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Tissue specific mutagenic and carcinogenic responses in NER defective mouse models

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Abstract

Several mouse models with defects in genes encoding components of the nucleotide excision repair (NER) pathway have been developed. In NER two different sub-pathways are known, i.e. transcription-coupled repair (TC-NER) and global-genome repair (GG-NER). A defect in one particular NER protein can lead to a (partial) defect in GG-NER, TC-NER or both. GG-NER defects in mice predispose to cancer, both spontaneous as well as UV-induced. As such these models (*Xpa*, *Xpc* and *Xpe*) recapitulate the human xeroderma pigmentosum (XP) syndrome. Defects in TC-NER in humans are associated with Cockayne syndrome (CS), a disease not linked to tumor development. Mice with TC-NER defects (*Csa* and *Csb*) are – except for the skin – not susceptible to develop (carcinogen-induced) tumors. Some NER factors, i.e. XPB, XPD, XPF, XPG and ERCC1 have functions outside NER, like transcription initiation and inter-strand crosslink repair. Deficiencies in these processes in mice lead to very severe phenotypes, like trichothiodystrophy (TTD) or a combination of XP and CS. In most cases these animals have a (very) short life span, display segmental progeria, but do not develop tumors. Here we will overview the available NER-related mouse models and will discuss their phenotypes in terms of (chemical-induced) tissue-specific tumor development, mutagenesis and premature aging features.

Keywords: Nucleotide excision repair; Global genome repair; Transcription coupled repair; Mouse models; Xeroderma pigmentosum; Cockayne syndrome; Trichothiodystrophy; Segmental progeria; Inter-strand cross-link repair; Carcinogenesis; Mutagenesis; Chemical exposure

1. Role of NER in the prevention of gene mutations and cancer

1.1. General introduction into NER

The genetic information of the cell is not carried by a stable, rigid macromolecule, but by the rather vulnerable DNA. Numerous physical and chemical agents of both endogenous as well as environmental origin continuously challenge its integrity. Alterations in the DNA of somatic cells – from small point mutations affecting only one base pair to large deletions or rearrangements – increase with age [1] and are primarily responsible for the age-related increase in cancer rate. An immediate effect of DNA damage may be physical interference with the cellular machines responsible for gene transcription [2,3]. As a result, inappropriate changes in gene expression may occur, leading to cellu-

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lar dysfunction. In proliferative cells, DNA damage may additionally block DNA replication and prevent cell division [2,3]. To counteract such deleterious effects, the cell is equipped with a wide variety of genome care taking mechanisms including various DNA repair machineries with partially overlapping substrate specificity. The vital importance of DNA repair mechanisms as caretakers of the genome is best demonstrated by the consequences of their absence or dysfunction in a variety of rare autosomal recessive disorders. A striking example is the repair pathway nucleotide excision repair (NER). Three different photosensitive diseases are associated with this pathway: (i) xeroderma pigmentosum (XP), (ii) Cockayne Syndrome (CS) or (iii) trichothiodystrophy (TTD). The diagnostic features of XP are, besides the photosensitivity: a dry scaly skin (xeroderma), abnormal pigmentation in sun-exposed skin-areas (pigmentosum), and a 1000-fold increased risk of developing UV-induced skin cancer, primarily basal and squamous cell carcinomas and melanomas. Besides this skin cancer predisposition, a 10–20-fold increased risk of developing several types of internal cancers before the age of 20 has been described [4]. CS and TTD do not show any increased cancer risk, but rather attribute hallmarks of premature aging, as manifested by severe mental and physical retardation. In addition to the progeroid symptoms observed in both CS and TTD, further TTD-features are brittle hair and nails and ichthyosis.

Complementation studies have shown the involvement of seven genes in XP (*XPA* through *XPG*) [4] and two genes in CS (*CSA* and *CSB*) [5,6]. A subset of mutations in *XPB*, *XPD* and *XPG* can lead to the combined phenotype of XP and CS. In contrast to classical CS-patients, these patients are cancer prone [4]. TTD has been associated with mutations in XPB, XPD and the recent discovered TFB5 subunit of TFIIH [4,7]. To understand how mutations in different NER factors, or even how different mutations in the same NER factor, cause these different diseases, detailed knowledge on the function of these factors is needed.

1.2. NER at the molecular level

Nucleotide excision repair is capable of removing numerous types of helix-distorting lesions, including UV-induced photoproducts. Other substrates for NER include reactive oxygen species (ROS)-induced 5′,8-purine cyclodeoxynucleotides [8,9] and bulky lesions, which could for example originate from polycyclic aromatic hydrocarbons (as present in tobacco smoke and smog). NER functions by a “cut and patch”-like mechanism in which damage recognition, local opening of

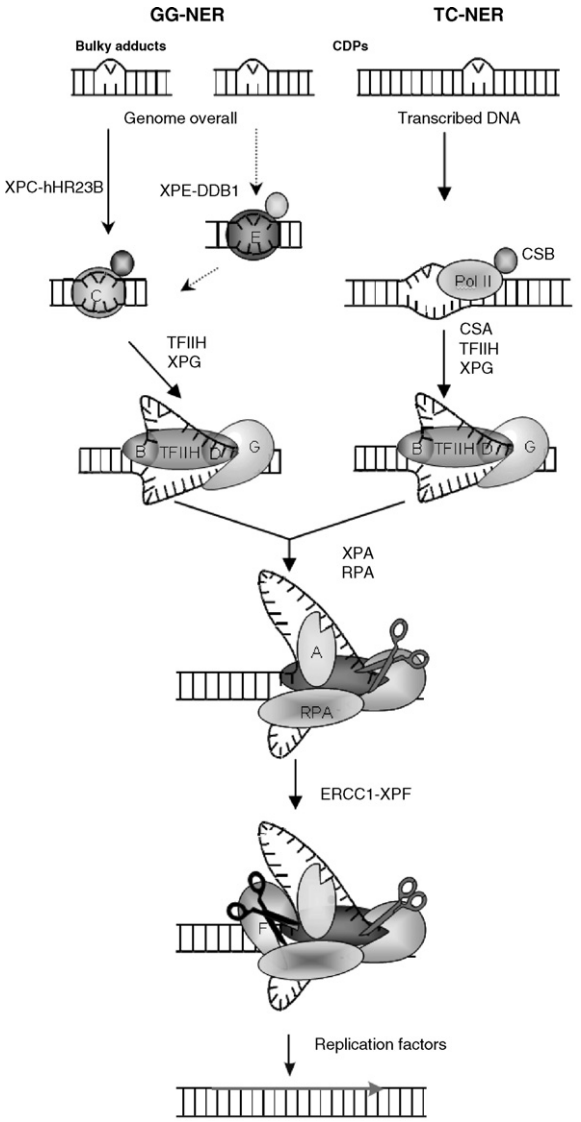

Fig. 1. Nucleotide excision repair. This figure shows the principle of nucleotide excision repair (NER) and its two subpathways, global genome NER (GG-NER) and transcription-coupled NER (TC-NER) and the various proteins involved.

the DNA helix around the lesion, damage excision and gap filling occur in successive steps (Fig. 1). NER is composed of two subpathways, global genome NER (GG-NER) and transcription-coupled NER (TC-NER), which share the same core mechanism but differ in the way lesions are recognized.

The first step in GG-NER is damage recognition by the heterodimer XPC/hHR23B [10–12], which binds with higher affinity to helix-distorting DNA lesions than to non-damaged double stranded DNA (dsDNA) [13,14]. Since damage recognition is highly dependent on the degree of DNA helix distortion, DNA lesions that only