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Mini review

DNA damage response and transcription

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ABSTRACT

A network of DNA damage surveillance systems is triggered by sensing of DNA lesions and the initiation of a signal transduction cascade that activates genome-protection pathways including nucleotide excision repair (NER). NER operates through coordinated assembly of repair factors into pre- and post-incision complexes. Recent work identifies RPA as a key regulator of the transition from dual incision to repair-synthesis in UV-irradiated non-cycling cells, thereby averting the generation of unprocessed repair intermediates. These intermediates could lead to recombinogenic events and trigger a persistent ATR-dependent checkpoint signaling. It is now evident that DNA damage signaling is not limited to NER proficient cells. ATR-dependent checkpoint activation also occurs in UV-exposed non-cycling repair deficient cells coinciding with the formation of endonuclease APE1-mediated DNA strand breaks. In addition, the encounter of elongating RNA polymerase II (RNAPIIo) with DNA damage lesions and its persistent stalling provides a strong DNA damage signaling leading to cell cycle arrest, apoptosis and increased mutagenesis. The mechanism underlying the strong and strand specific induction of UV-induced mutations in NER deficient cells has been recently resolved by the finding that gene transcription itself increases UV-induced mutagenesis in a strand specific manner via increased deamination of cytosines. The cell removes the RNAPIIo-blocking DNA lesions by transcription-coupled repair (TC-NER) without displacement of the DNA damage stalled RNAPIIo. Deficiency in TC-NER associates with mutations in the CSA and CSB genes giving rise to the rare human disorder Cockayne syndrome (CS). CSB functions as a repair coupling factor to attract NER proteins, chromatin remodelers and the CSA-E3-ubiquitin ligase complex to the stalled RNAPIIo; CSA is dispensable for attraction of NER proteins, yet in cooperation with CSB is required to recruit XAB2, the nucleosomal binding protein HMGN1 and TFIIS. The molecular mechanisms by which these proteins bring about efficient TC-NER and trigger signaling after transcription arrest remain elusive; particularly the role of chromatin remodeling in TC-NER needs to be clarified in the context of anticipated structural changes that allow repair and transcription restart.

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1. DNA damage and genome integrity

Maintenance of genomic integrity in an environment of genotoxic stress is a prerequisite for proper cell function and of prime clinical importance in relation to the development of cancer and age-related disease. The mammalian genome is protected against genotoxic insults by a network of DNA damage response (DDR) mechanisms triggered by the detection of DNA lesions through

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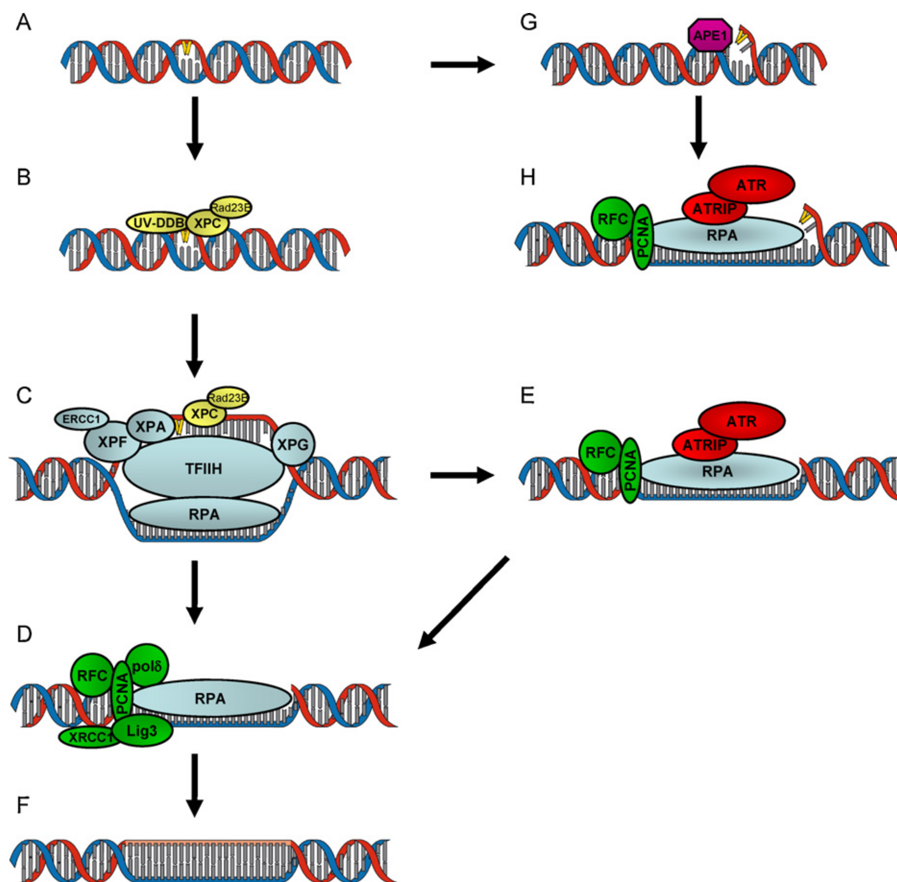

