNA-damaging agents, 203–204  
   epigenetic regulation, 617–623  
     chromatin structure, 617–619  
     DNA methylation role, 619–622  
     histone modifications role, 622–623  
     ncRNAs involvement, 623  
   future perspective, 218  
   MMR, 211–212  
   NER, 209–211  
   photoreactivation, 206–208  
     CPD photolyase enzyme, 207f  
     proteins in photoreactivation and base excision repair pathways, 207t  
   proteins in DNA damage sensing and chromatin composition in plants, 205t  
   sensing DNA damage, 204–205  
 Plant homeodomains (PHD), 490–491  
 Plants, 615–616, 625  
 Plaque-to-plaque transfers, 38  
 Plasmids, 88–89, 196  
 Plastid-bearing eukaryotes, 4  
 Plk. *See* Polo-like kinase (Plk)  
 PME-5, 175–176  
 PMS. *See* Post-meiotic segregation (PMS)  
 PNET. *See* Primitive neural ectodermal tumor (PNET)  
 PNKP. *See* Polynucleotide kinase/phosphatase (PNKP)  
 Pol. *See* Polymerase (Pol)  
 Pol1-dependent nucleolar compartmentalization, 528  
 Pol1. *See* RNA-polymerase-1 (Pol1)  
 POLH gene, 262  
 Polo-like kinase (Plk), 381  
   PLK1, 230, 383  
 Poly-ADP-ribose (PAR), 233  
 Poly(ADP-ribose) glycohydrolase (PARG), 169, 478  
 Poly(ADP-ribose) polymerase (PARP), 208–209, 276, 478  
   PARP-1, 169, 329, 347, 464  
 Poly(ADP) ribose (pADPr), 478  
 Polycarbonyl-group protein binding (PcG protein binding), 418  
 Polycyclic aromatic hydrocarbons (PAH), 286, 544–545, 561–562  
 Polymerase (Pol), 329, 655  
   fidelity, 23–24, 29, 31  
   Pol $\delta$ , 414  
   Pol III, 76  
   Pol IV, 70–71  
   Pol  $\theta$ , 329  
   Pol V, 70–71  
   Pol  $\beta$ , 169, 208, 464  
   Pol  $\lambda$ , 323  
   Pol  $\mu$ , 323  
 Polynucleotide kinase/phosphatase (PNKP), 279–280, 330, 464  
 Polyomaviruses, 40  
 polyP. *See* Polyphosphate (polyP)  
 Polyphenols, 548  
 Polyphosphate (polyP), 72  
   polyphosphate-mediated starvation response, 72  
 Polyphosphate kinase (Ppk), 72  
 Polyunsaturated fatty acids (PUFA), 546–547  
 Pol $\delta$ . *See* Polymerase delta (Pol $\delta$ )  
 Pol $\eta$ , 261  
   RAD18-binding motif, 261  
 Polt. *See* DNA polymerase iota (Polt)  
 Polk. *See* DNA polymerase kappa (Polk)  
 Population, mutant allele fixation in, 6–7  
 Post-meiotic segregation (PMS), 304  
   PMS2, 414–416  
 Post-replication mismatch repair. *See also* Mismatch repair (MMR)  
   cartoon scheme for MMR, 305f  
   licensing targeted excision, 310–311  
   MMR, 304, 306t  
   MutL homologs, 308–310, 309f  
   MutS and MutL proteins activation, 304–305  
   MutS homologs, 305–308  
   single-strand gapped DNA formation, 305  
   strand discrimination, 311–312  
 Post-TLS repair, 313  
 Postreplication repair (PRR), 257, 258f, 303, 498–499  
 Posttranscriptional gene silencing, (PTGS), 590  
 Posttranscriptional processes, 357  
 Posttranslational modifications (PTMs), 392, 488  
 POT1. *See* Protection of telomere 1 (POT1)  
 6–4PP. *See* 6–4 photoproducts (6–4PP)  
 PP1-alpha catalytic subunit (PP1 $\alpha$ ), 374  
 PP1C $\alpha$ . *See* PP1-alpha catalytic subunit (PP1 $\alpha$ )  
 PP2A. *See* Protein phosphatase 2A (PP2A)  
 Ppk. *See* Polyphosphate kinase (Ppk)  
 PPOX. *See* Protoporphyrinogen oxidase (PPOX)  
 PPR protein. *See* Pentatricopeptide repeat protein (PPR protein)  
 Ppx. *See* Exopolyphosphatase (Ppx)  
 PR. *See* Progesterone receptor (PR)  
 Precatastrophic phase, 377  
 Premature aging syndromes, 362  
 Prenatal alcohol exposure, 593  
 pri-miRNA. *See* Primary transcript (pri-miRNA)  
 Primary transcript (pri-miRNA), 590  
 Priming, 93  
 Primitive cell-cycle checkpoint, 55–56  
 Primitive neural ectodermal tumor (PNET), 574  
 PRMT. *See* Arginine methyltransferases (PRMT)  
 PRO. *See* *Procera* (PRO)  
 Pro-CO complexes, 148  
*Procera* (PRO), 192  
 Progeny genomes, 22–23  
 Progerin, 453  
 Progesterone receptor (PR), 473–474  
 Programmed double-strand breaks, 326–328  
   V(D)J recombination, 327f  
 Prokaryotes, 5–6  
 prokaryotic siRNAs (psiRNA), 88  
 Proliferating cell nuclear antigen (PCNA), 208, 258–259, 314, 414, 464, 645  
   modification, 499  
 Proline-rich linker, 309–310  
 Protection of telomere 1 (POT1), 354, 359  
 Protein activator of PKR (PACT), 426  
 Protein kinase R (PKR), 41–42  
 Protein phosphatase 2A (PP2A), 324  
 Protein(s), 622–623  
   kinases, 230  
   phosphorylation, 228–229  
   synthesis, 528, 531  
 Proteome profiling, 166  
 Proto-oncogenes, 558  
 Protoporphyrinogen oxidase (PPOX), 189–190  
 Protospacer adjacent motif (PAM), 91, 193  
 PRR. *See* Postreplication repair (PRR)  
 psiRNA. *See* prokaryotic siRNAs (psiRNA)  
 PSU1 loci, 401  
 PTEN gene, 346, 546–547  
 PTGS. *See* Posttranscriptional gene silencing, (PTGS)  
 PTMs. *See* Posttranslational modifications (PTMs)  
 3'-PUA. *See* 3'-Phospho- $\alpha$ ,  $\beta$ -unsaturated aldehydes (3'-PUA)  
 PUFA. *See* Polyunsaturated fatty acids (PUFA)  
 Pulmonary dysfunction syndromes, 572

