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Nucleotide excision repair in humans

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ABSTRACT

The demonstration of DNA damage excision and repair replication by Setlow, Howard-Flanders, Hanawalt and their colleagues in the early 1960s, constituted the discovery of the ubiquitous pathway of nucleotide excision repair (NER). The serial steps in NER are similar in organisms from unicellular bacteria to complex mammals and plants, and involve recognition of lesions, adducts or structures that disrupt the DNA double helix, removal of a short oligonucleotide containing the offending lesion, synthesis of a repair patch copying the opposite undamaged strand, and ligation, to restore the DNA to its original form. The transcription-coupled repair (TCR) subpathway of NER, discovered nearly two decades later, is dedicated to the removal of lesions from the template DNA strands of actively transcribed genes. In this review I will outline the essential factors and complexes involved in NER in humans, and will comment on additional factors and metabolic processes that affect the efficiency of this important process.

Contents

1. Introduction

Living organisms across the evolutionary scale protect their genetic material against the constant threats posed by environmental agents and byproducts of cellular metabolic processes. Even the simplest unicellular beings possess mechanisms for the prevention and repair of damage to their DNA.

Here I will review the nucleotide excision repair (NER) pathway, a versatile mechanism that removes helix-distorting DNA lesions and structures from the genome. Several other dedicated pathways that have evolved to deal with different classes of lesions or non-canonical forms of DNA will be addressed in other sections in this volume.

The NER process begins with the recognition of a DNA lesion. Then, dual incisions of the damaged DNA strand, one on either side of the lesion, are produced. The lesion-bearing oligonucleotide is removed, a patch is synthesized using the undamaged complementary strand as a template, and the patch is ligated to the contiguous strand.

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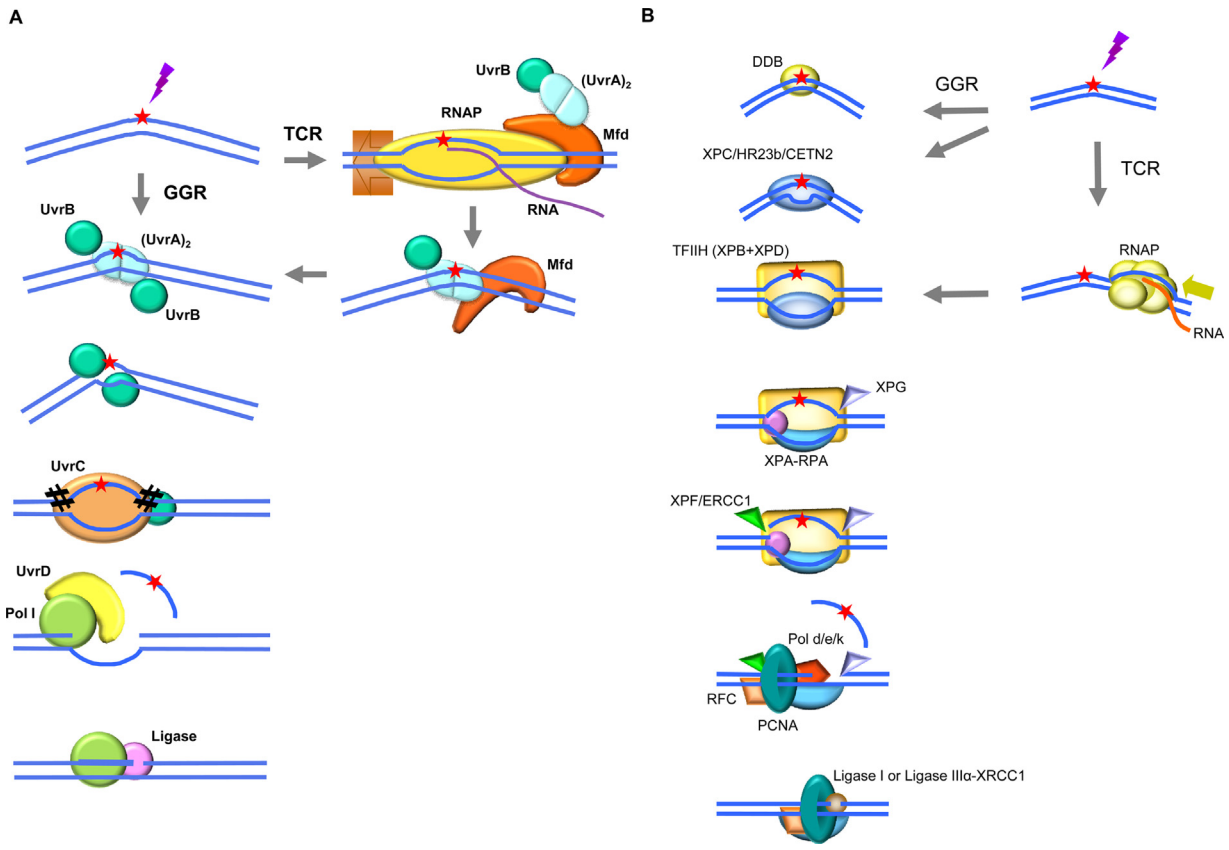

