Biochimica et Biophysica Acta 1799 (2010) 62–68

Contents lists available at ScienceDirect

Biochimica et Biophysica Acta

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

Review

Regulation of chromatin structure and function By HMGN proteins

Yuri Postnikov *, Michael Bustin

Protein Section, Laboratory of Metabolism, Center for Cancer Research, National Cancer Institute, National Institutes of Health, 37 Convent Drive, Bethesda, MD 20892, USA

ARTICLE INFO

Article history:
Received 15 October 2009
Received in revised form 18 November 2009
Accepted 20 November 2009
Available online 27 November 2009

Keywords:
High Mobility Group Protein
Chromatin
Nucleosomes
Histones
Epigenesis

ABSTRACT

High mobility group nucleosome-binding (HMGN) proteins are architectural non-histone chromosomal proteins that bind to nucleosomes and modulate the structure and function of chromatin. The interaction of HMGN proteins with nucleosomes is dynamic and the proteins compete with the linker histone H1 chromatin-binding sites. HMGNs reduce the H1-mediated compaction of the chromatin fiber and facilitate the targeting of regulatory factors to chromatin. They modulate the cellular epigenetic profile, affect gene expression and impact the biological processes such as development and the cellular response to environmental and hormonal signals. Here we review the role of HMGN in chromatin structure, the link between HMGN proteins and histone modifications, and discuss the consequence of this link on nuclear processes and cellular phenotype.

Published by Elsevier B.V.

1. Introduction

The chromatin fiber stores and organizes the genetic information encoded in the sequence of the DNA and contains the epigenetic regulatory information encoded in histone variants and in the covalent chemical modifications of nucleosomes. The structure of the chromatin fiber and the accessibility of nucleosomes to various regulatory factors are key elements affecting DNA-dependent nuclear activities such as transcription, replication, recombination and repair and the orderly progression of biological processes such as the cell cycle, development and differentiation. The ability of chromatin to affect this wide range of processes is related to its dynamic structure; chromatin compaction impedes accessibility to nucleosomes and represses genomic activity, whereas chromatin decompaction is associated with increased accessibility to the nucleosomal DNA and gene activation. Because the interaction of HMGN with chromatin affects both the structure of the chromatin fiber and the levels of histone modifications they impact numerous biological processes. In this review, we focus on the role of HMGN in chromatin dynamics and in regulating the levels of histone modifications and highlight recent findings on their role in determining the cellular phenotype. Additional information of the properties of these and other HMG proteins can be found in previous reviews [1–5]. In addition, reviews by Mahadevan, Hansen, Hock, Gerlitz, Rochman and Furusawa in this issue present more information and additional insights into various aspects of HMGN structure and function.

1.1. HMGNs: non-histone proteins that bind to nucleosomes

The HMGN protein family consists of 5 members encoded by 5 specific genes with a similar intron–exon organization. HMGN proteins share a common domain structure: a bipartite nucleosome localization signal, a conserved 30-amino acid long nucleosome-binding domain (NBD) and a less conserved C-terminal that is enriched in negatively charged residues (Fig. 1). The most recently HMGN discovered, HMGN5, contains a long C-terminal region that contains 13 highly negative repeated sequences motifs (see Rochman this issue and [6,7]). Embedded in the NBD of all HMGNs is an absolutely conserved octapeptide, RRSARLSA, which is encoded by a specific exon and is considered to be the signature of this protein family. This “NBD core” acts as a module that anchors the HMGN proteins to nucleosome core particles. Detailed analyses of numerous deletion and point mutants of HMGNs revealed that while several regions of the protein affect the chromatin-binding affinity of the HMGNs, the conserved NBD core is the sole determinant of the specific interaction of HMGN with nucleosome core particles. *In vivo* and *in vitro* studies demonstrated that even a single mutation in the R-S-RL motif contained in the NBD core will abolish the specific interaction of HMGNs with nucleosome cores. Any of these point mutants will bind to DNA better than to isolated core particles [8].

All HMGNs have a high content of charged amino acids and a disordered secondary structure (Fig. 1). Disordered proteins can form multiple complexes and interact with many proteins [9–11]. Indeed, it has been demonstrated that both HMGN1 and HMGN2 form multiple metastable protein complexes, and that the chromatin interaction of HMGN in the context of a complex is different from that of purified HMGN [12]. The potential ability of HMGN proteins to participate in numerous multiprotein complexes may have significant implications

* Corresponding author. Tel.: +1 301 496 2885.
E-mail address: Yupo@helix.nih.gov (Y. Postnikov).

1874-9399/$ – see front matter. Published by Elsevier B.V.
doi:10.1016/j.bbagrm.2009.11.016

for their biological functions. Conceivably, HMGN proteins facilitates the interaction of protein complexes or of specific proteins, with chromatin [12–16].

HMGNs are the only nuclear proteins known to specifically recognize the generic structural features of the 147 base pair nucleosome core particles, the building block of the chromatin fiber. These proteins bind to nucleosome particles better than to either purified DNA or to histones. In vitro analyses demonstrated that the binding of HMGNs to chromatin is highly dependent on ionic strength. At low ionic strength, nucleosome core particles (CP) can bind either one or two molecules of HMGN with very high affinity [17–19]. Under these conditions, the CP complexes formed can contain different HMGN variants (i.e. one HMGN1 and one HMGN2). However, at higher ionic strengths, which are close to physiological, the interaction of HMGNs with CPs is highly specific. Under these conditions, the association constant of HMGN with CP is significantly lower and the only complexes detected are CPs associated with two molecules of one type of HMGN variant. Thus, addition of CPs to a mixture of HMGN1 and HMGN2, or HMGN2 and HMGN5, results in complexes containing two molecules of either HMGN1, or HMGN2, or HMGN5, per core particle. CPs associated with two different type of HMGN variants (i.e. an HMGN1 and an HMGN2) were not detected [7,19]. Significantly, experiments with chromatin isolated from nuclei suggested that also in living cells the CPs contain only one type of HMGN variant [20].

