REVIEW ARTICLE

MOLECULAR ORIGINS OF CANCER

DNA Damage, Aging, and Cancer

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DNA DAMAGE HAS EMERGED AS A MAJOR CULPRIT IN CANCER AND MANY diseases related to aging. The stability of the genome is supported by an intricate machinery of repair, damage tolerance, and checkpoint pathways that counteracts DNA damage. In addition, DNA damage and other stresses can trigger a highly conserved, anticancer, antiaging survival response that suppresses metabolism and growth and boosts defenses that maintain the integrity of the cell. Induction of the survival response may allow interventions that improve health and extend the life span. Recently, the first candidate for such interventions, rapamycin (also known as sirolimus), has been identified.[1] Compromised repair systems in tumors also offer opportunities for intervention, making it possible to attack malignant cells in which maintenance of the genome has been weakened.

Time-dependent accumulation of damage in cells and organs is associated with gradual functional decline and aging.[2] The molecular basis of this phenomenon is unclear,[3-5] whereas in cancer, DNA alterations are the major culprit. In this review, I present evidence that cancer and diseases of aging are two sides of the DNA-damage problem. An examination of the importance of DNA damage and the systems of genome maintenance in relation to aging is followed by an account of the derailment of genome guardian mechanisms in cancer and of how this cancer-specific phenomenon can be exploited for treatment.

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DNA DAMAGE AND AGING

Biologic molecules are susceptible to spontaneous chemical reactions, mostly hydrolysis. Enzymatic reactions have an error rate, and their reaction products (including free radicals, such as reactive oxygen and nitrogen species)[2,6] can have harmful effects on other biologic molecules. Furthermore, elements in the environment — x-rays, ultraviolet (UV) radiation, and numerous chemicals — continuously damage cellular structures.[3-5] DNA is an important target for time-dependent deterioration, as highlighted by the rapidly expanding family of rare inherited disorders called segmental progeroid syndromes, in which genome maintenance is compromised and many features of aging are accelerated[7,8] (for details see the Supplementary Appendix, available with the full text of this article at NEJM.org). These syndromes indicate that DNA is a critical target of aging and that genome maintenance is a major anti-aging mechanism.

THE MAGNITUDE OF DNA DAMAGE

DNA is the only biologic molecule that relies solely on repair of existing molecules, without any remanufacture; accumulates damage over a lifetime; and is represented by only one copy in most cells (with maternal and paternal DNA considered to be

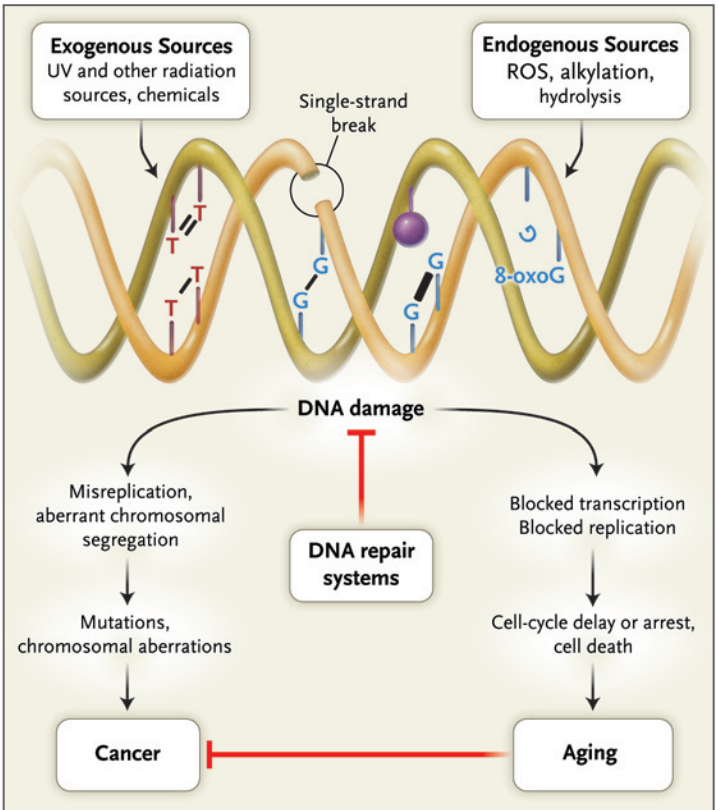

Figure 1. Sources and Consequences of DNA Damage.

