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HMG chromosomal proteins in development and disease

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Abstract

The high mobility group (HMG) proteins are a superfamily of abundant and ubiquitous nuclear proteins that bind to DNA and nucleosomes and induce structural changes in the chromatin fiber. They are important in chromatin dynamics and influence DNA processing in the context of chromatin. Results emerging from studies of human disease, genetically modified mice and cells with altered HMG expression indicate that the expression of the HMG proteins is developmentally regulated and that changes in HMG protein levels alter the cellular phenotype and can lead to developmental abnormalities and disease. Here, we focus on the biological function of HMG proteins and highlight their possible roles in cellular differentiation and in the etiology of various diseases.

Introduction

Proper cellular differentiation in the developing organism depends on the correct execution of a preprogrammed and orderly process involving multiple changes in gene expression. Aberrant gene expression leads to developmental abnormalities and is the underlying cause of many diseases, including cancer. The structure of the chromatin fiber has a key role in regulating the fidelity of gene expression and chemical changes in histones and DNA are important mediators of epigenetic regulation. Thus, it can be expected that the high mobility group (HMG) superfamily of chromatin binding proteins, which have been shown to affect the structure and activity of the chromatin fiber, would affect development and tumorigenesis.

It is now clear that HMGs impart structural and functional plasticity to the chromatin fiber; however, their biological function seems complex and their effects on the cellular phenotype are still not fully understood. New insights into the mechanisms of action and cellular function of HMG proteins are emerging from imaging studies of their interaction with chromatin in living cells, and from analyses of organisms in which their expression levels have been altered. Here, we focus on the distinct roles of the three HMG families in modulating developmental processes and tumorigenesis.

HMG proteins: dynamic remodelers of chromatin architecture

HMG proteins are grouped into a superfamily by their similarity in physical and chemical properties and because all act as architectural elements that affect multiple DNA-dependent processes in the context of chromatin. This superfamily consists of three families, HMGA, HMGB and HMGN; all HMGs are characterized by a carboxy terminus rich in acidic amino acids, but each has a unique functional motif (Figure 1a), induces specific changes in its binding sites (Figure 1b) and participates in distinct cellular functions.

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The HMGA family consists of four members, each containing several 'AT-hooks', the functional motif characteristic of this protein family. Through these hooks, HMGAs bind preferentially to AT-rich stretches in B-form DNA and induce conformational changes that promote subsequent recruitment of additional components to the binding sites (Figure 1). HMGA proteins have an acidic C-terminal tail, which could be important for protein-protein interactions [1,2].

The HMGB family consists of three variants, each containing two functional motifs (HMG boxes) and a highly acidic C-terminal. The HMG boxes are formed by three α-helices folded together to an L-shaped structure part of which penetrates the minor groove and sharply bends the DNA. Slight differences between the HMG boxes confer specificity to the various HMGB proteins, whereas the acidic tails modulate their affinity for a variety of distorted DNA structures (Figure 1).

The HMGN protein family is characterized by a positively charged domain, the nucleosome binding domain, and by an acidic C-terminal, the chromatin unfolding domain. HMGNs bind specifically to nucleosomes and alter both the local and the higher order structure of the chromatin fiber.

HMG proteins bind to chromatin without any known preference for the underlying DNA sequence; their functional specificity could depend on interactions with specific regulatory factors, or on their ability to continuously target a specific subset of chromatin conformations. Possible mechanisms by which HMGs alter the architecture and function of chromatin are depicted in Figure 1. Several reviews provide extensive information on the structure and architectural functions of HMG proteins [1-7].

On the basis of many *in vitro* experiments, HMGs are viewed as architectural components that remodel the structure of chromatin. More recent imaging experiments with living cells show that the interaction of these proteins with chromatin is highly dynamic, that they are not stably associated with specific sites and that each HMG molecule can sample the nucleosomes for potential binding sites. In living cells, HMG molecules continuously hop from one binding site to another in a 'stop and go' fashion. The average 'stop' stage lasts several seconds and is longer than the 'go' stage; therefore, most of the time the HMG molecules are bound to chromatin. However, at the level of local binding sites there is a continuous turnover of HMG proteins. Furthermore, each HMG protein competes for chromatin binding sites with other members of the same family and with histone H1. Thus, in living cells HMGs remodel chromatin as members of a dynamic network of chromatin-binding proteins, which are likely to include other proteins transiently binding to chromatin. The kinetic properties of chromatin-binding proteins such as the HMGs provide a mechanism for functional redundancy among related proteins. The function of a missing protein can be partially compensated by a closely related protein, as is the case for histone H1: deletion of one variant leads to increased synthesis of other histone H1 variants.