Purines, 12  
 Putative CBS, 105  
 Putative mechanism, 354  
 Pyrimidine dimmers, 206  
 (6–4) pyrimidone photoproducts (6–4PP). *See*  
 6–4 photoproducts (6–4PP)  
*Pyrococcus furiosus* (*P. furiosus*),  
 92, 194

## Q

QCT. *See* Quinocetone (QCT)  
 QDE-1. *See* Quelling deficient-1 (QDE-1)  
*qde-2* expression, 435–436  
 quantitative PCR (qPCR), 167, 533  
 Quasispecies, viruses as, 23  
 Quelling deficient-1 (QDE-1), 435  
 Quinocetone (QCT), 548  
 Quinolone antibiotics, 71

## R

*R*-genes. *See* Resistance genes (*R*-genes)  
*R*-loop hybrids. *See* RNA–DNA hybrids  
 (R-loop hybrids)  
 Rad9–Rad1–Hus1 complex (9–1-1 complex),  
 175, 375  
 Rad17–replication factor  
 C complex, 375  
 RAD18 protein, 258, 263f  
 activation, 260–262  
 damage–tolerance, 257–258  
 DDR, 257–258  
 DNA damage–avoidance mechanisms,  
 257–258  
 DNA replication–independent RAD18  
 activation and TLS, 262–264  
 functions in error-free PRR via template  
 switching, 264–265  
 identification of RAD18–RAD6, 258–259  
 physiological roles, 266  
 developmental roles, 266  
 in tumorigenesis, 266–267  
 PRR, 257  
 RAD18-mediated PCNA  
 monoubiquitination, 259  
 structure, 259–260  
 TLS polymerase switch, 259  
 TLS-independent roles in genome  
 maintenance, 265–266  
 transcriptional and posttranslational  
 regulation, 262  
 TS-independent roles in genome  
 maintenance, 265–266  
*Rad18*<sup>−/−</sup> mice, 266  
 Rad50 protein, 118, 121–123  
 Rad51 protein, 124, 338, 587, 636  
 loading, 339–341  
 paralogs, 339–341  
 protein monomers, 172  
 Rad52 protein, 214, 532  
 Rad53 protein, 381  
 Rad54 protein, 339  
 RAD54a protein, 205  
 RadA protein, 655  
 Radiation  
 dosage, 571–572  
 radiation-induced genome instability,  
 586–588  
 bystander effects, 588  
 transgenerational effects, 586–588  
 transgenerational genome instability,  
 586–588  
 risk, 603–604  
 Radiosensitive severe combined immunodeficiency (RS-SCID), 322, 326  
 Radiotherapy (RT), 574–575  
 Radium emanation, 575  
 Radon gas, 575–577  
 “Radon spas”, 576  
 RAG. *See* Recombination activating gene  
 (RAG)  
 RAP1. *See* Repressor/activator protein 1  
 (RAP1)  
 Rb. *See* Retinoblastoma (Rb)  
 RB tumor-suppressor protein. *See* Retino-  
 blastoma tumor-suppressor protein (RB  
 tumor-suppressor protein)  
 RBE. *See* Relative biological effectiveness  
 (RBE)  
 RCM. *See* Repressive chromatin marks (RCM)  
 rDNA. *See* Ribosomal DNA (rDNA)  
 RdRp. *See* RNA-dependent RNA polymerase  
 (RdRp)  
 Re-assortment, 26  
 Reactive oxygen species (ROS), 163, 203,  
 266–267, 277, 321, 447, 469–470,  
 493–494, 511, 558, 569–571, 602, 635  
 ROS1, 620–621  
 Really-interesting gene (RING), 258–259  
*rec* gene, 148  
 RecA proteins, 218  
 RecBCD end-processing complex, 63–64  
 Recombination, 28  
 initiation, 147  
 repair, 61–62  
 resolution and dissolution of intermediates,  
 125–126  
 Recombination activating gene (RAG), 327  
 Recombination signal sequences (RSS), 327  
 Recombination-dependent DNA replication. *See*  
 Break-induced replication (BIR)  
 RecQ, 592  
 RECQ-related diseases, 450–453. *See also*  
 NER-related diseases  
 ICLR pathway, 451f  
 types of DNA arrangements, 451f  
 RECQL4, 452  
 Red meats, 544–545, 545f  
 Reduced potassium dependency protein 3/  
 histone deacetylase 1 (RPD3/HDA1),  
 623  
 Regulating gene transcription, 410–411  
 Relative biological effectiveness (RBE), 573,  
 601–602  
 Rep. *See* Replication–initiation protein (Rep)  
 Repair model, 391–392, 397–398  
 Repair synthesis, 288–289  
 Repeat variable diresidue (RVD), 191  
 Repeat-induced point mutation (RIP), 435