DNA damage can be induced by exogenous physical agents, by endogenous chemical genotoxic agents that are the products of metabolism, such as reactive oxygen species (ROS), or by spontaneous chemical reactions, such as hydrolysis. Examples of DNA damage are ultraviolet (UV)-induced photoproducts (left), interstrand and intrastrand crosslinks, bulky chemical adducts (purple sphere), abasic sites, and oxidative damage such as 8-oxoguanine (8-oxoG). The consequences of DNA damage are essentially twofold. After misrepair or replication of the damaged template, surviving cells may be subject to permanent changes in the genetic code in the form of mutations or chromosomal aberrations, both of which increase the risk of cancer. Alternatively, damage may interfere with the vital process of transcription or induce replication arrest, which may trigger cell death or cellular senescence, contributing to aging. Damage-induced cell death protects the body from cancer. G denotes guanine, and T thymidine.

distinct). It is by far the largest molecule that can accumulate numerous lesions yet must be kept intact, at least in germline and proliferating cells, to function properly. The bases in DNA are highly vulnerable to chemical modification, which can cause numerous lesions (Fig. 1). When these lesions are converted into mutations by means of faulty repair or replication errors, the changes are permanent and continually exert their effect, even in descendant cells. One important consequence of mutations is the loss of tumor-suppressor genes and the improper activation of oncogenes, which trigger uncontrolled cellular proliferation and the development of malignant cells. Genome instability is the hallmark of all forms of cancer.[9] An additional complication linked to DNA is that the epigenome may also be subject to time-dependent, semipermanent changes[10]; indeed, there is convincing evidence that epigenetic changes contribute to cancer.[11]

DNA integrity is threatened from three sides. First, spontaneous reactions (mostly hydrolysis) intrinsic to the chemical nature of DNA in an aqueous solution create abasic sites and cause deamination.[12,13] Second, our own metabolism generates reactive oxygen and nitrogen species, lipid peroxidation products, endogenous alkylating agents, estrogen and cholesterol metabolites, and reactive carbonyl species,[14] all of which damage DNA. Reactive oxygen and nitrogen species alone generate several kinds of single-strand breaks and more than 70 oxidative base and sugar products in DNA.[13] Third, DNA is damaged by exogenous physical and chemical agents, but this damage is to some extent avoidable. The estimated numbers of single-strand breaks and spontaneous base losses in nuclear DNA are as high as 10^4 per cell per day.[12,13] Together with other types of spontaneous damage, the total may be close to 10^5 lesions per cell per day.[12] A single day in the sun can induce up to 10^5 UV photoproducts in each exposed keratinocyte, and inflammation can cause high levels of oxidative damage locally.

DNA injury can induce mutations that cause cancer or cell death or senescence, contributing to aging. The type of damage that occurs is important for the type of outcome. Some lesions are primarily mutagenic, others mainly cytotoxic or cytostatic (Fig. 1). Many DNA lesions lead to both types of outcomes in different ratios, depending on the location and number of lesions, cell type, and stage in the cell cycle and differentiation. A well-known mutagenic injury is 7,8-dihydro-8-oxoguanine, an oxidative lesion that on DNA replication pairs equally well with the cytosine (normal pairing) and adenine (abnormal pairing), causing GC→TA transversions.[15] In contrast, double-strand breaks that are induced by ionizing radiation or that occur during the processing of interstrand cross-links are primarily cytotoxic or cytostatic.

GENOME MAINTENANCE

An elaborate genomic maintenance apparatus controls DNA damage. It consists of multiple repair pathways, each focusing on a specific category of DNA lesion, and various checkpoint, signal-transduction, and effector systems connected with replication, transcription, recombination, chromatin remodeling, and differentiation.[16] The maintenance system determines a cell's fate: survival, replicative senescence, or death.[17,18] Genome maintenance also includes a complex telomere-processing machinery[19] and guards the integrity of mitochondrial DNA.[20] One of the main functions of the system is to ensure faithful transmission of genetic information to progeny and functional integrity in long-lived, nondividing cells, such as neurons.

The enormous investment that cells are prepared to make in genome maintenance is illustrated by the class of repair proteins that can be used only once. For instance, O-6-methylguanine-DNA methyltransferase repairs a single O-6-methylguanine lesion by transferring the methyl from a guanine in DNA to a cysteine in the enzyme, thereby inactivating itself.[21] Similarly, recognition of a UV-induced dimer in DNA by nucleotide-excision repair may require the sacrifice of a UV DNA damage binding protein 2 (xeroderma pigmentosum group E).[22,23] Moreover, DNA damage induces well over 900 distinct phosphorylation events involving more than 700 proteins[24]; repair of a single double-strand break may require more than 10^4 ATP molecules, which are used in signaling, the generation of repair foci, and the formation of the RAD51 nucleofilament, an intermediate in recombination repair. The complexity of genome maintenance underscores the importance of preserving genome integrity.