The competitive and dynamic behavior of HMGs could probably minimize any deleterious effects due to changes in HMG protein levels. However, the data available reveals that loss of any HMG leads to detectable phenotypic changes, an indication that even members of the same HMG family cannot fully compensate for loss of a close variant. Here, we summarize the main findings leading to the suggestion that members of the HMG superfamily affect developmental processes and could have a role in the etiology of certain diseases.

HMGA proteins

HMGA proteins are present in stem cells, and it has been suggested that HMGA2 is necessary for the commitment of mouse embryonic stem cells to the skeletal muscle lineage [8]. HMGAs

are relatively abundant in undifferentiated and proliferating cells of early embryos and undetectable in fully differentiated cells. The developmentally regulated expression of HMGA proteins suggests a role in differentiation processes. Indeed, the phenotypes of *Hmga1*$^{-/-}$ and *Hmga2*$^{-/-}$ mice indicate that the two regulate distinct differentiation processes within a cell type-specific context (Table 1). For example, *Hmga1*$^{-/-}$ mice suffer from cardiac hypertrophy and hematological malignancies and develop type 2 diabetes, due to an HMGA-dependent downregulation of the insulin receptor [9,10]. *Hmga2*$^{-/-}$ mice are pygmies [11,12] and their spermatogenesis is deficient leading to sterile males [13], whereas transgenic mice overexpressing a truncated version of *Hmga2* are giant, obese and develop lymphomas [1, 14]. These phenotypes can be directly linked to the well established role of HMGA2 in pre-adipocyte precursor cell proliferation [12].

HMGA overexpression is a hallmark of several malignant and benign tumors [1,4] (Table 2). The faulty expression of many genes in malignant and benign human tumors is a direct result of HMGA overexpression [4,15,16]. In human epithelial cells, HMGA1 promotes tumor progression and epithelial-mesenchymal transition (EMT) [17]; EMT occurs during movements of embryonic cell layers and during metastasis. Likewise, recent studies indicate that HMGA2 is an important mediator of transforming growth factor (TGF-β) signaling that controls epithelial differentiation, tumor invasiveness and metastasis [18].

HMGA1 and HMGA2 are both implicated in the etiology of lipomas (benign tumors composed of mature fat cells) [1]. Rearrangements of the HMGA2 gene involving 12q13-15 chromosomal translocations are perhaps the most common rearrangement in human benign tumors of mesenchymal origin. Many studies link these translocations and overexpression of HMGA2 to several types of benign tumors. Overexpression of HMGA2 is sufficient to induce benign tumors in mice [19].

The involvement of HMGAs in specific gene expression is crucial for their diverse roles in differentiation and tumorigenesis. In humans, HMGA overexpression in malignant and benign tumors causes aberrant expression of genes that regulate cell proliferation or apoptosis [4,15, 16]. Recently described interacting partners, such as nuclear factor (NF)-κB [20] and the tumor suppressors p53 [21,22] or pRB [23], provide a clue to how HMGA proteins could influence gene expression in cancer. However, HMGA proteins also inhibit nucleotide excision repair [7,24], which could mean that HMGA proteins promote tumorigenesis by increasing genome instability.

Besides their obvious roles in oncogenesis, an antioncogenic potential was recently attributed to HMGA1 proteins. Antiproliferative activities were observed in lymphoproliferative disorders [9] and during cellular senescence [25], which prevent rather than promote malignant transformation. In the context of cellular senescence, HMGAs modulate global chromatin architecture by contributing to the formation of senescence-associated heterochromatin foci.

In addition to altering chromatin architecture, HMGAs affect several distinct cellular processes. It is likely that the ability of HMGA to participate in several type of processes is conferred by their interaction with a wide range of partners, including transcription factors, components of the splicing machinery, proteins involved in replication and chromatin assembly factors [26].