Fig. 1. Schematics of NER in the prototypic bacterium *E. coli*, and in humans.
A. NER in *E. coli*
The UvrAB complex binds to the DNA and recognizes and verifies the damage to be repaired. UvrA dissociates from the preincision complex leaving one or two molecules of UvrB bound to the DNA. UvrC interacts with UvrB and catalyzes two nicks in the DNA, one on either side of the lesion. The combined action of UvrD (helicase I) and DNA polymerase I removes the oligonucleotide containing the lesion, as well as UvrB and UvrC, from the DNA and results in the synthesis of a patch using the undamaged complementary strand as a template. DNA ligase I seals the patch to the contiguous DNA strand. In TCR, Mfd is activated by binding to a stalled RNA polymerase (RNAP). It dissociates the RNAP and nascent transcript from the DNA and recruits UvrA complexed with UvrB. Repair then proceeds through the same reaction sequence as GGR.
B. NER in humans
Higher eukaryotes utilize different mechanisms for detecting DNA alterations in actively transcribed genes and in the genome as a whole. In TCR, RNAPII is arrested at a lesion. TCR factors are recruited; the polymerase is removed or backtracked to allow access to TFIIH and other NER repair enzymes. In GGR, a helix distorting lesion or structure can be directly recognized by XPC complexed with hRAD23B and centrin 2 (CETN2). Certain lesions such as CPD, which do not significantly destabilize DNA duplexes, are first recognized by DDB2 (XPE) in complex with DDB1, creating a kink that is recognized by XPC. The XPC-hRAD23b-CETN2 complex melts the DNA around the lesion and attracts the multiunit complex TFIIH. TCR and GGR converge; XPB and XPD unwind the DNA to create a ~30-nucleotide bubble. Once the pre-incision complex is assembled, XPA, RPA and XPG are recruited and the XPC complex is released. XPA binds the DNA near the 5' side of the bubble, and RPA binds the ssDNA opposite the lesion, protecting it from degradation and coordinating excision and repair events. XPG and ERCC1-XPF associate with TFIIH. ERCC1-XPF makes the first incision, and repair synthesis proceeds for several nucleotides displacing the damaged strand; XPG incises the 3′ single/double strand junction, and ligase I or ligase IIIα-XRCC1 seal the DNA..

NER removes lesions from the entire genome, albeit with varying efficiencies; in the early 1980s it was discovered in mammalian cells that certain lesions such as UVC-induced cyclobutane pyrimidine dimers (CPD) were excised more rapidly from the transcribed strands of active genes than from the opposite strands. This process was named transcription-coupled repair (TCR), and has been defined as a subpathway of NER; repair in the global genome is known as global genomic repair (GGR). TCR was subsequently shown to operate for other so-called bulky adducts, and in *Escherichia coli*, in yeast and in other organisms, reviewed in [1,2].

2. Global and transcription-coupled repair in human cells

NER in eukaryotes has been the subject of extensive reviews, for example [3,4], and human disorders caused by defective NER have been described [5–7]. The sequence of events in human GGR is the same as that in unicellular prokaryotes, but the process is more complicated and the number of proteins involved is much larger than in *E. coli*, as shown in Fig. 1. Importantly, in *E. coli* the same six NER factors are required for GGR and for TCR, while in humans TCR can be completed in the absence of the GGR damage recognition factors XPE, XPC or hRAD23b [1].

2.1. Damage recognition

2.1.1. Global genomic repair

In GGR, a helix distorting lesion or structure can be directly recognized by XPC, complexed with hRAD23B and centrin 2 (CETN2). Certain lesions such as CPD, which do not significantly destabilize DNA duplexes, are first recognized by DDB2 (XPE) in complex with DDB1, creating a kink that is recognized by XPC. DDB1 and DDB2 are part of the CUL4-ROC1 ubiquitin ligase complex that ubiquitylates DDB2, XPC and histones after DNA damage has occurred. XPC has been shown to bind the strand opposite the lesion, thus explaining its universal capacity for recognition of diverse types of lesions [8]. The XPC-hRAD23b-CETN2 complex melts the DNA around the lesion and recruits the multiprotein complex TFIIH.

2.1.2. Transcription-coupled repair

Humans have four RNA polymerases, the nuclear RNAPI, II and III, and a single-polypeptide mitochondrial mtRNAP that is simi-