THE DNA-REPAIR TOOLBOX

In addition to having repair systems consisting of a single protein, such as O-6-methylguanine-DNA methyltransferase, the genomic maintenance system includes at least six multistep repair pathways, each covering a specific subclass of DNA lesion[25] (Fig. 2). One such pathway, base-excision repair, removes subtle modifications of DNA, including oxidative lesions, small alkylation products, and different kinds of single-strand breaks.[26-28] After a damaged base is removed, the injured strand is incised at the resulting abasic site and refilled by means of DNA synthesis. In the process, some flanking sequences may be replaced. Nucleotide-excision repair eliminates helix-distorting DNA damage, a broad category of damage that affects one of the two DNA strands.[23,29] Transcription-coupled repair, which is strongly linked with nucleotide-excision repair and possibly with base-excision repair, targets only lesions that obstruct transcription.[30,31]

Nonhomologous end joining and homologous recombination repair various types of double-strand breaks. Nonhomologous end joining simply brings two ends together, but bases may be lost or added as it occurs. This inaccurate process takes place mostly before replication, in the absence of an identical copy of DNA. After replication, homologous recombination, acting through a series of complex DNA transactions, uses the identical sister chromatid to properly align the broken ends and unerringly insert missing information.[32,33] Interstrand cross-link repair works on the cytotoxic cross-links that covalently attach both strands, preventing strand separation and effectively arresting transcription and replication. This process probably involves a combination of pathways, using part of the homologous-recombination machinery in conjunction with more than 13 Fanconi's anemia proteins and one of the nucleotide-excision repair endonucleases.[34-36]

Some types of damage escape detection by repair proteins,[23] and the lesions may accumulate. At least five specialized translesional polymerases allow replication to bypass such lesions in the template, resulting in a somewhat elevated mutation rate[37] that contributes to the gradual accumulation of mutations in somatic tissues.[38] Figure 2 provides an overview of the relative effects of repair mechanisms on mutagenesis and cell survival.

DISEASES OF NUCLEOTIDE-EXCISION REPAIR

Nucleotide-excision repair eliminates helix-distorting lesions — such as those caused by UV-induced photoproducts — in a multistep, "cut-and-patch" reaction that involves more than 30

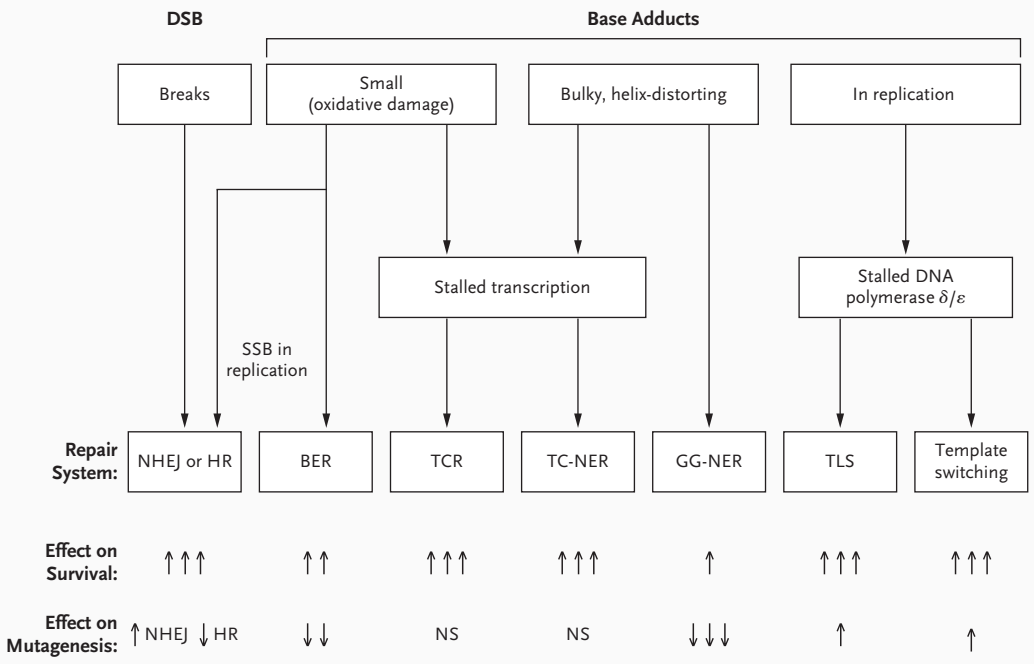

Figure 2. DNA Lesions, Corresponding DNA Repair and Maintenance Systems, and Their Effect on Cellular Survival and Mutagenesis.