HMGB proteins

HMGB proteins function as intranuclear and extracellular regulatory proteins. In the nucleus, HMGBs are the most abundant HMG proteins and regulate numerous activities, including transcription, replication and repair [5]. HMGB1 is secreted from macrophages and from necrotic cells, and it affects cell migration and tumor invasiveness and acts as a cytokine that mediates the response to infection, injury and inflammation [27].

In mice, there are three HMGB variants, HMGB1, HMGB2 and HMGB3, all of which are expressed in early embryos. During embryonic development, HMGB2 and HMGB3 are selectively down-regulated: HMGB2 remains highly expressed in lymphoid organs and testes, whereas HMGB3 is expressed mainly in primitive hematopoietic cells [28-30]. By contrast, HMGB1 continues to be expressed in all embryonic and adult cells [31]. The biological significance of the down-regulation of the HMGB variants is not fully understood. Induced overexpression of HMGBs alters the cellular transcription profile through interaction with transcription factors; however, no systematic studies on the effects have been done [5].

Studies with *Xenopus* eggs and *Drosophila* embryos, which contain large amounts of maternal HMGB but little or no histone H1, provide insights into one possible developmental function of these proteins. During early development of these organisms, the HMGB1:H1 ratio switches and increased histone H1 levels lead to changes in chromatin structure and gene expression [32,33]. These observations suggest that HMGB1 has a role in maintaining the chromatin structure, especially in early embryogenesis. However, neither HMGB1 protein nor mRNA is stored in the mouse oocyte, suggesting that the role of HMGB1 in the early embryogenesis of mammalians is different from those in other species [34].

Analyses of animals with altered HMGB levels reveal functional specificity among the various HMGB variants (Table 1). Thus, although all HMGB variants are structurally similar and induce similar architectural changes in chromatin, they have specific biological functions. The molecular mechanisms conferring functional specificity to the HMGB variants have not been studied in detail. They might reflect variant-specific interactions with regulatory molecules that target the HMGB variants to specific chromatin sites.

Like HMGA proteins, HMGBs are involved in regulating DNA repair processes [7]. However, HMGB proteins either promote lesion repair or induce apoptosis. Moreover, HMGBs preferentially bind to cisplatin-modified DNA or to misincorporated nucleoside analogs and consequently inhibit nucleotide excision repair by steric hindrance, a fact that is of great value in cancer treatment [35,36]. *Hmgb1*$^{-/-}$ mice have increased chromosomal instabilities [6], an observation that links aberrant expression levels of HMGB proteins to the chromosomal instabilities frequently found in cancer cells.

As an extracellular component, HMGB1, but not HMGB2, has been linked to diseases such as sepsis, arthritis and cancer (Table 2) [27]. HMGB1 is secreted from necrotic cells and macrophages [37,38] and acts as a cytokine that can induce necrotic cell death [27]. Although HMGB1 itself has weak proinflammatory activity, a recent study showed that the activity is enhanced by lipids that bind to HMGB1 [39]. By binding to RAGE (receptor for advanced glycation end products) and perhaps other membrane receptors, the extracellular HMGB1 enhances cell migration, tumor growth and metastasis [40]. It might be relevant that the expression levels of HMGB1 in colon, breast, gastric and gastrointestinal cancer cells are upregulated [31,41]. Additional information on the extracellular functions of HMGB1 is available in several recent reviews [27].

HMGN proteins

HMGN proteins are found only in vertebrates, and detailed developmental studies on HMGN expression patterns in *Xenopus* and mice show that the expression level of HMGN proteins is tightly linked to differentiation [42,43].

Like HMGBs and HMGAs, the *HMGN1* and *HMGN2* genes are ubiquitously and highly expressed in all embryonic tissues. During mouse embryogenesis, these two HMGN genes are progressively down-regulated throughout the entire embryo, except in committed but continuously renewing cell types undergoing active differentiation, such as the basal layer of

the epithelium or in kidney cells undergoing mesenchyme to epithelium transition [43,44]. Likewise, experiments with tissue culture cells show that HMGN expression is down-regulated during myogenesis, erythropoiesis and osteogenesis [42,43]. In C2C12 myoblast cells, aberrant expression of *Hmgn1* inhibits myotube formation [45], whereas in primary limb bud mesenchymal cells overexpression of HMGN1 inhibits chondrocyte differentiation [43]. Depletion of HMGNs in one-cell or two-cell mouse embryos delays subsequent embryonic cleavages [46].

