DNA Repair 36 (2015) 122–136

Contents lists available at ScienceDirect

DNA Repair

journal homepage: www.elsevier.com/locate/dnarepair

High mobility group (HMG) proteins: Modulators of chromatin structure and DNA repair in mammalian cells

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ARTICLE INFO

Article history:
Available online 16 September 2015

Keywords:
Nucleotide excision repair (NER)
Base excision repair (BER)
Double-strand break repair (DSBR)
Mismatch repair (MMR)
Chromatin remodeling
HMGA
HMGB
HMGN

ABSTRACT

It has been almost a decade since the last review appeared comparing and contrasting the influences that the different families of High Mobility Group proteins (HMGA, HMGB and HMGN) have on the various DNA repair pathways in mammalian cells. During that time considerable progress has been made in our understanding of how these non-histone proteins modulate the efficiency of DNA repair by all of the major cellular pathways: nucleotide excision repair, base excision repair, double-stand break repair and mismatch repair. Although there are often similar and over-lapping biological activities shared by all HMG proteins, members of each of the different families appear to have a somewhat 'individualistic' impact on various DNA repair pathways. This review will focus on what is currently known about the roles that different HMG proteins play in DNA repair processes and discuss possible future research areas in this rapidly evolving field.

Contents

Abbreviations: APE1, apurinic/apyrimidinic endonuclease 1; AP site, apurinic/apyrimidinic site; ATM, ataxia telangetasia mutated; bp, base pair; BER, base excision repair; ChIP, chromatin immunoprecipitation; *cis*-DDP or cisplatin, *cis*-diamminedichloroplatinum(II); CHUD, chromatin unfolding domain; CPD, cyclobutane pyrimidine dimer; CSA, Cockayne Syndrome A; CSB, Cockayne Syndrome B; dRP, 5′deoxyribose phosphate; DDR, DNA damage response; DSB, DNA double-stranded break; ERCC1, excision repair cross-complementing rodent repair deficiency, complementation group 1; 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; HR, homologous recombination; hRPA, human replication protein A; KO, knock-out; ICL, DNA inter-strand crosslink; Ig, immunoglobulin; IR, ionizing radiation; MEF, mouse embryo fibroblast; MMS, methyl methansulfonate; Mw, molecular weight in kDA; mtTFA, mitochondrial transcription factor; NBD, nucleosome binding domain; NCP, nucleosome core particle; NHEJ, non-homologous end joining; NLS, nuclear localization signal; PAR, poly(ADP-ribose); RAG1 and 2, recombination activating genes 1 and 2; RARP-1, poly(ADP-ribose) polymerase 1; RSS, recombination signal sequence; PTM, post-translational modification; RD, regulatory domain; RNAPII, RNA polymerase II; RPA, replication protein A; TcR, T-cell receptor; TCR, transcription coupled repair; TdT, terminal deoxynucleotidyltransferase; *trans*-DDP, *trans*-diamminedichloroplatinum(II); TRE, tetracycline response element promoter; UV, ultraviolet light; wt, wild-type; V(D)J recombination, recombination between variable(V), joining (J), and diversity (D) lymphocyte gene segments; 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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http://dx.doi.org/10.1016/j.dnarep.2015.09.015
1568-7864/