Double-strand breaks (DSBs) in DNA are highly cytotoxic and cytostatic forms of damage. They are repaired through nonhomologous end-joining (NHEJ), which simply joins the ends of DNA strands and is associated with an elevated risk of mutagenesis, or through homologous recombination (HR), which takes place after replication and uses the intact copy on the sister chromatid to properly align and seal the broken ends in an error-free manner. HR is also involved in bypassing interstrand cross-links (not shown) and in repairing single-strand breaks (SSBs) and blocking lesions encountered during replication. In mammals, NHEJ is important for the repair of somatic (differentiated) cells and proliferating cells in the G1 stage, whereas HR is important for early embryogenesis and repair of proliferating cells in the S or G2 stage. NHEJ promotes cellular survival in the presence of highly cytotoxic DSBs and may thereby enhance mutagenesis. HR also promotes cellular survival, but without inducing mutations. Base-excision repair (BER) is involved with small DNA adducts (mainly oxidative and alkylating lesions), some of which may be highly mutagenic (e.g., 7,8-dihydro-8-oxoguanine), and some cytotoxic. When these lesions block elongating RNA polymerase, transcription-coupled repair (TCR) removes the damage, allowing the vital transcription to resume. BER prevents mutagenesis and promotes cellular survival. Transcription-coupled nucleotide-excision repair (TC-NER) is specific to transcription-blocking bulky adducts, which are eliminated throughout the entire genome by the global genome nucleotide-excision repair (GG-NER) system (Fig. 3). DNA damage that blocks the regular replication machinery involving DNA polymerase δ/ε (e.g., breaks and cross-links) can be repaired, bypassed by homologous recombination, which involves template switching and strand displacement, or bypassed by translesional synthesis (TLS), a specialized, relatively error-free (but still somewhat mutagenic) means of bypassing a specific subgroup of lesions. Arrows pointing upward indicate increases in cell survival or mutagenesis after DNA damage, and arrows pointing downward indicate decreases; the greater the number of arrows, the stronger the effect. NS denotes no significant effect.

proteins[29,39] (Fig. 3). It has two branches: global genome repair, which probes the genome for strand distortions,[23,29] and transcription-coupled repair, which removes distorting lesions that block elongating RNA polymerases.[30,31] Transcription-coupled repair is probably part of a broader pathway of transcription-coupled repair that includes a subgroup of nucleotide-excision–repair factors[40,41] and that also removes transcription-blocking oxidative damage.

XERODERMA PIGMENTOSUM

People with rare, inherited defects in nucleotide-excision repair all have hypersensitivity to the sun that is due to defective handling of UV damage, but the clinical features are otherwise extremely