Replication  
 checkpoint, 257  
 errors, 513  
 BS, 515  
 RTS, 515  
 WS, 514–515  
 in nucleus, 400–403, 401f  
 replication-related proteins, 395  
 replication–initiation paucity model, 401, 403  
 stress, 495, 498, 513  
 BS, 515  
 checkpoint signaling, 500–502  
 chromatin, 500–502  
 DDT, 498–502, 499f  
 EF-DDT, 500  
 fork stability/restart by HR upon, 341–342  
 histone H3–K79me3 modification, 501f  
 model of NuA4, 502f  
 PCNA modification, 499  
 RTS, 515  
 TLS–damage tolerance, 500  
 WS, 514–515  
 timing, 400  
 Replication factor A2 (Rfa2), 382  
 Replication factor C (RFC), 211, 414–416,  
 465–468  
 Replication fork, 492  
 collapse model, 401  
 HR in reactivation, 342f–343f  
 DNA DSB–repair pathway choice and  
 consequences, 343–344  
 fork stability/restart, 341–342  
 Replication fork block site (RFB), 532  
 Replication protein A (RPA), 118–120,  
 170–172, 211, 261, 305, 363, 375,  
 414–416, 464–465, 655  
 RPA–ssDNA, 261  
 Replication–initiation protein (Rep), 192  
 Replicative templates, 26  
 Repressive chromatin marks (RCM), 624f  
 Repressor/activator protein 1 (RAP1), 354, 359  
 Resistance genes (*R*-genes), 621–622  
 Resolvases, 146  
 Restore model, 391–392, 397–398  
 Restriction–modification system (RMS), 87  
 Restriction–modification systems, 62–64, 63f  
 Resveratrol (RSV), 548  
 Retinoblastoma (Rb), 373  
 Retinoblastoma tumor-suppressor protein (RB  
 tumor-suppressor protein), 456–457  
 Retroviruses, 23  
 Reverse transcriptase, 23–27  
 Reverse-transcriptase domain  
 (RT domain), 356  
 Rfa2. *See* Replication factor A2 (Rfa2)  
 RFB. *See* Replication fork block  
 site (RFB)  
 RFC. *See* Replication factor C (RFC)  
 RFS-1 Interacting Protein (RIP-1), 172  
 RFS-1, 172  
 Ribonucleoprotein (RNP), 354, 591–592  
 5S RNP, 530  
 Ribonucleotide reductase (RNR), 263  
 Ribosomal deficiency of nucleolar stress,  
 530–531

Ribosomal DNA (rDNA), 399, 435–436, 519, 527–528  
 neurodegeneration-associated instability, 531  
 in brain, 533–534  
 mechanisms in nonneuronal systems, 532–533  
 neurodegeneration-associated instability of rDNA, 534–535, 535f  
 in nonneuronal systems, 531–532  
 theory of aging, 519  
 Ribosomal proteins (RPs), 529–530  
 ribosomal RNAs (rRNAs), 425  
 Riboviruses, 23  
 RING. *See* Really-interesting gene (RING)  
 RING domains, 259–260  
 RING finder protein 8 (RNF8), 231, 323–324  
 Ring-shaped structure, 396  
 RIP. *See* Repeat-induced point mutation (RIP)  
 RIP-1. *See* RFS-1 Interacting Protein (RIP-1)  
 RISC. *See* RNA-induced silencing complex (RISC)  
 RMS. *See* Restriction-modification system (RMS)  
 RN5S loci, 401  
 RNA interference (RNAi), 106–107, 166  
 RNAi system, 88  
 RNA PolII. *See* RNA polymerase II (RNA PolII)  
 RNA polymerase (RNAP), 59  
 RNA polymerase II (RNA PolII), 464–465  
 RNA viruses, 21. *See also* DNA viruses  
 advantage of mutability, 31  
 benefit, 30  
 cellular factors on virus mutation rate, 27–28  
 elegant studies, 30  
 genetic heterogeneity, 29  
 genome structures and genome replication strategies, 24f  
 infection cycle, 22f  
 mechanisms underlying genetic robustness in, 28–29  
 multiplication, 21–23  
 neutral networks, 29f  
 recombination, 25–26, 26f  
 replication mechanisms, 23  
 replication mode on mutation frequency, 27  
 viral determinants of mutation rate, 25  
 viral polymerase as source of error, 23–24  
 virus genetic variability, 30–31  
 viruses as quasispecies, 23  
 virus–host “arms race”, 30–31  
 RNA-binding proteins, 425  
 RNA-dependent RNA polymerase (RdRp), 23, 435  
 RDR6a, 190  
 RNA-induced effects, 557–558  
 RNA-induced silencing complex (RISC), 590  
 RNA-polymerase-1 (Pol1), 527–528  
 DNA damage–sensing role, 528  
 RNA-polymerase-2 (Pol2), 528  
 RNA-Polymerase-3 (Pol3), 532  
 RNA–DNA hybrids (R-loop hybrids), 403  
 RNAi. *See* RNA interference (RNAi)  
 RNAP. *See* RNA polymerase (RNAP)  
 RNF8. *See* RING finder protein 8 (RNF8)

RNP. *See* Ribonucleoprotein (RNP)  
 RNR. *See* Ribonucleotide reductase (RNR)  
 RNU1 loci, 401  
 Rod/Zwilch/Zw10 complex (RZZ complex), 176–177  
 ROS. *See* Reactive oxygen species (ROS)  
 Rothmund–Thomson syndrome (RTS), 448, 450–453, 514–515  
 RPA. *See* Replication protein A (RPA)  
 RPD3/HDA1. *See* Reduced potassium dependency protein 3/histone deacetylase 1 (RPD3/HDA1)  
 RpoS-mediated stress response, 71  
 RPs. *See* Ribosomal proteins (RPs)  
 rRNAs. *See* ribosomal RNAs (rRNAs)  
 RS-SCID. *See* Radiosensitive severe combined immunodeficiency (RS-SCID)  
 12-RSS. *See* 12 Base pair spacer (12-RSS)  
 23-RSS. *See* 23 Base pair spacer (23-RSS)  
 RSS. *See* Recombination signal sequences (RSS)  
 RSV. *See* Resveratrol (RSV)  
 RT. *See* Radiotherapy (RT)  
 RT domain. *See* Reverse-transcriptase domain (RT domain)  
 RTS. *See* Rothmund–Thomson syndrome (RTS)  
 RVD. *See* Repeat variable diresidue (RVD)  
 RZZ complex. *See* Rod/Zwilch/Zw10 complex (RZZ complex)