In *Xenopus*, HMGN proteins are absent from cleavage stages and synthesis starts with the activation of the embryonic genome at the midblastula transition (MBT). Alteration of HMGN levels after, but not before, the MBT leads to altered expression of mesoderm-specific genes and to developmental defects [42]. Taken together, the available data indicate that proper differentiation requires regulated levels of HMGN expression. It is not yet clear whether HMGNs affect the expression of a subset of specific genes or whether they act as general cofactors that optimize cell-specific transcription profiles.

So far only *Hmgn1*$^{-/-}$ mice have been generated and they appear normal [47]. However, they are subfertile and hypersensitive to various stress conditions, such as exposure to UV light or ionizing irradiation [47-49] and show abnormalities in the development and maintenance of the corneal epithelium [49]. These abnormalities could be linked to the high expression of HMGN1 in the basal layer of the corneal epithelium where it colocalizes with p63, a protein involved in the regulation of epithelial differentiation [49]. Cells derived from *Hmgn1*$^{-/-}$ mice have an altered transcription profile and are hypersensitive to stress [47,50]. It is likely that partial functional redundancy with HMGN2 dampens the deleterious effects of loss of HMGN1 [43].

The incidence of tumors in *Hmgn1*$^{-/-}$ mice is almost twice that of wild-type mice, and *Hmgn1*$^{-/-}$ cells have an increased tumorigenic potential, as measured by colony formation in soft agar and generation of tumors in nude mice [48]. This increased tumorigenic potential could be due to faulty DNA repair. *Hmgn1*$^{-/-}$ mice and cells are hypersensitive to UV and ionizing radiation [47,48]. The UV hypersensitivity of *Hmgn1*$^{-/-}$ cells is related to the ability of HMGN to ‘unfold’ chromatin, leading to the suggestion that HMGN increases the accessibility of the damaged DNA sites to the repair machinery [47]. HMGN1 could also have a unique role in transcription-coupled repair because it is specifically recruited by Cockayne syndrome protein A to the RNA polymerase stalled at the UV-damaged sites [51]. The hypersensitivity of *Hmgn1*$^{-/-}$ mice to ionizing radiation might be due to their impaired ability to activate the G2-M checkpoint [48], a fault leading to increased genomic instability and cancer. HMGNs might influence DNA repair processes by altering the ability of repair factors to reach the damaged sites or by affecting chromatin modifications necessary for proper repair. Thus, given that HMGN1 modulates the rate of stress-induced histone modifications, it is possible that it also affects the modification of the core histones during DNA repair.

The mouse *Hmgn1* gene is located on chromosome 16 in a region syntenic with the human Down syndrome region on chromosome 21 [52]. Cells from Down syndrome patients and from the Ts1Cje mouse, which serves as an animal model for this disease, carry three alleles of the HMGN1 gene and expresses elevated levels of HMGN1 protein [53]. The exact role of HMGN1 in Down syndrome is not understood; however, given the complex phenotype of this syndrome, which includes faulty DNA repair, and given the pleiotropic effects on the chromatin caused by altered HMGN1 expression, it is possible that elevated HMGN1 is a contributing factor in the development of this prevalent birth defect.

In addition to HMGN1 and HMGN2, the HMGN family contains three more proteins, NSBP1 (also called NBD-45), HMGN4 and HMGN3a/b [54,55], which are expressed in a tissue- and

developmental stage-specific manner [54,56]. Thus, whereas HMGN1 and HMGN2 are involved in general cellular differentiation, the newer members of the family could be involved in tissue-specific events.