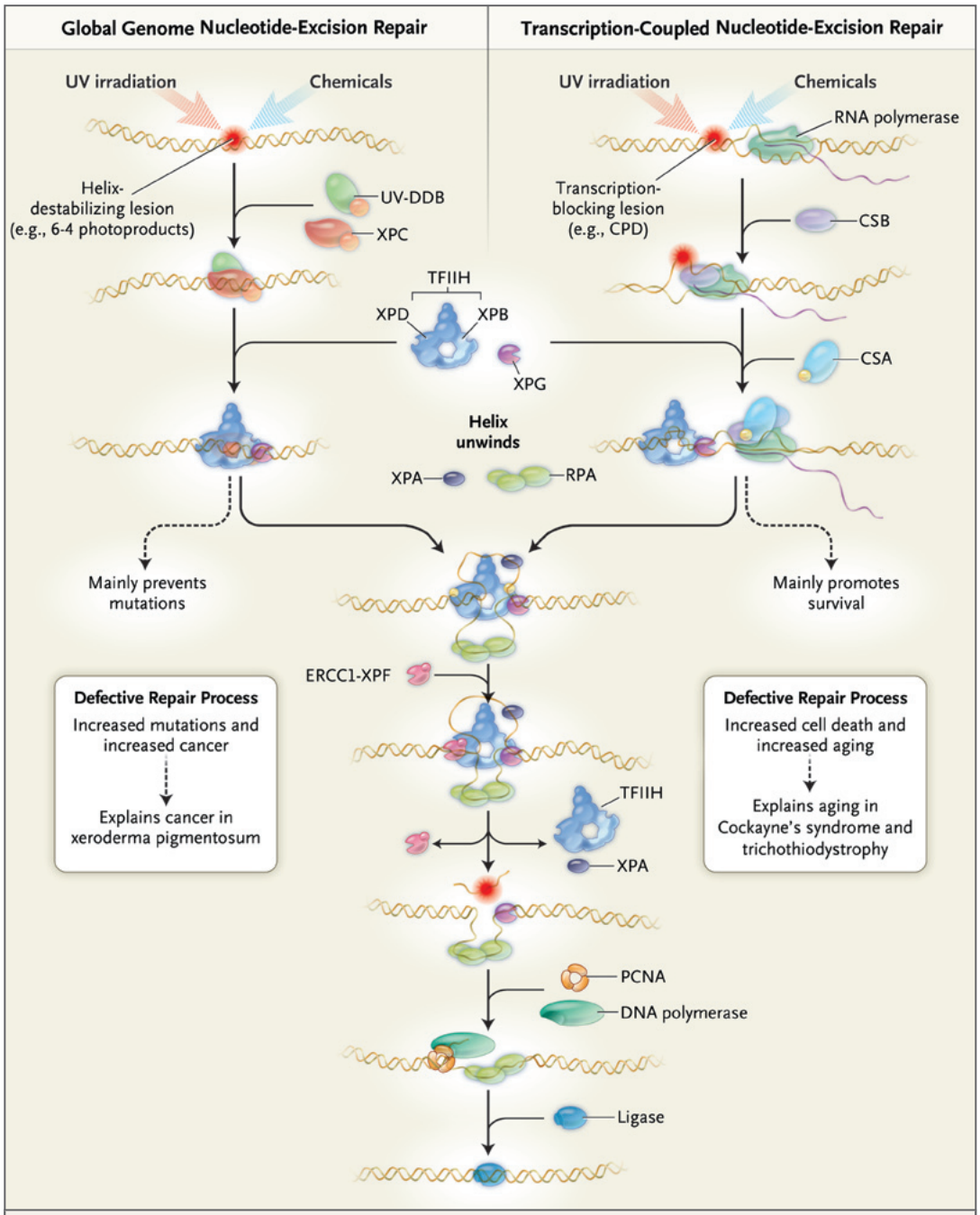

Figure 3. Molecular Mechanisms of Nucleotide-Excision Repair.

Damage to DNA that occurs anywhere in the genome (e.g., photoproducts resulting from exposure to ultraviolet [UV] radiation) is recognized by the XPC and XPE (or UV-DDB) protein complexes, which are specific components of the global genome nucleotide-excision repair (NER) system. Damage that actually blocks transcription (e.g., cyclobutane pyrimidine dimers [CPDs] resulting from exposure to UV radiation) is detected by the transcription-coupled NER system (TC-NER) system, which involves the CSB and CSA proteins. The DNA helix is opened by the XPB and XPD helicases of the repair and transcription factor IIH (TFIIH), allowing damage verification by the XPA protein. Single-strand binding protein RPA prevents reannealing, and dual incisions in the damaged strand are made by the ERCC1-XPF and XPG endonucleases, excising the damage as part of a piece of 25 to 30 bases. The single-strand gap is filled by the replication machinery, and the final nick sealed by DNA ligase.

heterogeneous.[42] The prototypical nucleotide-excision–repair disorder, xeroderma pigmentosum, is manifested as sun-induced pigmentation abnormalities, a risk of skin cancer that is more than 2000 times the risk in the general population, and an increased risk of internal tumors. The syndrome results from defects in the system of global repair, with or without deficiencies in transcription-coupled repair of distorting lesions. Defective global genome repair causes damage to accumulate across the genome, inducing mutations and consequently cancer (Fig. 3). Patients with xeroderma pigmentosum in whom transcription-coupled repair is also affected have accelerated neurodegeneration, suggesting increased neuronal cell death due to accumulated endogenous damage.[43] Defects in the repair-enzyme genes *XPA* through *XPG* can cause xeroderma pigmentosum.

COCKAYNE'S SYNDROME

Impaired transcription-coupled repair has little effect on mutagenesis: it repairs only occasional lesions that stall transcription, ignoring damage in the opposite, nontranscribed strand. Nevertheless, a defect of this repair mechanism underlies severe progeroid syndromes. Mutations in transcription-coupled repair in the genes encoding CSA or CSB protein cause Cockayne's syndrome, which is characterized by early cessation of growth and development, severe and progressive neurodysfunction associated with demyelination, sensorineural hearing loss, cataracts, cachexia, and frailty. The average reported life span for patients with the disease is 12 years.[42] The defect in transcription-coupled repair impedes recovery from blocked transcription, which causes increased cell death after DNA damage.

Even though global genome repair is fully operational in persons with this syndrome, Cockayne cells may die prematurely, suggesting that low levels of endogenous damage that block transcription and are not dispensed with quickly enough by other repair systems are sufficient to produce this dramatic phenotype. The elimination of cells with low levels of damage protects the body from cancer at the expense of promoting aging, thus revealing a trade-off between these two outcomes of DNA damage (Fig. 1). This phenomenon explains why there has never been a report of cancer in a person with the Cockayne syndrome, despite the repair defect and premature aging. It indicates a clear dissociation between the outcomes of cancer and accelerated aging that result from DNA damage, depending on the type of repair process affected, and implies that mutations per se are not critical for the onset of aging-related diseases.

Specific mutations in the repair-enzyme genes *XPB*, *D*, and *G* produce a phenotype that reflects a combination of the traits associated with xeroderma pigmentosum and Cockayne's syndrome.[42] This observation indicates that simultaneous defects in global genome repair and transcription-coupled repair can cause mutagenesis and cancer in some tissues and accelerated cell death and premature aging in others.