## S

“S-box”, 262  
 S-phase checkpoint, 257  
 activation, 498  
 checkpoint signaling, 500–502  
 chromatin, 500–502  
 DDT, 498–502, 499f  
 EF-DDT, 500  
 histone H3–K79me3 modification, 501f  
 model of NuA4, 502f  
 PCNA modification, 499  
 TLS–damage tolerance, 500  
 s/n/y. *See* substitutions per nucleotide per year (s/n/y)  
 SAC. *See* Spindle assembly checkpoint (SAC)  
*Saccharomyces cerevisiae* (*S. cerevisiae*), 117–118, 147, 167, 258, 264, 357, 380–382, 384, 487  
 RAD18 and RAD6 genes, 258  
 SAF-A/B, Acinus and PIAS domain (SAP domain), 259–260  
 SAGA complex. *See* Spt-Ada-Gcn5-acetyltransferase complex (SAGA complex)  
 SAGA-like complex (SLIK complex), 489  
 SAH. *See* S-Adenosylhomocysteine (SAH)  
 SAHF. *See* Senescence-associated heterochromatin foci (SAHF)  
 SAM. *See* S-Adenosyl-L-methionine (SAM)  
 SAP domain. *See* SAF-A/B, Acinus and PIAS domain (SAP domain)  
 Satellites, 418–419  
 SAXS. *See* Small-angle X-ray scattering (SAXS)  
 SC. *See* Synaptonemal complex (SC)  
 Scaffolding proteins in BER, 282  
 scan RNAs (scnRNAs), 106–107, 426  
 model, 106–107, 107f  
 scaRNAs. *See* small Cajal body-specific RNAs (scaRNAs)  
 SCEs. *See* Sister chromatid exchanges (SCEs)  
*Schizosaccharomyces pombe* (*S. pombe*), 156, 357  
 SCID. *See* Severe combined immunodeficiency (SCID)  
 scnRNAs. *See* scan RNAs (scnRNAs)  
 SDI1. *See* Senescent cell–derived inhibitor 1 (SDI1)  
 SDSA. *See* Synthesis-dependent strand annealing (SDSA)  
 See d sequence, 193  
 Senescence, 250, 348  
 Senescence-associated heterochromatin foci (SAHF), 251, 517  
 Senescence-associated secretory phenotype, 250  
 Senescent cell–derived inhibitor 1 (SDI1), 248  
 Sensing DNA damage, 204–205  
 Sensors, regulation of, 428–429  
 Serine 345, 375  
 SET and ring-associated domain (SRA), 414  
 Severe combined immunodeficiency (SCID), 228, 324  
 Sexual reproduction, 102–103  
 sgRNA. *See* single-guide RNA (sgRNA)  
 Shelterin(s), 454–455  
 complex, 354, 358–360, 359f  
 mutations, 363  
 SHH pathway. *See* Sonic hedgehog pathway (SHH pathway)  
 SHM. *See* Somatic hypermutation (SHM)  
 Short interspersed nuclear elements (SINE), 412, 557  
 SINE B2, 588–590  
 Short interspersed nucleotide elements. *See* Short interspersed nuclear elements (SINE)  
 Short regularly spaced repeats (SRSRs), 88  
 Short-patch MMR system, 149  
 Sievert (Sv), 571  
 Signal recognition particle (SRP), 527–528  
 Signal(s), 608–609  
 transduction, 230–231  
 Simple sequence repeats (SSRs), 74  
 SIN3 transcription regulator family member B (SIN3B), 456–457  
 SIN3B. *See* SIN3 transcription regulator family member B (SIN3B)  
 SINE. *See* Short interspersed nuclear elements (SINE)  
 Single nucleotide polymorphism (SNP), 12, 413, 469  
 single-guide RNA (sgRNA), 425–426  
 Single-nucleotide filling (SN filling-BER), 281–282  
 Single-strand annealing (SSA), 120–121, 174, 191–192, 213–214, 234, 341  
 pathway of HR repair, 121f



