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Review

Systemic DNA damage responses in aging and diseases

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ABSTRACT

The genome is constantly attacked by a variety of genotoxic insults. The causal role for DNA damage in aging and cancer is exemplified by genetic defects in DNA repair that underlie a broad spectrum of acute and chronic human disorders that are characterized by developmental abnormalities, premature aging, and cancer predisposition. The disease symptoms are typically tissue-specific with uncertain genotype–phenotype correlation. The cellular DNA damage response (DDR) has been extensively investigated ever since yeast geneticists discovered DNA damage checkpoint mechanisms, several decades ago. In recent years, it has become apparent that not only cell-autonomous but also systemic DNA damage responses determine the outcome of genome instability in organisms. Understanding the mechanisms of non-cell-autonomous DNA damage responses will provide important new insights into the role of genome instability in human aging and a host of diseases including cancer and might better explain the complex phenotypes caused by genome instability.

1. The cellular DNA damage response (DDR)

The genetic information is constantly threatened by a plethora of genotoxic attacks. DNA damage can be caused by a variety of exogenous or endogenous agents. The first are environmental agents such as ultraviolet (UV) light, ionizing radiation (IR), as well as many genotoxic chemicals. The latter are by-products of cellular metabolic circuits such as oxidative respiration or events such as lipid peroxidation, which give rise to reactive oxidative species (ROS). In addition, spontaneous events constantly challenge the stability of DNA chemical bonds [1]. Depending on the source of damage, DNA can be affected in different ways, varying from single-strand breaks (SSBs), abasic sites and modified bases to highly toxic lesions such as small or bulky adducts and lesions, interstrand crosslinks (ICLs) and double-strand breaks (DSBs) (Fig. 1). Lesions might compromise DNA metabolism by interrupting replication or transcription. It is thought that DNA damage accumulation with aging results in loss of cellular functionality and ultimately degeneration of cells and tissues. Erroneous repair, however, can lead to mutations and chromosomal aberrations, which when affecting tumor suppressor genes, drive carcinogenesis. Alternatively, unrepaired DNA lesions can lead to cell malfunction or cell senescence and eventually cell death. Importantly, DNA damage compromises regenerative capacities of stem cells and disturbs tissue integrity ultimately driving multiple pathologies during the aging process. It is thus essential for the organism to preserve the stability and integrity of its genome.

The sophisticated machineries that respond to DNA damage are highly conserved throughout evolution. In addition to complex DNA repair pathways, special DNA damage-induced checkpoints temporarily halt cell cycle progression providing a time window for the cell to repair the lesions. The unscheduled cell cycle arrest in turn is associated with modulation of many of the cell's physiological circuits. Thus, the cellular response to DNA damage called 'the DNA damage response' (DDR) turned out to be a vast signaling network encompassing the repair mechanisms and numerous signaling pathways, presenting one of the most comprehensive cellular responses to a stimulus.

2. Defective DDR and human disease

The relationship between genome stability and human health is illustrated by the genome instability syndromes, typically characterized by progressive degeneration of specific tissues, cancer predisposition, chromosomal instability, and hypersensitivity to

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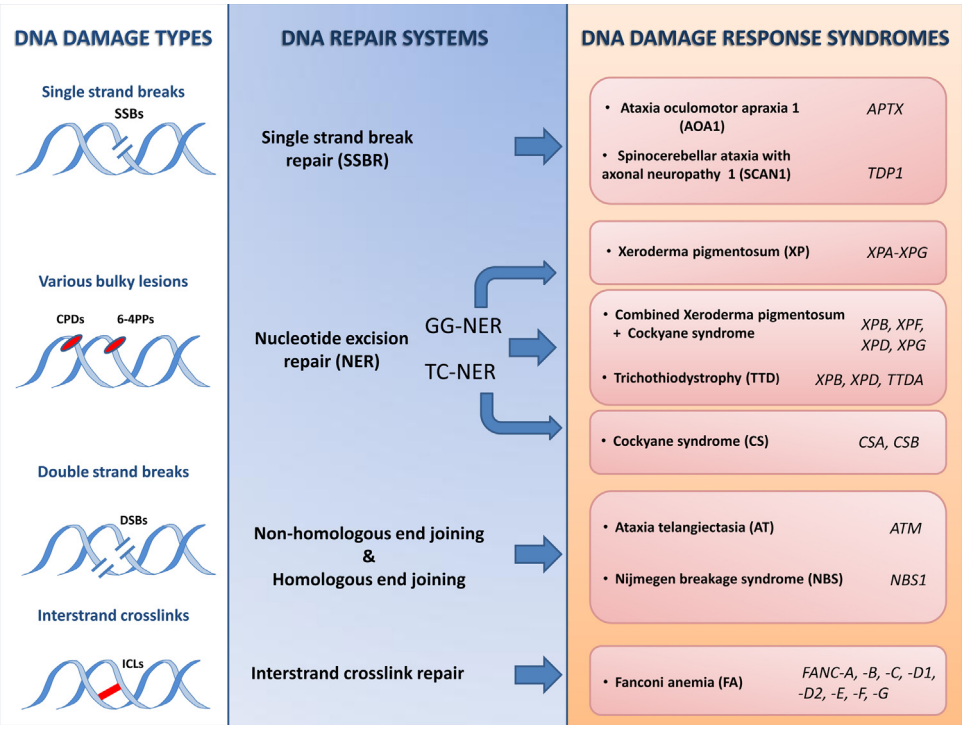