Perspective: HMG proteins as specific modulators of chromatin in development and disease

The cellular function and mechanism of action of structural chromatin proteins, such as the linker histone H1 and HMG proteins, is one of the most perplexing questions in chromosome biology. The wide range of cellular activities influenced by HMG proteins supports the hypothesis that these architectural proteins remodel the structure of chromatin; however, it also raises the question of which of the various cellular functions are most affected by these proteins. Do they affect cellular pathways in a specific way or are they just general co-factors that affect cellular homeostasis? The data available suggest that HMGs do indeed affect the transcription levels of many genes but at the same time also act as specific cofactors in distinct cellular pathways. For example, HMGB1 stabilizes the binding of the glucocorticoid receptor to chromatin [5], HMGA1 facilitates the formation of an enhanceosome on the promoter of the interferon-β gene [20], and HMGN1 is recruited by Cockayne syndrome protein A to the polymerase at UV-damaged DNA sites [51]. Given that HMGs can act both as non-specifically binding structural chromatin elements and as cofactors in specific pathways, an understanding of their main biological roles requires studies at the level of the entire organism.

A common property of all HMGs is that during embryonic development their expression is gradually down-regulated (Figure 2). This down-regulation could be related to changes in chromatin organization and in the cellular transcription potential that occur during development. In several experimental systems, up- or down-regulation of HMG expression results in significant changes in the developmental program, suggesting that proper development and differentiation requires regulated levels of HMG proteins. However, so far, analysis of HMG knockout mice indicates that loss of a single HMG protein does not significantly impair embryonic development, because mice lacking only one type of HMG protein are born alive. Functional redundancy among members of the same HMG family probably compensates for loss of each HMG variant, thereby enabling proper embryonic development. It will be of interest to examine the phenotype of compound mutant mice lacking more than one HMG variant.

Once born, all the HMG knockout mice develop distinct, and in some cases very severe, phenotypes (Table 1), including increased levels of various tumors (Table 2). It is conceivable that cellular mechanisms involving HMG functional redundancy are not as efficient in fully differentiated tissues, where the levels of these proteins are relatively low, as in developing tissues. The phenotypes of the HMG knockout mice suggest functional specificity of HMG variants in the differentiated tissues. Several mechanisms could account for functional specificity of HMG variants. One possibility is tissue-specific HMG variant expression. For example, HMGB2 is expressed in adult testis and *Hmgb2*$^{-/-}$ mice have defective spermatogenesis [29]. Alternatively, the chromatin structure of tissue-specific genes could be selectively susceptible to the architectural effects induced by the various HMG variants. However, the most likely possibility is that HMGs interact with tissue-specific regulatory factors that target the proteins to specific sites. Indeed, several reports indicate that all HMGs interact with a wide range of nuclear proteins. Thus, the biological effects of HMGs might depend on the availability of their interacting partners, which could vary among cells and which is not necessary constant throughout development. Variability in the levels of the HMG-interacting partners could explain the large range of biological functions affected by HMGs.

Furthermore, the main phenotypes observed in the HMG knockout mice could mask additional developmental defects. For example, it is likely that the early death of the *Hmgb1*$^{-/-}$ mice as a result of hypoglycemia [5] masks additional abnormalities in these mice. *Hmgn1*$^{-/-}$ mice that do survive show a wide range of phenotypes, including defects in the repair of DNA damaged by UV or ionizing radiation, defective stress responses and abnormal development of the corneal epithelium [47-50].

The structure of the chromatin fiber is an important factor in the regulation of gene expression and has a key role in determining the cellular phenotype. HMGs act as modulators of chromatin structure and have important roles in cellular differentiation and in the etiology of various diseases, including cancer.