- Single-strand break (SSB), 58, 163, 203, 233, 276, 282, 413–414, 464, 493, 513, 528, 569–571, 587, 635, 652f, 655  
 base damage and, 276  
 alkylation, 277  
 deamination, 277  
 oxidation, 277  
 protein, 305  
 with tyrosyl–DNA covalent linkage, 277  
 single-stranded DNA (ssDNA), 55–56, 70, 91, 118–120, 230–231, 261, 337, 354, 375  
 3′-ssDNA, 170–172, 468  
 breaks, 263  
 parvoviruses, 42–43  
 Singlet oxygen ( $^1\text{O}_2$ ), 203–204  
 siRNAs. *See* Small-interfering RNAs (siRNAs)  
 SIRT1 pathway. *See* Sirtuin–signaling pathway (SIRT1 pathway)  
 Sirtuin–signaling pathway (SIRT1 pathway), 169  
 Sister chromatid exchanges (SCEs), 258–259, 343  
 Site-specific inversion system, 75–76  
 SKOV-3 cells, 379  
 SKY. *See* Spectral karyotyping (SKY)  
 Sliding clamp model. *See* “Molecular switch”; model  
 Sliding-clamp model, 311  
 SLIK complex. *See* SAGA-like complex (SLIK complex)  
 Slippery DNA, 471–472  
 small Cajal body-specific RNAs (scaRNAs), 357  
 small nucleolar RNAs (snoRNAs), 425  
 small RNA (smRNA), 619  
 small RNA molecules (sRNA molecules), 106–107  
 in genome stability, 591–592  
 piRNA  
 biogenesis, 591–592  
 as mediators of epigenetic memory, 592  
 small RNA-mediated events, 590–592  
 Small ubiquitin-like modifier (SUMO), 491  
 Small-angle X-ray scattering (SAXS), 307–308  
 Small-interfering RNAs (siRNAs), 429, 558, 628  
 genome stability maintenance, 435–439  
 DNA strand break–induced small RNAs, 436–439, 438f  
 in *N. crassa*, 435–436  
 SMART. *See* Somatic mutation and recombination test (SMART)  
 SMC. *See* Structural maintenance of chromosomes (SMC)  
 smRNA. *See* small RNA (smRNA)  
 SN filling-BER. *See* Single-nucleotide filling (SN filling-BER)  
 snoRNAs. *See* small nucleolar RNAs (snoRNAs)  
 Snowball effects, 593  
 SNP. *See* Single nucleotide polymorphism (SNP)  
 SOD2. *See* Superoxide dismutase (SOD2)  
 Soft inheritance, 624  
 SOG1. *See* Suppressor of gamma response 1 (SOG1)  
 Somatic cell mutation  
 alterations in microsatellite repeats detected by PCR, 158f  
 MMR, 157  
 in chromosomal recombination, 159f  
 mutagenicity of X-ray irradiation in MMR-deficient, 159t  
 NDMA, 158–159  
 SMART, 157  
 somatic cell division, 158  
*spell1*, 157  
 X-ray irradiation, 158  
 Somatic hypermutation (SHM), 291  
 Somatic mutation  
 accumulation theory of aging, 511–512  
 rates evolution, 9–11  
 Somatic mutation and recombination test (SMART), 157  
 Somatic nuclei, 101–102  
 Somatic tissues, 587  
 Sonic hedgehog pathway (SHH pathway), 470–471  
 SOS response, 55–56, 70–71  
 Soybean (*Glycine max*), 190  
 SP1. *See* Specificity protein 1 (SP1)  
 Spartan, 261–262  
 Species, 3  
 Species-sensitivity distributions (SSD), 606–607  
 Specificity protein 1 (SP1), 362  
 Spectral karyotyping (SKY), 384  
*spellchecker1* gene (*spell1* gene), 156–157  
 Spermatogenic cell apoptosis, 592–593  
 Spindle assembly checkpoint (SAC), 176, 375, 491  
 Sporadic cancers. *See also* Hereditary cancer  
 genomic instability in, 474  
 chromothripsis, 477  
 CIN in sporadic cancers, 474–475  
 high-throughput sequencing studies on CIN, 475–476  
 hypothesis of mechanisms of CIN, 475  
 MSI in sporadic cancer, 477–478  
 oncogenes induce CIN, 476–477  
 Spt-Ada-Gcn5-acetyltransferase complex (SAGA complex), 489  
 SRA. *See* SET and ring-associated domain (SRA)  
 sRNA molecules. *See* small RNA molecules (sRNA molecules)  
 SRP. *See* Signal recognition particle (SRP)  
 SRSRs. *See* Short regularly spaced repeats (SRSRs)  
 SSA. *See* Single-strand annealing (SSA)  
 SSB. *See* Single-strand break (SSB)  
 SSB repair (SSBR), 282  
 SSD. *See* Species-sensitivity distributions (SSD)  
 ssDNA. *See* single-stranded DNA (ssDNA)  
 SSPE. *See* Subacute sclerosing panencephalitis (SSPE)  
 SSRs. *See* Simple sequence repeats (SSRs)  
 Stamping machine, 27  
*Staphylococcus epidermidis* (*S. epidermidis*), 88  
 Stationary models, 656–657  
 Stem cells, 356  
 Stichotrichia, 103  
 Stochastic effects, 574  
 Strand annealing, 125  
 Strand discrimination, 311–312  
 Strand exchange, 339–341  
 Strand invasion, 118–120  
 Strand-discrimination signal role in MMR, 656–657  
 Streffer group, 603  
*Streptococcus pyogenes* (*S. pyogenes*), 93, 193  
*Streptococcus thermophilus* (*S. thermophilus*), 88  
*Streptococcus*-like system, 90  
 Stress, 617–620  
 changes in chromatin structure, 618  
 DNA methylation role, 619–622  
 changes in transposon activity, 621–622  
 responses on genome instability, 69–70  
 cold shock response, 72  
 heat shock response, 72  
 interplay between bacteria stress responses, 70f  
 polyphosphate-mediated starvation response, 72  
 RpoS-mediated stress response, 71  
 SOS response, 70–71  
 stringent response, 72  
 stress-induced premature senescence, 250  
 transgenerational inheritance regulation of memory, 627–629  
 Stressors, 607  
 Stringent response, 72  
 Structural maintenance of chromosomes (SMC), 121–123  
 proteins, 205  
 SMC1, 232  
 SMC5/6, 265–266  
 Structure–function relationship, 395  
 Styrene, 545  
 Subacute sclerosing panencephalitis (SSPE), 27  
 substitutions per nucleotide per year (s/n/y), 38  
*Sulfolobus solfataricus* (*S. solfataricus*), 90  
*Sulfonylurea receptor* genes, 189–190  
 SUMO. *See* Small ubiquitin-like modifier (SUMO)  
 “Super-p53” mice, 244  
 Superoxide dismutase (SOD2), 277  
 Suppressor of gamma response 1 (SOG1), 204–205  
 Suppressor of variegation 3–9 homolog 1 (Suv39H1), 418  
*Suv39h1/2* double knockout, 418–419  
 SWI2/SNF2. *See* SWI2/SNF2 nonfermentable (SWI2/SNF2)  
 SWI2/SNF2 nonfermentable (SWI2/SNF2), 205  
 family proteins, 618–619  
 Symbiosis in genome evolution, 3  
 adaptive evolution, 4–5  
 changes in structure of organellar genome, 4  
 mutation rates in organellar genomes, 4–5  
 symbiotic interactions between viruses, prokaryotes, and eukaryotes, 5–6