Hydroxyl radical footprinting indicated that the path of HMGN1 on the surface of the nucleosomal DNA is indistinguishable from that of HMGN2 [21]. The bound HMGNs proteins protect the DNA from hydroxyl radical cleavage in each of the two major grooves of the DNA flanking the nucleosomal dyad axis and 25 base pairs from the ends. At the entry–exit points of the nucleosomal DNA, the proteins bridge two adjacent DNA helices on the surface of the particle, resulting in

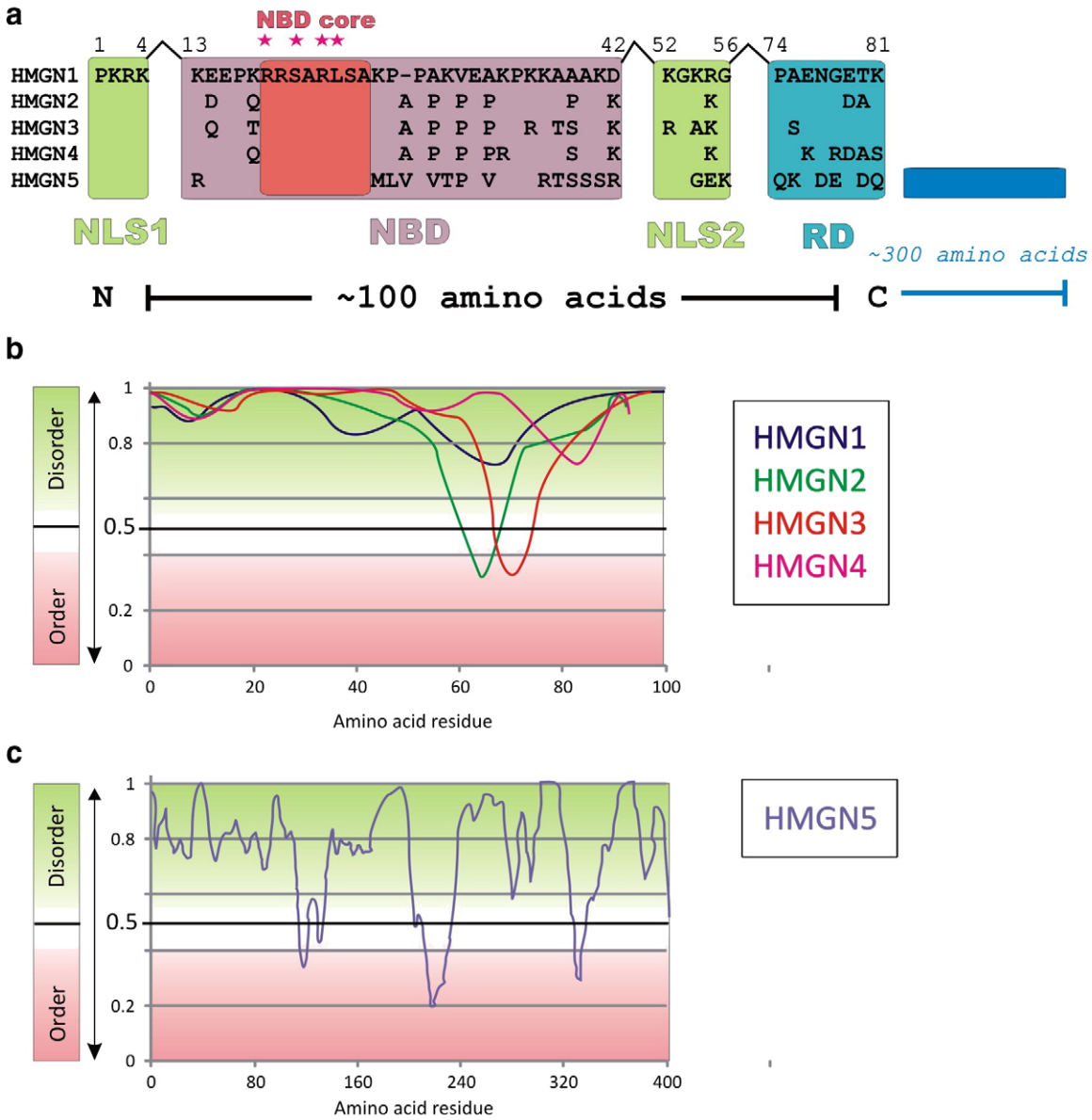

Fig. 1. Structural features of the high mobility group N (HMGN) proteins. (A) Functional domains of the high mobility group N (HMGN) proteins. Sequences of the human HMGN proteins are aligned. All HMGN proteins contain four functional domains (shadowed): two nuclear localization signal domains (NLS1 and NLS2, light green), a nucleosomal binding domain (NBD, light purple) and a regulatory domain (RD, cyan). The invariant amino acid residues within NBD domain are named as NBD core (shadowed by brick red) and four residues essential for specific binding to nucleosomes are marked by magenta stars above the core NBD. The RD domain is less conserved and has a net negative charge. The C-terminus of HMGN5 is ~300 amino acids longer than that of the other HMGNs. (B) Intrinsically disordered regions (IDRs) in HMGN family proteins. The sequences of human HMGN proteins have been analyzed by predictors of natural disordered regions (PONDR)—a series of neural network predictors (NNPs) that use amino acid sequence data to predict *disorder* in a given region [72]. Values greater than 0.5 represent intrinsically disorder regions in the protein. (C) A graph of intrinsically disordered regions in mouse HMGN5.