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Mini review

Facilitation of base excision repair by chromatin remodeling

John M. Hinz[a,*], Wioletta Czaja[b]

[a] School of Molecular Biosciences, Washington State University, Pullman, WA 99164-7520, USA
[b] Biochemistry and Molecular Biology, University of Georgia, Athens, GA 30602-7229, USA

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ABSTRACT

Base Excision Repair (BER) is a conserved, intracellular DNA repair system that recognizes and removes chemically modified bases to insure genomic integrity and prevent mutagenesis. Aberrant BER has been tightly linked with a broad spectrum of human pathologies, such as several types of cancer, neurological degeneration, developmental abnormalities, immune dysfunction and aging. In the cell, BER must recognize and remove DNA lesions from the tightly condensed, protein-coated chromatin. Because chromatin is necessarily refractory to DNA metabolic processes, like transcription and replication, the compaction of the genomic material is also inhibitory to the repair systems necessary for its upkeep. Multiple ATP-dependent chromatin remodelling (ACR) complexes play essential roles in modulating the protein-DNA interactions within chromatin, regulating transcription and promoting activities of some DNA repair systems, including double-strand break repair and nucleotide excision repair. However, it remains unclear how BER operates in the context of chromatin, and if the chromatin remodelling processes that govern transcription and replication also actively regulate the efficiency of BER. In this review we highlight the emerging role of ACR in regulation of BER.

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1. Prologue

Mick Smerdon must have a list somewhere of all of the pearls of wisdom his former mentors and peers have imparted, because he has gems of sagacious advice for nearly every circumstance, and always credits others for them. He has a humility and appreciation of those that came before him, those he credits as the giants upon whose shoulders we stand. He will not admit it, but he is the giant to whom so many of us owe our successes, and our admiration of him deserves no less fervor than that he has of his predecessors.

- John Hinz, research assistant, 2007–present

Postdoctoral training in DNA repair shop with Mick had truly inspired my career. Mick introduced me to the tremendous biomedical importance and intricate complexity of DNA repair and

* Corresponding author. Fax: +1 509 335 4159.
E-mail address: jmhinz@wsu.edu (J.M. Hinz).

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chromatin. I enjoyed our group lab meetings, with Mick's opening short anecdotes and segues, followed by great research presentations and learning how to "listen to what nature is telling us". I've learned that "in science we should be devil's advocates", and we should always question and revise scientific reasoning and data, as this approach underlines the excellence and integrity of research and ultimately leads to success. Thank you Mick for great mentoring and inspiration!

- *Wioletta Czaja, post-doc, 2010–2013*

2. Introduction

The folding of chromosomes into chromatin, entailing distinct levels of compaction among a variety of DNA-associated proteins, is essential for assuring the organization and condensation of the genetic material in the small volume of the nucleus. The first order of chromatin compaction is that of the nucleosome, its core consisting of ~147 bp DNA wrapped ~1.7 times around an octamer of DNA-contacting histone proteins (2 each of the four histones, H2A, H2B, H3, and H4), separated by short stretches of linker DNA (~20–90 bp in length) and associated linker histones (H1 or H5) [1]. The inherently inaccessible nature of the DNA within chromatin is the mechanism by which this structure regulates DNA dependent activities such as transcription and replication. Whether it is in response to environmental stimuli, or the differentiation of cells in a multicellular organism, it is the chromatin, and its epigenetic function of allowing selective access of transcription factors to specific DNA sequences, that promotes expression of the proteins necessary for cellular function. Access to target DNA sequences in chromatin is granted through the coordinated action of ATP-dependent chromatin remodeling (ACR) complexes, large protein assemblies that utilize the energy of ATP hydrolysis by a central ATPase subunit to slide, eject, and restructure nucleosomes [2]. Often recruited to chromosomal targets by posttranslational modifications to histones, these ACR complexes have some overlapping functions but also play distinct roles in gene expression, as well as regulating other DNA metabolic activities in the cell. Notably, in the tightly controlled genomic environment, in which the prevention of both specific and non-specific protein-DNA interactions are essential for its function, chromatin acts as an impediment for the DNA repair systems necessary for maintenance of the genomic material itself [3,4].