Symbiotic interaction, 3

between viruses, prokaryotes, and eukaryotes, 5–6

Synaptonemal complex (SC), 147, 170–172

Synthesis-dependent strand annealing (SDSA),

120, 143, 174, 213–214, 341, 468

“conversion-duplication” events, 144

D-loop, 144–145

dHJ, 143–144

HHR model, 144f

I-SceI, 145

Synthetic lethality, 478–480

System-Level Responses, 609

## T

T opposite G (T:G), 303

T-cell receptors (TCRs), 321

T-loop. *See* Telomere loops (T-loop)

T-lymphocytes, 22–23

T-PK. *See* Template pseudoknot (T-PK)

T:G. *See* T opposite G (T:G)

T4 mutators, 38–39

TADs. *See* Topologically associating domains (TADs)

TALE. *See* Transcription activator-like effector (TALE)

TALENs. *See* Transcription activator-like effector nucleases (TALENs)

Tamoxifen effects, 559–560

Tandem repeats, 411–412

TANK-1, 175–176

Taq. *See* *Thermus aquaticus* (Taq)

Targeted DNA-damaging cancer therapy, 247–248

Targeted gene replacement, 338

Targeting bacteriophage genomes, by CRISPR/CAS9, 425–426

TC-NER. *See* Transcription-coupled NER (TC-NER)

TCAB1. *See* Telomerase Cajal body protein 1 (TCAB1)

TCGA. *See* The Cancer Genome Atlas (TCGA)

TCR. *See* Transcription-coupled repair (TCR)

TCRs. *See* T-cell receptors (TCRs)

TDG. *See* Thymine DNA glycosylase (TDG)

TDPs. *See* Tyrosyl-DNA phosphodiesterases (TDPs)

TdT. *See* Terminal deoxynucleotidyl transferase (TdT)

TEBP  $\alpha$ . *See* Telomere end binding protein  $\alpha$ ; (TEBP  $\alpha$ )

Telomerase

activity in cancer, 362–363

regulation, 354–356

activity in cancer, 362–363

germ cells and embryogenesis, 356

stem cells, 356

RNA, 426

telomere–telomerase interactions and regulation, 360

Telomerase Cajal body protein 1 (TCAB1), 357

Telomerase reverse transcriptase (TERT), 354, 355f

organization, 356–357

Telomerase RNA component (TERC), 354, 357

Telomere end binding protein  $\alpha$  (TEBP  $\alpha$ ), 360

Telomere end binding protein  $\beta$  (TEBP  $\beta$ ), 360

Telomere length homeostasis, 360–362

AA, 361

DC, 361

IPF, 361–362

Telomere loops (T-loop), 358

Telomere(s), 353, 511, 519

DNA damage–prevention system, 363–364, 364f

as DNA damage–prevention system, 363–364, 364f

dysfunction, 521

human telomeres, 519

instability, 519

length, 354–356

embryogenesis, 356

germ cells, 356

homeostasis and related diseases, 360–362

stem cells, 356

premature aging syndromes, 362

shortening, 519

telomere-associated diseases

and premature aging syndromes, 362

shelterin mutations and telomere-related diseases, 363

telomerase activity in cancer, 362–363

telomere-interacting proteins

CST protein complex, 360

shelterin complex, 358–360, 359f

telomere–telomerase interactions and regulation, 360

telomeric DNA structure, 357–358

Telomeric DNA, 357–358, 358f, 519

Telomeric repeat-binding factors 1 (TRF1), 354, 358–359

Telomeric repeat-binding factors 2 (TRF2), 354, 358–359

Temozolomide (TMZ), 277, 417

Template pseudoknot (T-PK), 357

Template repeat (TR), 41

Template switching (TS), 25–26, 257

RAD18 functions in error-free PRR via, 264–265

Template-guided model, 109, 110f

Template-mediated repair, 141

TEN domain. *See* TERT N-terminal domain (TEN domain)

Ten–eleven translocation enzymes (TETs), 409–410

Teratogenic effects, 587

TERC. *See* Telomerase RNA component (TERC)

TERF1-interacting nuclear factor 2 (TIN2), 354, 359

Terminal deoxynucleotidyl transferase (TdT), 330–331

Terminal transferase, 353–354

TERT. *See* Telomerase reverse transcriptase (TERT)

TERT N-terminal domain (TEN domain), 356

TERT RNA-binding domain (TRBD domain), 356

*tert*-butylhydroperoxide (*tert*-BH), 169–170

TEs. *See* Transposable elements (TEs)

Testicular germ-cell tumor cell lines (TGCT cell lines), 375–376

Tet-repressor proteins (TetR), 399–400

*Tetrahymena*, 426

*T. thermophila*, 103, 353–354, 356–357

TETs. *See* Ten–eleven translocation enzymes (TETs)

TFIIH. *See* Transcription initiation factor IIH (TFIIH)

TFIIH complex

helicase complex, 450

in NER and transcription, 287–288

TFIIS. *See* Transcription elongation factor II-S (TFIIS)

TGCT cell lines. *See* Testicular germ-cell tumor cell lines (TGCT cell lines)

TGS. *See* Transcriptional gene silencing (TGS)

The Cancer Genome Atlas (TCGA), 373

Theory of evolution, 2

*Thermus aquaticus* (Taq), 305–306

*Thermus thermophilus* (*T. thermophilus*), 94

Thiopurines, 312–313

Thymine DNA glycosylase (TDG), 409–410

TIN2. *See* TERF1-interacting nuclear factor 2 (TIN2)

TIP60, 396

Tissue touch prints, 638

preparation, 638

TLPs. *See* Trait landing pads (TLPs)

TLS. *See* Translesion synthesis (TLS)

TMP. *See* Trimethylpsoralen (TMP)

TMV. *See* Tobacco mosaic virus (TMV)

TMZ. *See* Temozolomide (TMZ)

TNR. *See* Trinucleotide repeats (TNR)

Tobacco mosaic virus (TMV), 13

Topo1. *See* Topoisomerase-1 (Topo1)