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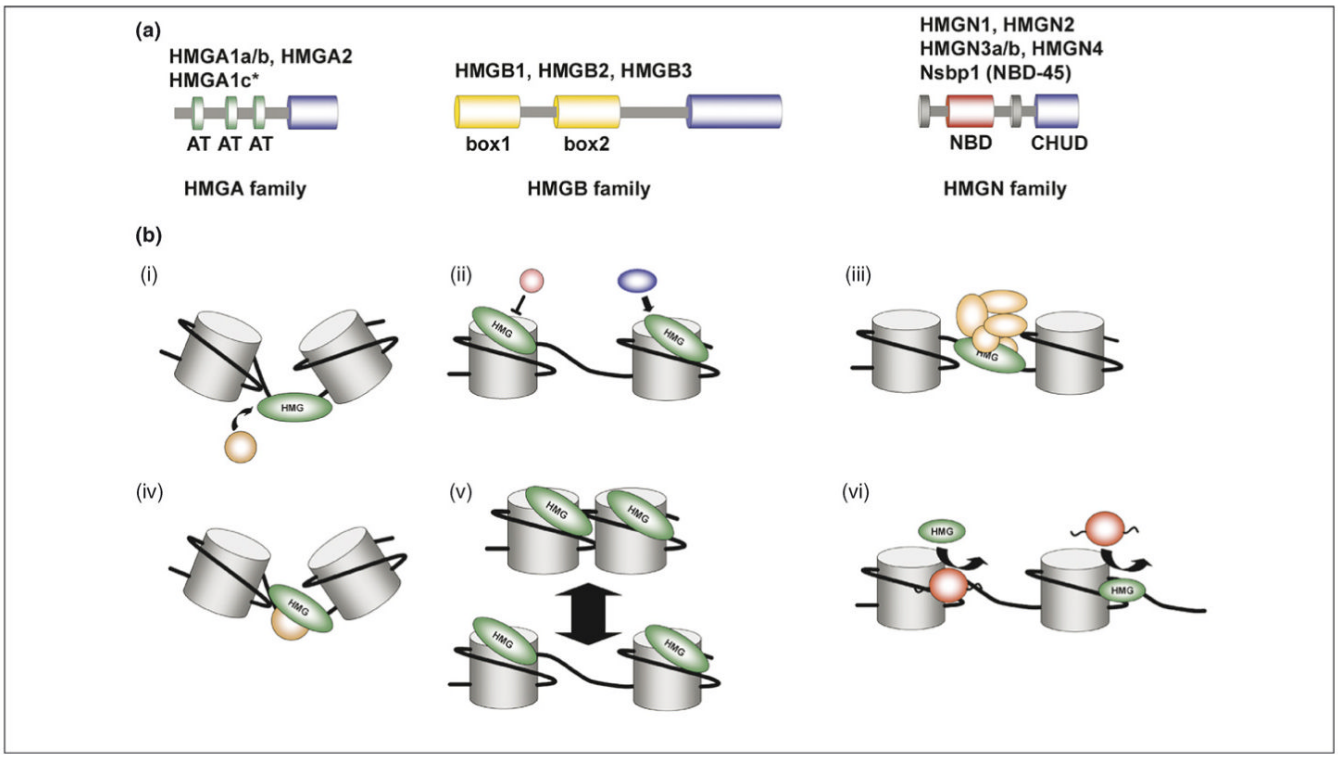

Figure 1.

Architectural functions of HMG proteins. (**a**) The main structural features of the HMGs. Family members are listed above each diagram. All HMGAs contain three AT hooks (green) and an acidic C-terminal part (blue), except HMGA1c, which contains only two hooks. Through these hooks HMGAs bind to AT-rich regions. Each of the three members of the HMGB family contains two HMG boxes (yellow) and an extended acidic C-terminus (blue). The HMGN proteins are characterized by a positively charged nucleosomal binding domain (NBD, red) and a negatively charged C-terminal region named chromatin unfolding domain (CHUD, blue). (**b**) HMG proteins alter chromatin structure by a variety of mechanisms. (i,ii) HMG proteins (green) alter the chromatin structure and facilitate the binding of additional factors (round shapes of various colors). This can be mediated through (i) their DNA bending activity, as has been shown for HMGA and HMGB proteins [2,5,7] or by (ii) either preventing or facilitating access of modulating factors to chromatin, as has been shown for HMGN proteins [50,65]. Given that HMGA proteins also bind to nucleosomes, a similar modulation of nucleosome accessibility is feasible. (iii) HMGs are part of the chromatin binding module of regulatory multiprotein complexes. A prominent example is the role of HMGA proteins in the formation of enhanceosomes [20]. (iv) HMG proteins facilitate structural transitions at sites to which they are targeted by specific regulatory factors. After targeting, HMGA or HMGB can induce DNA bending [5] and (v) chromatin unfolding by HMGN proteins or chromatin compaction by HMGA [25,66]. (vi) HMG proteins compete with other nuclear proteins for chromatin binding sites, altering the local or global structure of the chromatin fiber. The competition of HMG proteins with linker histones is an example of competition among chromatin binding proteins [67-69].