Fig. 1. Global genome NER. UV induces DNA photolesions, most notably CPD and 6-4PP (A). Repair is initiated by recognition of these DNA lesions by UV-DDB and XPC/RAD23B (B). XPC is essential for GG-NER whereas UV-DDB stimulates 6-4PP removal, but is indispensable for the removal of CPD lesion. Following demarcation of the damage, binding of additional pre-incision factors is facilitated (C). The helicase activity of TFIIH serves to open up the DNA whereas XPA is required for recruitment and activation of XPF/ERCC1. RPA is essential to activate the XPF/ERCC1 and XPG endonucleases that incise the damaged DNA (started by XPF/ERCC1-mediated 5′ incision) followed by removal of the damage containing oligo. Once removed a single stranded gap containing RPA remains. By utilizing proteins that also perform normal replicative DNA synthesis, such as RFC, PCNA and polymerase δ, the gap will be filled (D). Note that DNA polymerases such as polymerase ε and κ can also perform this task. Restoration of the DNA is completed by sealing the remaining nick using ligase3/XRCC1 or, alternatively, by ligase1 (F). If resynthesis is delayed, an intermediate gapped DNA structure is formed that activates the ATR kinase (E). Additional factors required for ATR activation such as TopBP1 and the 9-1-1 complex (not shown) are also expected to participate. Eventually these gaps will be filled by repair synthesis and ligated (F). If UV lesions are not readily removed, either due to high damage load or GG-NER deficiency, APE1 can incise directly 5′ of the 6-4PP. It is assumed that also in this APE1-dependent process, 6-4PP are not removed (G). This structure will be converted into a form that supports ATR signaling, possibly by resection of DNA 5′ of the lesion (H). Note that the exact nature of the structure is not known.

specific sensors. The subsequent step is the initiation of a signal transduction cascade including effector molecules which activate various genome-protection pathways i.e. DNA repair, cell cycle control, apoptosis, transcription and chromatin remodeling.

The multiprotein nucleotide excision repair (NER) system removes a wide variety of helix-destabilizing DNA lesions including those induced by UV-irradiation. This broad substrate recognition is achieved by two distinct subpathways of NER, which are triggered by DNA damage mediated structural alterations in the genome rather than direct recognition of the lesion itself. The first subpathway, global genome NER (GG-NER), is able to repair lesions throughout the entire genome by sensing the reduced rigidity of DNA imposed by the helix distortion [1]. The second subpathway, transcription-coupled NER (TC-NER), specifically repairs DNA lesions in genes that block the actively transcribing RNA polymerases II (RNAPIIo).

GG-NER and TC-NER differ by the mechanism of DNA lesion recognition in chromatin. GG-NER is initiated by UV-DDB and XPC/RAD23B mediated recognition of DNA helix distortions inflicted by DNA injuries, whereas RNAPIIo stalled at a DNA lesion efficiently triggers the recruitment of TC-NER specific factors. After recognition of the damage, both pathways utilize identical components for the assembly of the repair complex (pre-incision step); subsequently, the removal of the damage is accomplished by excising a short DNA fragment encompassing the lesion thereby maintaining the capacity to repair a broad spectrum of DNA damage [2]. The remaining gap is filled by DNA repair patch synthesis using the undamaged strand as template (post-incision step) (Figs. 1 and 2). The biological relevance of NER is underscored by severe clinical consequences including premature ageing, developmental abnormalities and extreme cancer-susceptibility associated with inherited NER defects. These defects lead to the rare autosomal inherited diseases xeroderma pigmentosum (XP), Cockayne syndrome (CS) and triochothiodystrophy (TTD) [3]. Eight complementation groups have been found in XP patients, the first 7 (XP-A to XP-G) are either defective in GG-NER exclusively, or in both GG-NER and TC-NER. The last complementation group (XP-V) is defective in DNA polymerase η (Polη), a Y family translesion polymerase that can carry out translesion synthesis past UV-induced DNA lesions. Despite detailed insights into the core NER reaction mechanism, relatively little is known about the molecular events that initiate and regulate this process.

Several lines of evidence suggest that GG-NER and TC-NER operate through coordinated assembly of repair factors into pre- and post-incision complexes; however, how this coordination is regulated in vivo is poorly understood. Although unwinding of the DNA

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