Fig. 1. Examples of distinct DNA damage repair and response defects leading to genetic disorders in humans. Various damage types including SSBs, bulky lesions, DSBs and ICLs require single strand break repair, nucleotide excision repair (NER), homologous and non-homologous end joining and interstrand crosslink repair, respectively. Defects in DNA damage response pathways lead to genome instability and consequently to complex syndromes characterized by tissue degeneration, cancer susceptibility, developmental defects, and premature aging.

DNA damaging agents [2,3]. The large variety of damage types requires specialized repair machineries. Mismatch repair (MMR) corrects errors that stem from mismatches that occurred during DNA replication, base excision repair (BER) removes small chemical alterations of bases, which could miscode and therefore result in mutagenesis. More complex damage types such as bulky lesions are resolved by nucleotide excision repair (NER), while homologous recombination and non-homologous end joining (HR and NHEJ) repair DSBs, and an elaborate enzymatic cascade repairs SSBs. The highly toxic ICLs are removed in a complex repair reaction involving the Fanconi anemia (FA) proteins [4]. While each of those repair systems is of paramount importance for human health, we will here focus on the consequences of dysfunctional NER and aberrant responses to DSBs to exemplify cell-autonomous and systemic DNA damage responses and their role in disease.

2.1. Complex consequences of DNA repair deficiencies in human disease: distinct outcomes of defects in nucleotide excision repair (NER) in development, aging, and cancer

Nucleotide excision repair deals primarily with helix-distorting DNA lesions such as UV-induced cyclobutane pyrimidine dimers (CPDs) and pyrimidine 6–4 pyrimidones (6–4PPs) that interfere with replication and transcription. These intrastrand dimers are resolved by removal of the damaged stretch of the strand and refilling of the gap by using the complementary strand as a template. The helix distortion is recognized by two different subpathways: global-genome NER (GG-NER) which scans the whole genome, and transcription-coupled NER (TC-NER) dealing with damage that blocks elongating transcription machineries. Defects in GG-NER give rise to the cancer-prone syndrome, xeroderma pigmentosum (XP). XP is characterized by pigmentation abnormalities, sun sensitivity, atrophic skin and most severely, leads to markedly elevated skin cancer. Mutations in one of seven genes (*XP-A* to *G*) that are involved in NER have been identified in XP patients. In addition, XP can be caused by mutations in *XP-V*, which instead of functioning directly in NER encodes the DNA polymerase eta that can bypass UV-induced lesions thus instead of repairing tolerates lesions during replication. By contrast, TC-NER defects do not lead to cancer susceptibility but instead cause Cockyane syndrome (CS) that is characterized by severe growth and intellectual impairment and multiple manifestations of premature aging. Mutations in the genes *CSA* and *CSB* (CS complementation group A and B) have been identified in CS patients. Specific mutations in the same two genes can give also rise to the even more severe cerebro-oculo-facio-syndrome (COFS) or the mild UV-hypersensitivity syndrome [5] with uncertain genotype–phenotype correlations. Notably, different mutations in the same gene can lead to different pathologies; for example, mutation in the *XPD* gene can lead either to XP or trichothiodystrophy (TTD). TTD patients share many similarities to CS patients, but in addition display characteristic brittle hair and nails[6]. Moreover, mutated *XPD*, *XPB*, *XPF* and *XPG* can result not only in XP but also in a very rare XP–CS combination depending on the specific mutations. Genetic mouse models were generated to further investigate the disease mechanisms underlying the distinct NER syndromes. NER-deficient mice recapitulate the UV sensitivity and develop skin cancer upon low doses of UV irradiation. Mutations in single genes, such as *Csa* or *Csb*, however, do not result in overt disease phenotypes as in the human patients [7]. Only further abrogation of NER by ablation of genes such as *Xpc* or *Xpa* recapitulate the severe growth retardation and premature aging observed in CS patients [8]. Mutations in *Ercc1*, *Xpf* or *Xpg*, in contrast, are sufficient for triggering postnatal developmental failure and accelerated tissue degeneration [9,10].

Taken together, these syndromes have established that specific molecular defects in responding to DNA damage lead to distinct pathological outcomes: mutations that increase the mutation rate, such as GG-NER defects, elevate cancer risk, while defects that ham-