TRICHOTHIODYSTROPHY

The helicases XPB and XPD are components of the repair and transcription factor IIH (TFIIH). Point mutations in the genes encoding XPB and XPD can cause an extreme progeroid syndrome called trichothiodystrophy, which has features of Cockayne's syndrome in addition to brittle (unfinished) hair and nails and ichthyotic skin.[42] Impairment of the additional basal transcription function of TFIIH accounts for the condition of the hair, nails, and skin.[44,45]

Informative mouse models of nucleotide-excision–repair syndromes reveal a striking correlation between the degree to which specific repair pathways are compromised and the severity of accelerated aging, strongly suggesting a causal relationship.[42,46,47] The features of progressive disease in these models include osteoporosis, kyphosis, osteosclerosis, neurodegeneration, photoreceptor loss, hearing loss, cessation of growth, early infertility, cachexia, frailty, liver and kidney aging, and depletion of hematopoietic stem cells, all of which highlight the importance and widespread effects of accumulating DNA damage.[45,48,49] The life span of these mice ranges from 3 to 5 weeks (for mice with Cockayne's syndrome and a mutant *XP* gene or mice with trichothiodystrophy and a mutant *XP* gene — both double mutants) to 2 years (for mice with Cockayne's syndrome or trichothiodystrophy), depending on the extent of the defect in nucleotide-excision repair or transcription-coupled repair. The dramatic phenotype of the mice with double mutations is best explained by the defect in global genome repair, which causes genomewide accumulation of spontaneous nucleotide-excision–

repair lesions. These lesions exacerbate the defect in transcription-coupled repair, leading to further cell death and loss of cell function.

Both the mice with trichothiodystrophy and the mice with Cockayne's syndrome have low rates of spontaneous cancer,[48] a finding that is consistent with the idea that the defect in transcription-coupled repair provides protection against carcinogenesis. Only after long-term exposure to high-intensity UV light do mice with Cockayne's syndrome have a moderately elevated frequency of skin lesions, presumably because occasional cells that escape death acquire oncogenic mutations.[50] The same principles deduced from defects in nucleotide-excision repair in relation to cancer and aging are also evident in other genomic maintenance systems[51-56] (Fig. 2, and the Supplementary Appendix). In the Werner syndrome, for instance, premature aging is caused by a defective RecQ-like DNA helicase that is involved in recombination repair and telomere metabolism.[5] Such findings provide support for the idea that genome maintenance, predisposition to cancer, and premature aging are intimately linked.

PROGERIA, AGING, AND THE SURVIVAL RESPONSE

Microarray expression analysis in progeriod mouse models of defective nucleotide-excision repair has revealed strong suppression of insulin-like growth factor 1 and key hormones of the somatotropic, lactotropic, and thyrotropic axes. In these mice, which have a life span of 3 to 8 weeks, there is overall suppression of growth, energy expenditure, and metabolism and up-regulation of antioxidant defenses.[49,57,58] Apart from differences in antioxidant defenses (more pronounced in rapid aging), inflammation, and protein glycation (more prominent in natural aging), the expression profiles of these mice are similar to those of wild-type mice that are 2.5 years old, an observation that strongly supports the relevance of premature aging to normal aging.

Somatotropic restraint, present in dwarf mice (e.g., Ames mutants with pituitary defects) and in normal mice after caloric restriction, is associated with longevity and suppression of cancer[59,60] — an association that is consistent with findings in species ranging from yeast to primates.[59-63] The expression profiles of mutant mice with defects in progeroid nucleotide-excision repair and a very short life span most resemble the profiles of mice with the longest life span: dwarf mice subjected to caloric restriction.[57] Apparently, mice with mutations in genome repair respond to the accumulation of DNA damage by shifting from a mode of growth to one of maintenance, reflecting an attempt to survive the damage. In wild-type mice exposed to subtoxic doses of a pro-oxidant or DNA cross-linking agent for a long period, there is also suppression of the somatotropic axis.[49,51] Suppression of the somatotropic axis has also been found after exposure to UV light in wild-type mouse cells.[64] A similar finding was also reported in a mouse model of the Hutchinson–Gilford progeria syndrome, a disease caused by improper processing of the nuclear lamin A protein (see the Supplementary Appendix).[65]

In the absence of a repair defect, constitutive suppression of the somatotropic axis promotes longevity and reduces the incidence of cancer, at least under laboratory conditions. Since this universal response probably evolved to allow organisms to survive food shortages or other adverse conditions, including high levels of DNA damage, it is called the survival response.[57] Somatotropic suppression in old mice is consistent with the idea that normal aging is also associated with constitutive wakening of the survival response due to the continuous presence of stress.

DNA DAMAGE AND DNA MAINTENANCE IN CANCER

DNA damage and genome maintenance are highly relevant to all aspects of oncology. Most mutations and large genomic alterations (deletions, translocations, loss of heterozygosity, and amplifications) that are relevant to cancer originate from DNA injury or aberrant genome maintenance. In addition, the epigenetic code is not indefinitely stable. In addition to the spontaneous reactions that occur, affecting chromatin and DNA methylation, genome maintenance itself involves extensive alterations in the components of chromatin.[66,67] For instance, repair of double-strand breaks involves extensive phosphorylation of histone H2AX followed by modification of histones by ubiquitination and sumoylation,[66] all of which are required for efficient double-strand break repair. Repair of single-strand breaks involves the formation of large chains of

poly(adenosine diphosphate [ADP]–ribose) on target proteins by the enzyme poly(ADP–ribose) polymerase (PARP); the chains of poly(ADP–ribose) probably serve as a platform to recruit the appropriate mechanism of repair. It is likely that the degeneration of the epigenetic code that facilitates oncogenesis originates in part from both damage and the subsequent genome maintenance.[68] Little is known about the maintenance machinery of the epigenome and its contribution to aging and cancer.[69]

