Multi-author Review
DNA Repair in Mammalian Cells

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So DNA repair really is that important?

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Introduction (Part of a Multi-author Review)

DNA is constantly under attack from environmental agents, either physical agents such as UV light and ionizing radiation, or chemical pollutants found in food and air that can result in crosslinks, bulky chemical adducts, base alkylations, and other DNA alterations. But even in the most pristine environment DNA damage cannot be avoided, as several endogenous compounds, such as by-products of oxygen metabolism, constantly challenge DNA integrity. In addition, the amount of DNA contained in a mammalian cell implies that even a minute rate of decay translates into a high amount of damage. For instance, it is estimated that a human cell faces over 10^4 spontaneous depurination events every day, together with hundreds of deaminations and depyrimidinations [1].

Under these conditions, one wonders how genetic stability can be maintained during a lifetime, let alone across many generations. The answer is of course that DNA can be repaired, mostly thanks to the redundancy provided by its double-helical structure, which allows for one strand to serve as a template in repairing the other. Interestingly, this seemingly obvious possibility had apparently eluded Watson and Crick in 1953, who did not mention DNA repair among the genetical implications of the structure of DNA [2]. It is only a decade later that Phil Hanawalt demonstrated 'repair-replication' [3]. In this case, it was due to nucleotide excision repair (NER), but nature has evolved a whole collection of DNA repair systems that deal with the various insults to which DNA is submitted (Fig. 1).

The most simple and elegant system is undoubtedly direct damage reversal (DDR): Given a chemical modification of the DNA, simply revert it and return the DNA to its original state. Unfortunately, not many lesions can be repaired in this way. The review by Ecke et al. in this issue discusses most of them: alkylated bases, which are reverted by two distinct DDR mechanisms, and three types of dipyrimidine crosslinks each reverted by a distinct enzyme. One could also classify DNA ligases as DDR enzymes, given that they are able to close some types of single-strand breaks, but most of the time some end-processing is required, thereby disqualifying the process as direct reversal (see [4] for a recent review on single-strand break repair).

Base excision repair (BER) employs a more versatile strategy. A battery of specific enzymes called glycosylases recognize various lesions, mostly small alterations in the DNA bases such as oxidations or alkylations. Glycosylases then detach the damaged base from its deoxyribose, leaving an abasic site behind. At this point, all lesions look the same, and a common set of enzymes can carry on the subsequent reactions: nicking the DNA backbone, removing the deoxyribose, and filling the gap. Depending on which polymerase is used for the latter step, the one-nucleotide gap may be extended by displacing the existing strand 3′ to the gap, forming a flap that must subsequently be excised. The review by Robertson et al., aptly entitled 'BER: the long and short of it', discusses these two subpathways as well as important considerations on the structure and the evolution of BER enzymes, and on BER knockout mice.

Nucleotide excision repair takes the above strategy one step further and, for most lesions, dispenses with a