The DNA repair systems in the cell play a key role in prevention of mutations and chromosomal rearrangements, and ensure genomic stability, through the recognition and removal of the respective DNA lesions for which each is responsible. Among these is Base Excision Repair (BER) that is responsible for remediation of the numerous and wide ranging chemical modifications to bases. These potentially mutagenic lesions include, but are not limited to, many species of oxidation, methylation, deamination or complete loss of the base (from hydrolysis of the N-glycosidic bond), which occur at rates estimated as high as 100,000 lesions/cell/day [5,6]. As the majority of DNA in the eukaryotic cell is associated with nucleosomes, many chemical modifications normally repaired by BER are physically occluded by chromatin-associated proteins and thus could remain unrecognized or unrepaired indefinitely. Hence, it is logical to postulate that factors that provide accessibility to the DNA for transcription and replication, including the activity of ACR complexes, contribute to the efficiency of BER. Indeed, there is already strong evidence for a directed active role of these remodeling factors in facilitating other DNA repair systems, including double-strand break repair (DSBR) and nucleotide excision repair (NER) [7] (see elsewhere in this issue).

In this review, we will discuss the evidence for the role of the ACR complexes in promoting BER. We summarize the available data that support the conclusion that BER is enabled by the processes of ACR, though it currently remains unclear if these chromatin remodeling activities are employed to directly support this excision repair system.

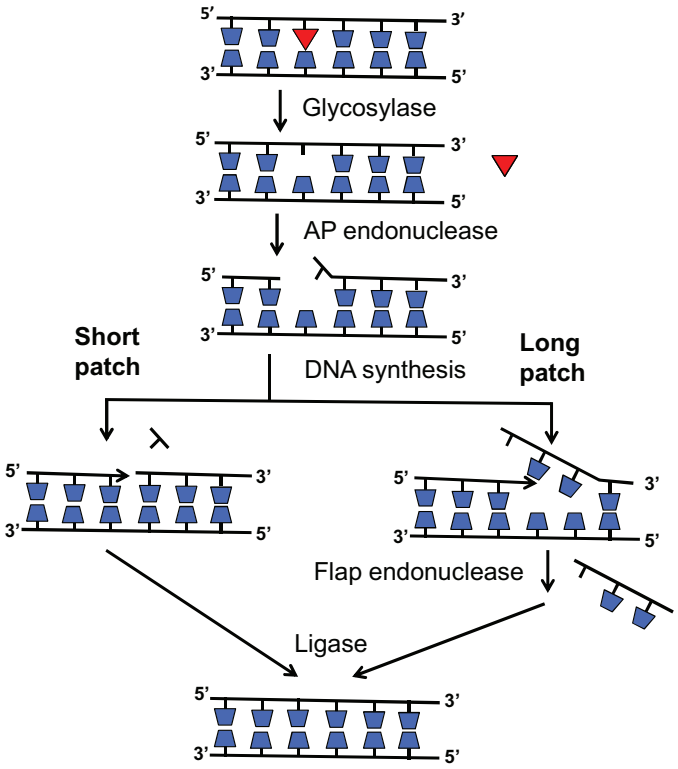

Fig. 1. Basic schematic of Base Excision Repair. A chemically modified base (red triangle) is recognized by a glycosylase, which cleaves the N-glycosidic bond leaving an abasic (AP) site. An AP endonuclease cleaves the DNA backbone on the 5′ side of the AP site, creating a single-strand break. BER is resolved in a "short patch" or "long patch" of DNA synthesis. In short patch repair the deoxyribose phosphate is removed and a single nucleotide is inserted and the site of the break. In long patch repair, up to 13 nucleotides are inserted, and the displaced strand entailing the abasic deoxyribose phosphate is cleaved by a "flap" endonuclease. Repair is completed by the action of a ligase.

3. Base excision repair

BER constitutes the highly conserved stepwise process of a series of enzymes that each act upon the product of the previous step for the removal of base lesions and intermediates created at each stage of repair (see elsewhere in this issue and Fig. 1). Repair is initiated by recognition of a chemically modified base by one of a number of different DNA glycosylases, each with a range of specificity for distinct lesions, such that together they recognize a wide breadth base modifications. Upon binding to the lesion, the glycosylase cleaves the N-glycosidic bond, separating the damaged base from its deoxyribose sugar moiety, creating an apurinic/apyrimidinic (AP) site [8,9]. AP sites can also form by the spontaneous hydrolysis of the N-glycosidic bond, and these abasic lesions, like the modified bases, are potentially mutagenic when replicated [10,11]. In metazoans, AP sites are bound by the primary AP endonuclease APE1, which cleaves the DNA backbone on the 5' side of the abasic deoxyribose phosphate, creating a single-strand break (or nick) in the DNA [12]. The synthesis step of BER employs either repair polymerase Pol β, which binds to the cleaved abasic sites and uses the intact, undamaged strand as a template for DNA synthesis, adding a single nucleotide (called short patch repair), or one of the processive polymerases, Pol δ or Pol ϵ, adding up to 13 nucleotides (called