1. Introduction

1.1. Chromatin remodeling, DNA repair and HMG proteins

Compaction of eukaryotic DNA into nucleosomes and higher order chromatin structures introduces major impediments that must be overcome for critical biological processes such as DNA replication, transcription and repair to occur. With respect to the latter, early pioneering work by Smerdon and Lieberman [1] demonstrated that reversible changes in both chromatin nuclease digestion sensitivity and nucleosome arrangements occur during the repair of UV-induced DNA lesions in mammalian cells. It is now recognized that the condensed structure of chromatin/nucleosomes must be 'remodeled' in order to facilitate the efficient repair of not only UV-induced lesions but many other types of DNA damage as well. In an *in vivo* chromosomal context DNA repair can conceptually be broken down into "access", "repair" and "restore steps", each of which involves complex and dynamic molecular events [2]. A detailed discussion of the myriad array of chromatin modifying enzymes and ATP-dependent chromatin remodeling complexes that are involved in these repair processes is beyond the scope of this article and the reader is referred to a number recent reviews on the subject [3–6]. The scope of this review is more restricted and focuses on the roles that the High Mobility Group (HMG) of non-histone proteins play in modulating DNA damage recognition and repair in the context of chromatin in eukaryotic cells. As will be discussed, many, but not all, of the effects of HMG proteins on repair are mediated through their ability to modulate higher order chromatin compaction and nucleosome structure through interactions with, or effects on, chromatin modifying enzymes and energy-dependent remodeling complexes. Superimposed on these chromatin 'remodeling' activities, HMG proteins can also modulate repair by directly influencing the activity of specific steps in various repair pathways and by functioning as 'architectural' transcription factors that regulate the expression of many different genes, a number of which are involved in DNA repair processes. Thus HMG proteins appear to function as molecular 'Swiss Army Knives' that can participate in regulating both chromatin structure and gene transcription during DNA lesion repair.

1.2. HMG protein families

There are three major families of HMG proteins, HMGA, HMGB and HMGN [7,8] whose physical properties and complex biological roles have been extensively described in recent reviews [9–23]. The focus of only a few of these, however, has been on the similarities and differences in the roles that these different families of non-histone protein play in DNA repair processes [24]. Members of all of the HMG families have been implicated in modulating the efficiency of the major DNA repair pathways: nucleotide excision repair (NER), base excision repair (BER), double-strand break repair (DSBR), mismatch repair (MMR) and others. This review will discuss what is currently known about the different HMG protein families and their roles in these various repair pathways.

2. HMGN proteins: facilitators of DNA repair

2.1. The HMGN family

A number of excellent reviews on both the aspects of signaling to chromatin through post-translational modifications of HMGN proteins and also their role(s) in DNA repair have recently been published [25-28]. The HMGN (previously called HMG-14/17) family consists of five closely related proteins: HMGN1 (HMG-14), HMGN2 (HMG-17), HMGN3a, HMGN3b, HMGN4 and HMGN5 (a.k.a., NSBP1, or NBP-45; [28]). The HMGN proteins are small (~10 kDa) and so far have only been found in higher eukaryotes [29].

The distinguishing feature of HMGN family members is that, in contrast to other HMG proteins, they contain a unique and highly conserved peptide motif, the nucleosome binding domain (NBD; [30]) that allows them to specifically bind to nucleosome core particles (NCPs) both *in vitro* and *in vivo,* hence their name [7]. It has been estimated that most cells only contain enough HMGN protein to bind to ~1–5 % of the nucleosomes [26]. In addition to the NBD, all HMGN proteins contain two short, and highly conserved, nuclear localization sequences (NLS1 and NLS2) that flank the NBD. Most (but not all; *e.g.*, HMGN3b) of the proteins also have a C-terminal domain regulatory domain (RD; [27]) that originally was called the chromatin unfolding domain (CHUD; [31]) because of its ability to disrupt histone H1-dependent chromatin condensation and thus enhance transcription [32]. Following the subsequent discovery that this domain also affects the level of phosphorylation and acetylation of histone H3 in chromatin [33], it was assigned the more general RD name.

In vivo fluorescence recovery after photobleaching (FRAP) experiments involving green fluorescent protein (GFP)-tagged proteins have demonstrated that movement inside living cells of all of the HMG proteins, including members of the HMGN family, is dynamic and rapid with very fast kinetics of both nucleosomes and chromatin association and dissociation [10,34–36]. HMGN proteins, for example, have been shown to have a chromatin residence time of less than 30 s and a diffusion rate that allows travel through the nucleus in less than 1 min [34]. Importantly it has also been demonstrated that direct protein–nucleosome interactions are responsible for these *in vivo* kinetics since disruption of HMGN1 binding to NCPs (*via* mutations in the NBD) accelerates HMGN kinetics, lowering residence time to 3–4 s [35]. Such highly dynamic nucleosome interactions allows the HMGN proteins to regulate the chromatin structure both locally and globally [27,31,37,38].