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Functional interplay between histone H1 and HMG proteins in chromatin☆

Yuri V. Postnikov *, Michael Bustin

Protein Section, Laboratory of Metabolism, Center for Cancer Research, National Institutes of Health, Bethesda, MD 20892, USA

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ABSTRACT

The dynamic interaction of nucleosome binding proteins with their chromatin targets is an important element in regulating the structure and function of chromatin. Histone H1 variants and High Mobility Group (HMG) proteins are ubiquitously expressed in all vertebrate cells, bind dynamically to chromatin, and are known to affect chromatin condensation and the ability of regulatory factors to access their genomic binding sites. Here, we review the studies that focus on the interactions between H1 and HMGs and highlight the functional consequences of the interplay between these architectural chromatin binding proteins. H1 and HMG proteins are mobile molecules that bind to nucleosomes as members of a dynamic protein network. All HMGs compete with H1 for chromatin binding sites, in a dose dependent fashion, but each HMG family has specific effects on the interaction of H1 with chromatin. The interplay between H1 and HMGs affects chromatin organization and plays a role in epigenetic regulation. This article is part of a Special Issue entitled: Histone H1, edited by Dr. Albert Jordan.

1. Introduction

Chromatin dynamics play a key role in the ability of regulatory factors to access their target sites and in various processes that ultimately affect gene expression. A major group of nuclear proteins known to affect chromatin structure and function are named "chromatin architectural proteins". Architectural proteins are defined as structural proteins, devoid of enzymatic activity, that bind to nucleosomes without apparent DNA sequence specificity and change the local and global architecture of chromatin.

Two major groups of proteins are known to function as architectural proteins in all vertebrate cells. The first group is the linker H1 protein family, the focus of this special BBA issue. Histone H1 is the most abundant family of chromatin binding proteins; most nuclei contain sufficient protein to bind to all nucleosomes. The second major group of architectural proteins is the High Mobility Group (HMG) protein superfamily [1–7]. In general, H1 proteins promote and stabilize the formation of compact chromatin structures [8–11], while HMG proteins promote chromatin decompaction and the formation of distorted DNA structures. In the nucleus, H1 and HMG protein variants are mobile, they move rapidly throughout the entire nuclear space, interact transiently with nucleosomes and their chromatin interactions seem to be interdependent [11–14]. H1 and HMGs were the first nuclear proteins shown to affect the structure of the chromatin fiber and their properties and chromatin interactions have been the subject of several reviews [1,4,5,10–12,15–17]. In this review we focus on the interplay between H1 and HMG architectural proteins.

2. HMG proteins

The HMG superfamily is composed of three families: HMGN, HMGB, and HMGA proteins [2,6]. The structural features and biological properties of these proteins have been described in several reviews and in a special issue of BBAGRM [5,15,18].

Each HMG family has a distinct protein structure and a distinct DNA or chromatin binding motif [1,2,4]. The HMG box is the functional motif of the HMGB proteins, the AT hook is the functional motif of the HMGA family, and the nucleosomal binding domain (NBD) is the functional motif of the HMGN family. Through these functional motifs HMGs bind to specific structures in DNA or chromatin, with low if any specificity for the DNA sequence. All non-chromatin-bound HMG are highly disordered proteins, a structural characteristic they share with linker H1 variants, endowing them with the ability to form multiple protein–protein interactions [19]. All HMGs promote chromatin decompaction and generate a chromatin configuration that alters various DNA-dependent activities such as transcription, replication and the repair of damaged DNA. HMGs affect genomic functions not only by directly binding to chromatin but also by interacting with regulatory factors that affect gene expression. All three families are ubiquitously present in all vertebrate cells; in addition, proteins containing the functional motifs of HMGA and HMGB were found in most eukaryotes and have also been detected in bacteria.

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* Corresponding author at: NIH, Bldg. 37 Room 3122, 37 Convent Drive, Bethesda, MD 20892, USA.
E-mail address: PostnikY@mail.nih.gov (Y.V. Postnikov).

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The human HMGN family consists of 5 members with a similar structure: a bipartite nuclear localization signal, a conserved, positively charged nucleosome binding domain, and a C-terminal regulatory domain. The nucleosome binding domain contains the invariant octapeptide RRSARLSA which serves as the signature motif of this protein family [3,20]. As elaborated below, this octapeptide serves as the anchoring point of HMGNs on the nucleosome [20]. Genome wide, HMGN proteins preferentially bind to DNase I hypersensitive sites, the hallmark of regulatory chromatin sites [21–23]. HMGNs have been shown to modulate the global and local structure of chromatin [24], and the levels of histone modifications [25,26], factors which may be involved in their ability to affect gene expression [27].

HMGB proteins contain two HMG boxes, and a negatively charged C-terminal domain [28]. Through the HMG box these proteins bend DNA in a sequence-independent fashion. In addition, HMGB proteins were shown to bind preferentially to pre-bent DNA or DNA with distorted geometry [4].

The hallmark of the HMGA proteins is the "AT hook", a palindromic sequence containing the invariant tripeptide GRP, flanked by arginine residues. Most HMGA proteins contain several AT-hooks. The AT hook binds preferentially to the minor groove of short stretches of AT-rich DNA [17].