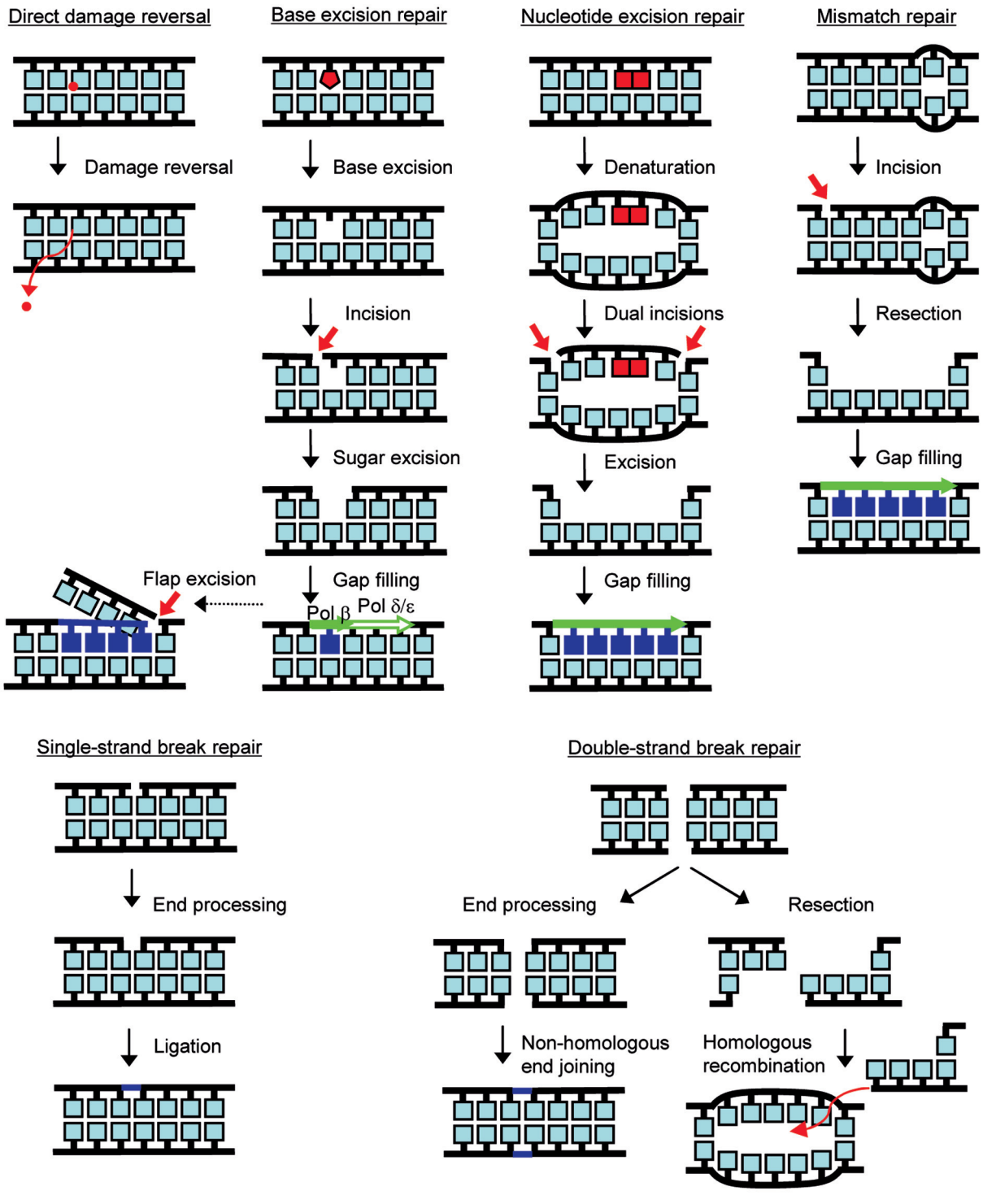

Figure 1. Simplified view of the various DNA repair systems. See text for details.

lesion-specific recognition enzyme altogether. Instead, a common set of NER enzymes sense the distortion caused by the presence of a lesion and incise the damaged strand upstream and downstream of the lesion. A short piece of single-stranded DNA spanning the lesion can then be removed, and the resulting gap filled in by the replicative DNA polymerases. I selfishly reserved for myself the privilege of describing this highly versatile DNA repair pathway, and of discussing its regulation and the clinical implications of its dysfunction.

A peculiarity of NER is that it can be coupled to transcription. In this case, RNA polymerase II serves as the lesion sensor. As it is stalled by a blocking lesion, it triggers preferential repair of the transcribed strand of active genes over that of the non-transcribed stand, or of the rest of the genome. Most cells in our organism replicate very slowly (if at all), and even fast replicating cells can be temporarily halted at cell cycle checkpoints. By contrast, all cells constantly depend on transcription. It thus makes perfect sense that a mechanism exists to direct NER to transcribed genes with higher priority. Whether other repair pathways, such as BER, are also coupled to transcription is a burning question, which Silvia Tornaletti addresses along with other current issues in her excellent review on transcription-coupled repair.

Repairing mismatches is particularly challenging, in that there is no actual DNA damage: the two strands simply carry different information. How are mismatch repair systems to decide which strand carries invalid information and should be corrected? This largely depends on the nature of the mismatch and the circumstances that caused its appearance, and calls for different repair strategies. This is discussed in the review by Kunz et al., which takes the original approach of focusing on mismatches to better understand their repair.

Double-strand breaks are probably the most toxic lesions of all, as a single unrepaired break is sufficient to cause cell death. This may be why two distinct systems are dedicated to their repair: non-homologous end joining (NHEJ) and homologous recombination (HR). It may also be because there are different sorts of breaks, or because the efficiency of each system varies during the cell cycle. NHEJ essentially rejoins the broken ends, possibly after some processing of the ends that may result in loss of genetic information. This mechanism will not work with breaks caused by the collapse of a replication fork, where only one end is available. In HR, the broken end(s) invades an unbroken molecule and uses it as a template for repair. Obviously, it is easier to achieve in G2 phase when a sister chromatid is conveniently close by, rather than in G1 when the homologous chromosome has to be located. In addition, HR itself can be divided between several distinct mechanisms, depending on the nature of the break. These complex issues are discussed and beautifully illustrated in the review by Pardo et al.

I feel very lucky that I was able to recruit such an impressive set of authors for this series of reviews on DNA repair. I am deeply grateful to Andrés Aguilera, Bert van der Horst, Arne Klungland, Primo Schär, and Sivia Tornaletti for agreeing to contribute an article. Each of them is a leader in her/his field and they, and their co-authors, did a wonderful job of presenting the basic information in a clear and detailed manner, before moving on to the most recent developments and burning issues. Thanks to them I am confident that, at the end of this set of reviews, the reader will be convinced that DNA repair is not only an important, but also a most fascinating topic.

1 Lindahl, T. (1993) Instability and decay of the primary structure of DNA. Nature 362, 709–715.
2 Watson, J. D. and Crick, F. H. (1953) Genetical implications of the structure of deoxyribonucleic acid. Nature 171, 964–967.
3 Pettijohn, D. and Hanawalt, P. (1964) Evidence for repair-replication of ultraviolet damaged DNA in bacteria. J. Mol. Biol. 9, 395–410.
4 Caldecott, K. W. (2008) Single-strand break repair and genetic disease. Nat. Rev. Genet. 9, 619–631.