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Mini review

Role of high mobility group (HMG) chromatin proteins in DNA repair

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Abstract

While the structure and composition of chromatin not only influences the type and extent of DNA damage incurred by eukaryotic cells, it also poses a major obstacle to the efficient repair of genomic lesions. Understanding how DNA repair processes occur in the context of nuclear chromatin is a current experimental challenge, especially in mammalian cells where the powerful tools of genetic analysis that have been so successful in elucidating repair mechanisms in yeast have seen only limited application. Even so, work over the last decade with both yeast and mammalian cells has provided a rather detailed description of how nucleosomes, the basic subunit of chromatin, influence both DNA damage and repair in all eukaryotic cells. The picture that has emerged is, nonetheless, incomplete since mammalian chromatin is far more complex than simply consisting of vast arrays of histone-containing nucleosome core particles. Members of the "High Mobility Group" (HMG) of non-histone proteins are essential, and highly dynamic, constituents of mammalian chromosomes that participate in all aspects of chromatin structure and function, including DNA repair processes. Yet comparatively little is known about how HMG proteins participate in the molecular events of DNA repair in vivo. What information is available, however, indicates that all three major families of mammalian HMG proteins (i.e., HMGA, HMGB and HMGN) participate in various DNA repair processes, albeit in different ways. For example, HMGN proteins have been shown to stimulate nucleotide excision repair (NER) of ultraviolet light (UV)-induced cyclobutane pyrimidine dimer (CPD) lesions of DNA in vivo. In contrast, HMGA proteins have been demonstrated to preferentially bind to, and inhibit NER of, UV-induced CPDs in stretches of AT-rich DNA both in vitro and in vivo. HMGB proteins, on the other hand, have been shown to both selectively bind to, and inhibit NER of, cisplatin-induced DNA intrastrand cross-links and to bind to misincorporated nucleoside analogs and, depending on the biological circumstances, either promote lesion repair or induce cellular apoptosis. Importantly, from a medical perspective, the ability of the HMGA and HMGB proteins to inhibit DNA repair in vivo suggests that they may be intimately involved with the accumulation of genetic mutations and chromosome instabilities frequently observed in cancers. Not surprisingly, therefore, the HMG proteins are being actively investigated as potential new therapeutic drug targets for the treatment of cancers and other diseases.

Keywords: Neucleotide excision repair; Base excision repair; Chromatin dynamics; HMGA; HMGB; HMGN

Abbreviations: ara-C, 1-β-D-arabinofuranosylcytosine; ATM, ataxia telangetasia mutated; bp, base pair; BER, base excision repair; ChIP, chromatin immunoprecipitation; *cis*-DDP or cisplatin, cis-diamminedichloroplatinum(II); DSB, DNA double-stranded break; ERp60, protein disulfide isomerase ERp60; dG^S, 2′-deoxy-6-thioguanosine; 5FdU, 5-fluoro-2′-deoxyuridine; FRAP, fluorescence recovery after photobleaching; GGR, global genomic repair; GAPDH, glyceraldehyde 3-phosphate dehydrogenase; GFP, green fluorescent protein; HAT, histone acetyltransferase; HMG, high mobility group; kDA, kilodalton; HSC70, heat shock protein 70; hRPA, human replication protein A; LEF-1, lymphoid enhancer-binding factor-1; NER, nucleotide excision repair; MMR, mismatch repair; Mw, molecular weight in kilodaltons; mtTFA, mitochondrial transcription factor; RPA, replication protein A; SRY, the mammalian testis-determining factor; TCR, transcription coupled repair; *trans*-DDP, trans-diamminedichloroplatinum(II); TRE, tetracycline response element promoter; tsHMG, testis-specific HMG domain protein; UBF, RNA polymerase 1 transcription factor; UV, ultraviolet light; XP, xeroderma pigmentosum; XPA, XPC, Xeroderma pigmentosum complementation group proteins A and C, respectively; 6-4PP, 6-4 pyrimidine-pyrimidone photoproducts

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Contents

1. Introduction

The mammalian HMG proteins [1] are founding members of a class of gene regulatory molecules called "architectural transcription factors" [2] that recognize DNA structure, rather than sequence, and introduce structural alterations in both DNA and chromatin substrates following binding [3,4]. Although historically these gene-regulatory proteins have not enjoyed the same glamour and attention as other nuclear components, numerous reviews have been written on HMG proteins. In addition to their role(s) in transcription, they are now widely recognized as essential components of the nucleus that participate in a diverse array of other normal processes including chromatin and nucleosome remodeling, chromosomal changes during the cell cycle, DNA replication, genetic recombination, DNA repair, apoptosis, and serving as molecular chaperones, to mention a few examples [4–15]. HMG proteins are also of considerable medical importance because they are involved in a number of pathological conditions including cancer, retroviral integration, as well as cytokine functioning to signal tissue damage when released into the extracellular milieu by necrotic and inflammatory cells [16,17]. Although all HMG proteins share many biochemical and biophysical characteristics, including their solubility in dilute acid solutions, they can be divided into three readily identifiable families (HMGA, HMGB and HMGN) that have their own unique and characteristic functional motifs, are expressed naturally at different stages, induce specific changes in DNA and chromatin substrates, and differentially affect a distinct set of cellular processes [3,5].

Important for this review is the fact that members of all three HMG families have recently been demonstrated to influence DNA repair processes, but in markedly different ways. For example, both in vivo and in vitro the HMGB proteins have been shown to specifically bind to, and inhibit repair of, the major DNA adduct of the anticancer drug cisplatin [18,19], as well to either stimulate or inhibit repair of non-natural nucleoside analogs that have been misincorporated into DNA [20]. Similarly, recent evidence indicates that overexpression of HMGA proteins in cells inhibits NER of UV-induced CPDs and increases their sensitivity to killing by UV light, a phenotype that is characteristic of cells that are deficient in nucleotide excision repair [21]. In both of these cases, a major contributing factor to repair inhibition appears to be tight binding of the HMGA and HMGB proteins to damage-distorted DNA substrates, thus resulting in the formation of stable protein–DNA complexes that shield lesions from repair processes. In contrast to the inhibitory effects of the HMGA and HMGB proteins, the HMGN proteins have been shown to enhance the rate of repair of UV induced photolesions in vivo. This occurs as a consequence of altering/loosening the packing of nucleosomes in the vicinity of the lesions thereby facilitating access of repair proteins to the damaged DNA [22]. Nevertheless, the molecular details of how any of the HMG proteins actually participate in the recognition and repair of DNA lesions in vivo largely remain to be determined.

2. HMG protein families: structure and substrate binding properties

The classification of nuclear proteins into HMGA, HMGB and HMGN families is based on the structure of their DNA binding domains as well as their substrate binding specificities [23]. The HMGA (formerly HMG-I/Y; Mw ∼10 kDa) family is so called because it preferentially binds to the minor groove of AT-rich regions of DNA via three peptide motifs called "AT-hooks" [24]. Members of the HMGB family (formerly HMG-1 and −2; Mw ∼25 kDa) are characterized by the presence of two DNA-binding motifs called "B-boxes", each of which resembles a boomerang as the result of folding of three α helices and an extended