3. HMG–H1 interactions

The precisely organization of H1 in nucleosomes is not known; however it has been established that the globular domain of histone H1 contacts the DNA near the nucleosome dyad axis and adjacent linker DNA, and thus stabilizes DNA wrapping around the histone octamer [29–32]. While the binding of H1 to the surface of nucleosomes is directed by the globular domain, the chromatin-condensing functions of the protein are primarily provided by the highly basic C-terminal domain which is thought to interact primarily with the negatively charged linker DNA [33]. Yet, the interactions of the C-terminal tail of H1 with linker DNA are not solely determined by charge, since fluorescence recovery after photobleaching (FRAP) and NMR results suggest that specific residues in this domain, rather than the distribution of positively charged residues, are major factors in regulating its interaction with linker DNA [30,34,35]. The binding of histone H1 to the nucleosomes plays a pivotal role in the stabilization of the compact 30 nm structure of the chromatin fiber [31,32]. Differences among H1 variants in the amino acid sequence of the C-terminal domain, and variations in the position and orientation of the globular domains of H1 within the nucleosome may contribute to the heterogeneity of chromatin structure and also affect gene expression.

A distinguishing feature of all HMGNs is that they recognize specifically the generic structure of the nucleosome core particle. They bind better to nucleosomes than to free histones or purified DNA. Under physiological conditions nucleosomes bind two molecules of HMGNs. Significantly, even though most cells contain several HMGN variants, both in vivo and in vitro analyses indicated that the HMGN nucleosome complexes contain two molecules of the same HMGN variant; complexes containing two different variants (i.e. one HMGN1 and one HMGN2) are not detected [36]. The position of HMGN variants in nucleosomes was mapped by DNase I, by hydroxyl radical footprinting, by site specific cross-linking, and by a combination of methyl-transverse relaxation optimized nuclear magnetic resonance spectroscopy (methyl-TROSY) and mutational analysis [37–40]. In the HMGN–nucleosome complex, the invariant octapeptide RRSARLSA located in the NBD of HMGN, binds to a negatively charged patch formed by the H2A–H2B dimer. The N terminal region of the HMGN NBD contacts histone H2B and the DNA approximately 25 base-pairs away from the end of the 147 base pair nucleosomal core DNA, while the C-terminal region of the NBD contacts the DNA near its nucleosomal exit/entry. The C-terminal domain of the HMGN protein contacts the DNA in the two major grooves flanking the nucleosome dyad axis and is in close proximity to the N-terminal tail of H3, which protrudes beyond the periphery of the nucleosomal DNA [37,40].

The overlap between the location of the HMGN and the globular H1 near the dyad axis of the nucleosomes may play a major role in the interplay between these proteins in chromatin [15,37]. It is possible that negatively charged residues in the C-terminal domain of certain HMGNs, which are positioned near the linker DNA, may interfere with the interactions of H1 at this site [38]. Since H1 is known to facilitate and promote chromatin compaction HMGNs may decompact chromatin by interfering with the binding of H1 to nucleosomes. The chromatin-decondensing activity of HMGN can be also attributed to its interaction with the acidic patch of the H2A–H2B dimer and with the N-terminal of H3 since internucleosomal interaction have been shown to be facilities by the tail of H3 and by interactions between the N-terminal of H4 and the H2A.H2B acidic patch. We speculate that H1 could also interact with histone tails and if such interactions do indeed occur they could be affected by the presence of HMGNs and perhaps other HMG proteins, in particular members of the HMGB family which have a highly acidic C-terminal tail.

In addition, it has been demonstrated that the HMGN5 variant, which has a particularly long negatively charged C-terminal domain, targets the positively charged C-terminal region of histone H5 in the nucleoplasm, beyond the nucleosomal context [24]. Likely, similar interaction could occur between H1 and other HMGN variants.

HMGB proteins and histone H1 interact both in the context of chromatin and in the nucleoplasm. HMGB variants bind to purified DNA, to specific DNA structures such as four-way junctions, and to chromatin. Competition between HMGB1/-B2 proteins and linker histones for four-way junctions and cisplatin-modified DNA has been clearly demonstrated [41,42]. Although their organization in isolated nucleosomes or in chromatin is not fully understood, HMGB1/B2 seems to preferentially bind to linker DNA at the entry/exit of nucleosomes, next to the nucleosome dyad axis [43,44]. Since these are also major sites of H1–nucleosome interaction it is likely that this positional overlap plays an important role in the HMGB–H1 interplay in chromatin.

As chemical cross-linking and gel-filtration experiments with purified proteins have shown, an equimolar H1–HMGB1 complex is formed, which persists at physiological ionic strength [45]. According to NMR spectroscopy data, H1 linker histone binds, predominantly through its basic C-terminal domain, to the acidic tail of HMGB1, thereby disrupting intramolecular interaction of the HMGB tail with the DNA-binding faces of the HMG boxes. A potential consequence of this interaction is enhanced DNA binding by HMGB1, with a concomitantly lower affinity of H1 for DNA. In the context of chromatin, this might facilitate displacement of H1 by HMGB1 [45]. Indeed, mononucleosomes devoid of H1 but containing near stoichiometric amounts of HMGB1 are preferentially released upon micrococcal nuclease digestion [46]. Oxidation of HMGB1, which leads to the formation of disulfide bridges, abolishes its ability to compete with H1 [47].

HMGA1 proteins bind preferentially to the narrow minor groove of A/T-rich regions such as the highly repetitive alpha-satellite DNA. In addition, HMGA proteins recognize and bind to DNAs with unusual structural features, such as four-way, three-way or distorted DNA [17,48] and have been shown to bind specifically to isolated nucleosomes [49]. As discussed above, H1 also displays affinity for distorted DNA structures [41].

HMGA proteins co-localize with histone H1 at scaffold attachment regions (SARs), which are believed to be cis-acting regulatory elements located at the stem of large loops (domains) of gene-containing DNA [50]. It has been suggested that competition between HMGA1 and histone H1 for binding to AT-rich SAR elements affects chromatin compaction thereby impacting gene transcription [51]. Likely, competition between H1 and HMGAs extends beyond just the AT-rich elements in SARs, since their distribution in various fraction of micrococcal nuclease-digested chromatin is drastically different [51].

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