Some sources of carcinogenic DNA lesions originate in the environment. In cigarette smoke, for example, benzo(*α*)pyrene reacts with the 2-amino position of guanine. On DNA replication, the adducted G specifies incorporation of an A instead of C, irreversibly leading to G→T transversions. This carcinogen triggers an adduct and mutation profile in the *TP53* tumor-suppressor gene that strongly correlates with the *TP53* mutation profile in lung tumors from smokers but not in that from nonsmokers.[70] Endogenously generated DNA injury induced by reactive oxygen and nitrogen species, for example, may also instigate oncogenic mutations. Compounds in food may scavenge endogenous radicals and thereby neutralize their potential for induction of damage.

In addition to initiating carcinogenesis, genome instability also drives the progression from benign to malignant tumors by permitting additional genetic and epigenetic changes that facilitate evolution to a more aggressive state. The multitude of genetic changes needed for reaching malignancy requires crippling of genome maintenance.[71] Since most cancer therapies are based on damaging DNA, genome maintenance is also important for a therapeutic response and for resistance to therapy (e.g., through loss of the mechanisms facilitating cell death).

Not only does DNA damage initiate cancer, but cells may also induce DNA injury for protection against cancer. With every round of DNA replication, a number of protective telomeric repeats are lost at the ends of chromosomes because the telomerase enzyme that adds new repeats is silenced in most somatic cells.[72] Clonal outgrowth of a precancerous cell results in critically short telomeres that behave similarly to double-strand breaks, awakening the DNA damage-response system and triggering cell-cycle arrest and cell death. To grow, tumors must overcome this barrier, which explains why reactivated telomerase can be found in approximately 90% of all cancers.[72] And in view of the pivotal role genome maintenance plays in protection from cancer, it is not surprising that evidence of defective DNA damage repair is detected in essentially all tumors (one of the most frequently mutated genes is the *TP53* damage-response and repair gene[73]) and that many genome-instability syndromes are associated with increased susceptibility to cancer (see the Supplementary Appendix).

COMPROMISED GENOME MAINTENANCE AND CANCER THERAPY

Weakened repair of damaged DNA may be the Achilles' heel of tumors. Recently, tumors deficient in one of two proteins involved in the repair of double-strand breaks, BRCA1 or BRCA2, were found to be sensitive to inhibitors of PARP, a single-strand–break repair protein (Fig. 4).[75] Antitumor activity of the PARP inhibitor olaparib in carriers of the *BRCA* mutation has been reported in cases of breast, ovarian, and prostate cancer,[74] and its use may be even more promising for the treatment of early-stage tumors and sporadic cancers with similar defects, and possibly for prevention.[75,76] Given the complexity of DNA repair and response systems, there is likely to be further discovery of examples of the selective sensitivity of tumors to specific inhibitors or drugs on the basis of their weakened capacity for repair.

SUMMARY AND FUTURE PERSPECTIVES

DNA damage can trigger the development of cancer, accelerate aging, or both, depending on the type, amount, and location of the damage; the type of cell sustaining the damage and its stage in the cell cycle; and the specific repair, checkpoint, and effector systems involved. When the damage is not repaired, the outcome may be cancer or, if cell death or senescence occurs, protection from cancer, but the trade-off is acceleration of the aging process. The development of cancer