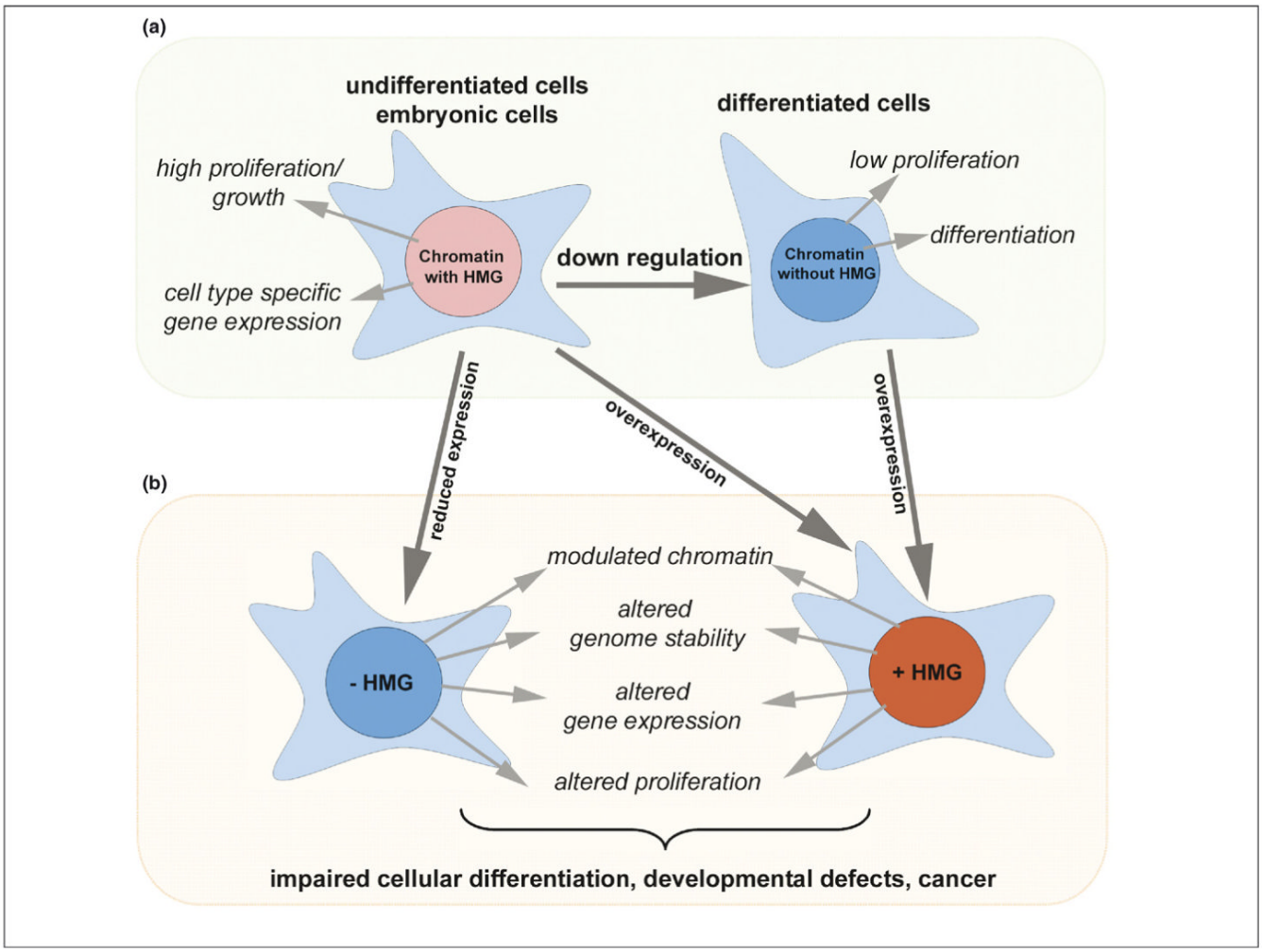

Figure 2.

Differential expression of HMG proteins and the effects of HMG levels on development and cancer. (**a**) In normal developmental conditions, the expression of HMGs is related to differentiation. Thus, in undifferentiated and embryonic cells, HMG-containing chromatin is linked to increased cellular proliferation and cell type-specific gene expression. During cellular differentiation the levels of HMG is down-regulated, and terminally differentiated cells have a low content of HMGs. (**b**) Deregulation of HMG expression leads to an abnormal situation. Increasing or decreasing HMG levels causes alterations in the cellular transcription profile and can lead to developmental defects, disease and cancer.