Topo2. *See* DNA topoisomerase-2 (Topo2)

Topoisomerase III (TopoIII), 341

Topoisomerase-I (TopoI), 528

Topoisomerases, 277

Topologically associating domains (TADs), 400

TOSCA protein, 156

Tp53 gene, 244, 346–347, 456, 469, 477

mutation, 469

TR. *See* Telomerase RNA component (TERC); Template repeat (TR)

tracrRNA. *See* transcribed crRNA (tracrRNA)

Trait landing pads (TLPs), 190–191

Trait stacking, 196

“*trans*-” models. *See* Stationary models

Trans-silencing effect (TSE), 434

Transcription

elongation factor, 401

factor p53, 232

factors, 395, 544

in nucleus, 400–403

Transcription activator-like effector (TALE), 191

Transcription activator-like effector nucleases (TALENs), 188, 191f, 662

for genetic engineering of plants, 191

in crops, 192–193

limitations, 193

in model plant species, 191–192

- Transcription elongation factor II-S (TFIIS), 210–211
- Transcription initiation factor IIH (TFIIH), 464–465
- Transcription-coupled NER (TC-NER), 59, 163, 167, 232–233, 283, 289–290, 448, 464, 494, 652f
- Transcription-coupled repair (TCR), 209, 636, 651
- Transcriptional gene silencing (TGS), 591
- Transcriptional regulation  
DNA damage–repair genes by DNA methylation, 417  
by DNA methylation, 411
- Transcriptional-repair coupling factor (TRCF). *See* Mfd protein
- Transcription–replication collisions  
model, 401
- Transcriptome profiling, 166
- Transduction, 79
- transencoded crRNA (tracrRNA), 92, 193
- transfer RNAs (tRNAs), 425
- Transformation, 80
- Transgenerational effects, 586–588  
caused by other mutagens, 592–593  
mechanisms, 590–592  
DNA methylation, 589–590  
histone modifications, 590  
small RNA-mediated events, 590–592
- Transgenerational genome instability, 586–588, 593f
- Transgenerational inheritance regulation  
mechanisms, 627. *See also* Plant genome stability  
DNA-repair factors, 628  
epigenetic regulators, 628–629
- Transgenerational radiation-induced effects, 588
- Transgenerational responses in plants. *See also* Plant genome stability  
piRNAs in, 434  
stress-induced epigenetic and genetic changes, 624f  
transgenerational changes  
changes in DNA methylation in progeny, 626  
in genome stability, methylation, and stress tolerance, 626–627  
in response to abiotic stress, 625–626  
transgenerational effects, 623–625
- Translesion synthesis (TLS), 257, 313, 498–499, 651  
DNA replication–independent RAD18 activation and, 262–264  
polymerase switch, 259  
TLS polymerase switch, 259  
TLS–damage tolerance, 500
- Translocation(s), 329–330, 393–394, 399  
model, 657
- Transparent Testa-4* (TT4), 189
- Transposable elements (TEs), 5–6, 411–412, 591
- Transposons, 78
- TRBD domain. *See* TERT RNA-binding domain (TRBD domain)
- TRF-homology domains (TRFH domains), 358–359
- TRF1. *See* Telomeric repeat-binding factors 1 (TRF1)
- TRFH domains. *See* TRF-homology domains (TRFH domains)
- Trichothiodystrophy (TTD), 447–450, 516
- Trimethylated lysine residues, 393
- Trimethylation of lysine 4 from histone H3 (H3K4me3), 393–394, 490–491, 623
- Trimethylpsoralen (TMP), 164
- Trinucleotide repeats (TNR), 412–413
- Triticum aestivum*. *See* Wheat (*Triticum aestivum*)
- tRNAs. *See* transfer RNAs (tRNAs)
- TS. *See* Template switching (TS)
- TSA. *See* Tyramide signal amplification (TSA)
- TSE. *See* Trans-silencing effect (TSE)
- TT4. *See* *Transparent Testa-4* (TT4)
- TTD. *See* Trichothiodystrophy (TTD)
- Tumor suppression  
p21 and, 249–250  
p53 in and DNA-damage response, 246–247
- Tumor-suppressor  
genes, 250  
proteins, 562
- Tumorigenesis, 572–573, 575  
RAD18 roles in, 266–267
- Tumors, misregulation of HR in, 346–347
- Two-step model, 343
- 2D gel electrophoresis, 120
- Tyramide signal amplification (TSA), 645
- Tyrosyl–DNA covalent linkage, SSBs with, 277
- Tyrosyl–DNA phosphodiesterases (TDPs), 280  
TDP1, 280–281  
TDP2, 280–281
- ## U
- 21U-RNAs, 432–434
- U-shaped response curve, 548
- Ubiquitin specific–processing protease 7 (USP7), 464–465
- Ubiquitin-binding motif (UBM), 259
- Ubiquitin-binding zinc finger (UBZ), 259
- Ubiquitin-like with PHD and ring finger domains 1 (UHRF1), 414, 418
- UBM. *See* Ubiquitin-binding motif (UBM)
- UBZ. *See* Ubiquitin-binding zinc finger (UBZ)
- UBZ4 domain, 259–260
- UDG. *See* Uracil DNA glycosylase (UDG)
- UHRF1. *See* Ubiquitin-like with PHD and ring finger domains 1 (UHRF1)
- Ultraviolet (UV), 163, 313–314  
irradiation, 57, 164, 166  
lesions, 644–646  
light, 232–233, 244, 258, 286, 447  
UV-A, 166, 206  
UV-B, 166, 206  
UV-C, 166, 206
- Ultraviolet radiation (UVR), 117–118, 206, 391, 493–494
- Uncertainty, 605. *See also* Genomic instability (GI); Low radiation–dose effects  
genetic background role, 607  
individual variation, 606  
lifestyle factors role, 607  
spectrum of effects, 605–606  
spectrum of responses, 606  
SSD, 607  
stressors role, 607  
unpredictable “zone”, 606f
- UNG. *See* Uracil DNA glycosylase (UNG)
- Uniformitarianism, 7
- United Nations (UN), 575
- Untranslated region (UTR), 590
- Unwinding of damaged DNA duplex, 286–288  
DNA nucleotide excision repair, 287f  
enzymes and reactions in NER pathway, 288t
- UPR<sup>mt</sup>. *See* Mitochondrial unfolded protein response (UPR<sup>mt</sup>)
- Uracil  
base excision repair and removal, 58  
uracil–DNA glycosylase homolog UNG–1, 169–170
- Uracil DNA glycosylase (UDG), 58, 208, 653  
UDG1, 58
- Uracil DNA glycosylase (UNG), 281–282
- USP7. *See* Ubiquitin specific–processing protease 7 (USP7)
- Ustilago maydis* (*U. maydis*), 118
- UTR. *See* Untranslated region (UTR)
- UV. *See* Ultraviolet (UV)
- UV-damaged DNA-binding protein (UV-DDB), 167, 464–465  
UV-DDB2, 286
- UV-DDB. *See* UV-damaged DNA-binding protein (UV-DDB)
- UV-sensitive syndrome A. *See* UV-stimulated scaffold protein A (UVSSA)
- UV-signature mutation, 470–471
- UV-stimulated scaffold protein A (UVSSA), 289, 464–465
- UVR. *See* Ultraviolet radiation (UVR)
- UVSSA. *See* UV-stimulated scaffold protein A (UVSSA)
- ## V
- V(D)J recombination, 324–328, 327f, 330–331, 472–473
- Vacuolar invertase* gene (*VInv* gene), 192–193
- Variable repeat (VR), 41
- Verminephrobacter eiseniae* (*V. eiseniae*), 89
- Versatile DNA-repair pathway, 59–60
- Vertebrate telomeres, 358–359
- Vibrio cholerae* (*V. cholerae*), 79  
virulence acquisition, 79f
- Vicia faba* (*V. faba*), 88
- VInv* gene. *See* *Vacuolar invertase* gene (*VInv* gene)
- Viral determinants of mutation rate, 25
- Viral polymerase as source of error, 23–24
- Virulence acquisition of *V. cholerae*, 79f
- Virus(es), 21  
cellular factors on mutation rate, 27–28  
genetic variability, 30–31  
as quasispecies, 23  
symbiotic interactions between viruses, prokaryotes, and eukaryotes, 5–6  
virus–host “arms race”, 30–31