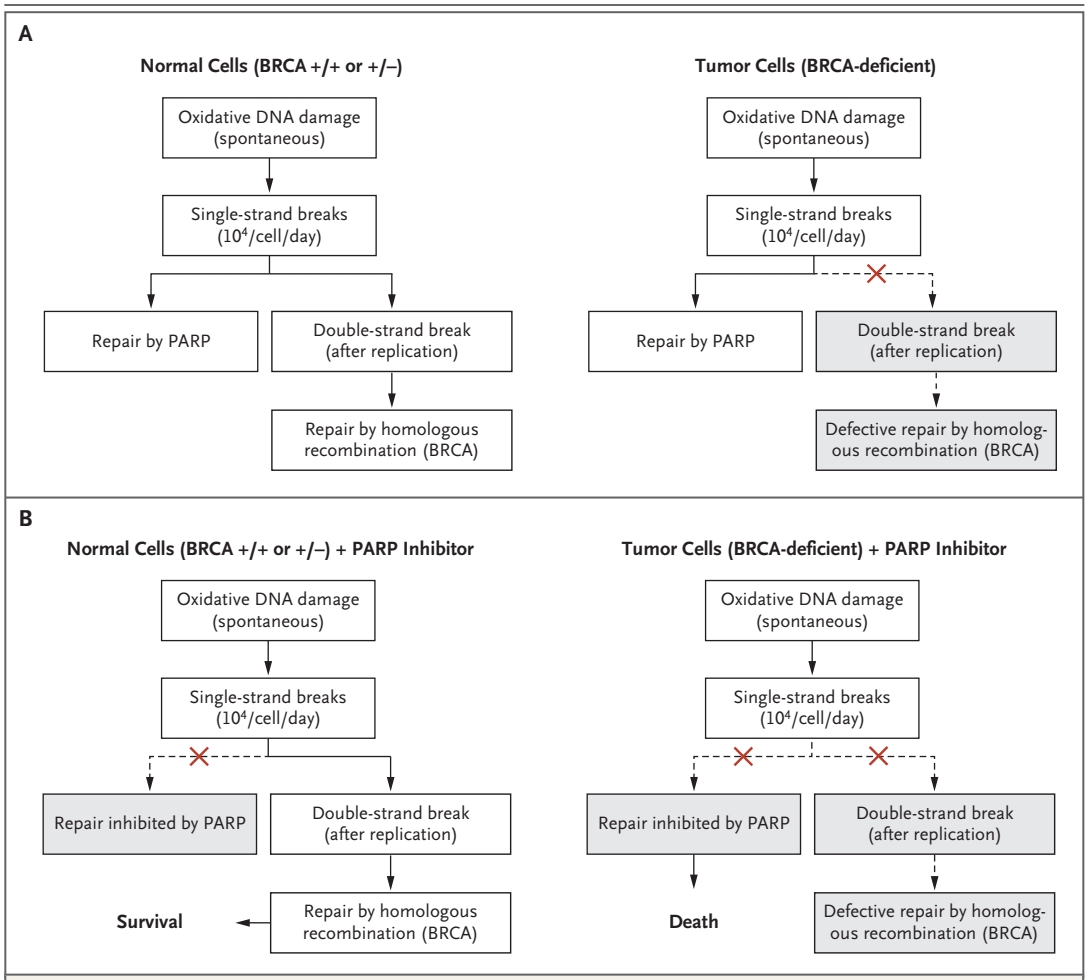

Figure 4. Presumed Rationale for the Synthetic Lethality of a BRCA1 or BRCA2 Deficiency in Tumors and Inhibition of PARP.

Carriers of germ-line mutations in one allele of the *BRCA1* or *BRCA2* double-strand–break repair genes are at increased risk for breast or ovarian cancer or for prostate cancer. The tumors in such patients have lost the remaining wild-type allele and are deficient in important branches of the homologous recombination system that repairs double-strand breaks and interstrand cross-links (Panel A, right). In contrast, normal tissues in these patients (Panel A, left), retain one copy of the wild-type allele, which is sufficient to carry out normal double-strand–break repair. Single-strand breaks are an important source of spontaneous double-strand breaks, which occur when single-strand breaks are encountered during replication and then are turned into double-strand breaks. To solve this problem, homologous recombination involving the BRCA1 and BRCA2 proteins allows complex DNA template switching and regression of the arrested replication fork. Different types of spontaneous single-strand breaks, caused by the action of reactive oxygen and nitrogen species, occur at an estimated daily rate of 10^4 per cell. The majority of clean breaks are quickly repaired by DNA ligases. However, when the ends need processing, poly(adenosine diphosphate [ADP]–ribose) polymerase (PARP) is required to engage the mechanism of base-excision repair. Potent inhibitors of PARP have been identified that greatly increase levels of persisting single-strand breaks. In normal cells from *BRCA1* or *BRCA2* carriers (which have one intact *BRCA* allele), the problem of persistent single-strand breaks causing double-strand breaks on replication can still be handled by the homologous recombination machinery when PARP inhibitors are present (Panel B, left). However, in tumor cells lacking both alleles of BRCA1 or BRCA2, this back-up repair solution is missing, and as a consequence, these cells have an exquisite sensitivity to PARP inhibitors, such as olaparib (Panel B, right). This principle of synthetic lethality has been used successfully in targeted cancer therapy without clinically significant side effects.[74] In Panels A and B, each red X and dashed arrow indicate a defective repair process.

and the process of aging can be delayed by reducing the load of DNA damage — by avoiding or limiting exposure to exogenous genotoxins and by suppressing metabolism — thereby producing fewer reactive species. However, DNA damage, like caloric restriction, can also elicit a protective survival response that promotes longevity and healthy aging. Recently, the use of sirolimus in mice was found to extend their life span and delay the development of conditions associated with aging, including cancer.[1] Sirolimus is one of presumably many compounds that may elicit the survival response. The frequent derailment of DNA damage-response systems in tumors presents another possible route by which new treatments can act selectively on the tumor.

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