Table 1

Phenotypes resulting from alterations in HMG proteins and their expression

Organism	HMG	HMG level	Phenotype	Refs
Mouse	*Hmga1*	*Hmga1*$^{+/-}$	Impaired spermatogenesis; cardiac hypertrophy	[9,57]
Mouse	*Hmga1*	Knockout	Type 2 diabetes; cardiac hypertrophy	[9,10]
Mouse	*Hmga1*	Knockout	Impaired lymphohematopoietic differentiation of embryonic stem cells	[58]
Mouse	*Hmga2*	Knockout	Pygmy; reduced fat tissue; impaired spermatogenesis	[11,12]
Mouse	*Hmga2*	Overexpression	Effects on myogenesis in embryonic stem cells	[8]
Mouse	Truncated *Hmga2*	Transgene producing overexpression	Obesity	[1]
Human	*HMGA1*	Reduced expression	Type 2 diabetes	[10]
Mouse	*Hmgb1*	Knockout	Animals die within 24 h of birth because of hypoglycemia	[59]
Mouse	*Hmgb2*	Knockout	Defect in spermatogenesis	[29]
Mouse	*Hmgb3*	Knockout	Erythrocythemia (increased number of erythrocytes)	[60]
Xenopus	*Hmgb3*	Knockdown	Reduction in eye and brain size	[61]
		Overexpression	Increase in eye and brain size	[61]
Mouse	*Hmgn1*	Knockout	Hypersensitive to UV and ionized radiation; increased tumorigenicity; cornea malformation	[47-49]
Mouse	*Hmgn1*	Increased expression level	Trisomy 16, Down syndrome model	[53]
Mouse	*Hmgn1, Hmgn2*	Reduced expression	Delayed cell cleavage during preimplantation development (the embryo eventually reaches the blastocyst stage)	[46]
Xenopus	*Hmgn1, Hmgn2*	Overexpression or disruption by antisense oligonucleotides	Imperfectly closed blastopore; distorted body axis; abnormal head structure; extended loss of mesodermal competence of animal cap	[42]

Table 2

The HMG protein family and cancer

Organism	HMG	HMG level	Cancer	Refs
Mouse	*Hmga1*	*Hmga1*$^{+/-}$ and knockout	High incidence of myelo-lymphoid malignancies	[9]
Mouse	*Hmga1*	Transgene producing overexpression	Mixed growth hormone- or prolactin-secreting pituitary adenomas and natural killer lymphomas; lymphoid malignancies	[16,62]
Mouse	*Hmga2*	Transgene producing overexpression	Induction of pituitary tumorigenesis (relieve of pRB mediated repression of E2F1)	[23]
Mouse	*Hmga2*	Transgene producing overexpression	Sufficient to induce benign mesenchymal tumors	[19]
Mouse	Truncated *Hmga2*	Transgene producing overexpression	High incidence of lymphomas, lipomas and lipomatosis	[1,14]
Human	*HMGA1*	Overexpression	Inhibition of nucleotide excision repair in breast cancer cells	[24]
Human	*HMGA1*	Overexpression	Tumor progression and mesenchymal transition of epithelial cells	[17]
Human	*HMGA1*	Small interfering RNA	Inhibition of p53 function in thyroid cancer cells; increase of p53-mediated apoptosis	[21,22]
Human	*HMGB1*	Overexpression	HMGB1 is overexpressed in breast, colon, gastric and gastrointestinal cancer cells	[31,41]
Mouse	*Hmgb1*	Knockout	Chromosomal abnormalities	[6]
Human	*HMGB1*	Extracellular HMGB1 released from monocytes, macrophages and necrotic cells	Involved in tumor growth, metastasis and invasion by activating the RAGE signaling pathway	[40]
Human	*HMGN2*	Deleted in the ring chromosome 1	Uterine leiomyoma (benign nodules in the uterus wall)	[63]
Mouse	*Hmgn1*	Knockout	Increased tumorigenesis	[48]
Human	*HMGN2*	Down-regulation	*Hmgn2* expression is down-regulated by p53 induction	[64]