Vitamins, 546–548  
     carotenoids, 547  
     minerals, 548  
 Vitro systems, 586  
 von Willebrand A domain (vWA), 323  
 VR. *See* Variable repeat (VR)  
 vWA. *See* von Willebrand A domain (vWA)

## W

WAF1. *See* Wild-type p53-activated factor 1 (WAF1)  
 Wee1 kinase, 247–248, 375  
 Werner syndrome (WS), 448, 450–453, 514–515  
     human premature aging syndromes, 514t  
 Werner syndrome ATP-dependent helicase (WRN), 402–403, 477  
 Western blotting of  $\gamma$ H2AX in animal tissues, 640–641  
 Wheat (*Triticum aestivum*), 195  
 WHO. *See* World Health Organization (WHO)  
 Wild-type cells (WT cells), 329  
 Wild-type p53-activated factor 1 (WAF1), 248  
 Wnt-signaling pathways, 559  
 World Health Organization (WHO), 575  
 WRAP53. *See* Telomerase Cajal body protein 1 (TCAB1)  
 WRN. *See* Werner syndrome ATP-dependent helicase (WRN)  
 WS. *See* Werner syndrome (WS)  
 WT cells. *See* Wild-type cells (WT cells)

## X

X-ray irradiation, 158  
 X-ray repair cross-complementing protein 1 (XRCC1), 208–209, 464  
 XAB2. *See* XPA-binding protein 2 (XAB2)  
*Xanthomonas*, 191  
*X. oryzae*, 621  
*Xenopus*, 592  
     oocyte, 382  
 Xeroderma Pigmentosum (XP), 167, 283, 447–450, 468, 470–471, 516, 636  
 Xeroderma pigmentosum, complementation group C (XPC), 167, 209–210, 448, 636  
 Xeroderma pigmentosum complementation group A (XPA), 167  
 Xeroderma pigmentosum–variant cells (XPV cells), 259  
 XP. *See* Xeroderma Pigmentosum (XP)  
 XPA. *See* Xeroderma pigmentosum complementation group A (XPA)  
 XPA-binding protein 2 (XAB2), 289  
 XPC. *See* Xeroderma pigmentosum, complementation group C (XPC)  
 XPE progeroid syndrome, 450  
 XPF–ERCC1 heterodimer, 450  
*XPO1*. *See* Exportin 1 (*XPO1*)  
 XPV cells. *See* Xeroderma pigmentosum–variant cells (XPV cells)  
 XRCC1. *See* X-ray repair cross-complementing protein 1 (XRCC1)

Xrcc4, 326  
 XRCC4:DNA ligase IV ligation, 659

## Y

Yeast, 117–118  
     mutants, 118  
     senescence, 348  
 Yeast equivalent of Ku (Yku), 126  
 Yellow fluorescent protein (YFP), 191–192

## Z

ZBTB24 mutations. *See* Zinc-finger and BTB domain containing 24 mutations (ZBTB24 mutations)  
 ZFNs. *See* Zinc-finger nucleases (ZFNs)  
 Zigzag model, 394  
 Zinc-finger and BTB domain containing 24 mutations (ZBTB24 mutations), 419  
 Zinc-finger nucleases (ZFNs), 188, 189f, 662  
     application  
         in crops, 190–191  
         in model plant species, 189–190  
     for genetic engineering of plants, 188  
     limitations, 191  
*ZmM11* gene, 621  
 Zn finger, RAN-binding domain containing 3 (ZRANB3), 264  
 Zucchini (Zuc), 430