Chapter 7

HMGB Proteins from Yeast to Human. Gene Regulation, DNA Repair and Beyond

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Abstract

HMGB proteins are characterized for containing one or more HMG-box domains and are well conserved from yeasts to higher eukaryotes. The HMG-box domain is formed by three α-helices with an L-shaped fold. Although HMGB proteins also have cytoplasmic and extracellular functions, they bind to nuclear or mitochondrial DNA in a highly dynamic process that affects chromatin organization. In this review, we mainly focus on HMGB proteins from yeast and their human homologs as functionally involved in DNA repair and transcriptional regulation. Recent research reveals that these proteins participate in epigenetic control of gene expression, aging, disease, or stem-cell biology.

Keywords: nonhistone proteins, epigenetics, transcriptional regulation

1. Introduction

Nucleosomes are fairly stable basic units of DNA packaging. Nevertheless, nucleosomal chromatin is surrounded by a highly dynamic protein pool that allows chromatin remodeling and favors replication, DNA repair, and gene transcription. Among proteins that transiently associate with chromatin are variants of the linker histone H1 family [1–3] and members of the high mobility group (HMG) protein superfamily [4–6]. Although HMG motifs are present in many nuclear proteins, the classification and nomenclature of the considered "canonical"

HMG proteins is organized in three families named HMGA, HMGB, and HMGN, each one having a specific functional domain: the "AT hook" in HMGA, the "HMG-box" in HMGB, and the "nucleosomal binding domain" in HMGN proteins [7].

Some HMGB proteins have been related to nuclear, extranuclear, and extracellular functions during inflammation, cell differentiation, cell migration, and tumor metastasis [8, 9]. Their HMG-box domain contains 65–85 amino acids and has a characteristic L-shaped fold formed by three α-helices with an angle of ≈80° between the two arms. The long arm, or minor wing, is composed by the extended N-terminal strand and third α-helix, while first and second α-helices form the short arm, or major wing (**Figure 1(a)**). Because of protein interaction in the minor groove, DNA-bending and widening of the double helix is produced (**Figure 1(b)**).

There are two broad subfamilies of HMGB-containing proteins, based on structural and phylogenetic studies. One class includes those that bind to distorted DNA with low or without sequence specificity (nonsequence specificity (NSS), HMG-box domains) and have, in general, two or more *in tandem* arranged HMG-box domains [10, 11]. Examples of proteins without sequence specificity are the mammalian Hmgb1-4 and Ubf proteins, Hmgd from *Drosophila*, or Nhp6a and Nhp6b from *Saccharomyces cerevisiae*. Their role is related to chromatin modification, participating in many different functions such as co-activation or silencing of transcription and V(D)J junction recombination. A second class of HMGB-containing proteins binds to DNA by recognizing a specific DNA sequence (sequence specificity (SS), HMG-box domains), and they usually contain a single HMG-box domain [10, 11]. They generally function as transcription factors, only expressed in a few cell types, and they also contain other regulatory associated domain. The determinants for DNA sequence specificity lie mainly in the minor wing of the HMG-box. Examples of this kind of HMGB proteins are the mammalian lymphoid enhancer factor (Lef-1), the sex determining factor (Sry), and the Sry-related HMG-box (SOX) family, or the hypoxic gene repressor (Rox1) from *S. cerevisiae*.

In this review, we focus on HMGB proteins from yeast, as functionally involved in DNA repair and transcriptional regulation, but also in their homologs from multicellular eukaryotes, with special reference to human proteins. Their functions may be modulated by nucleosome positioning and stability [12]. Interestingly, recent findings support that HMGB proteins may also

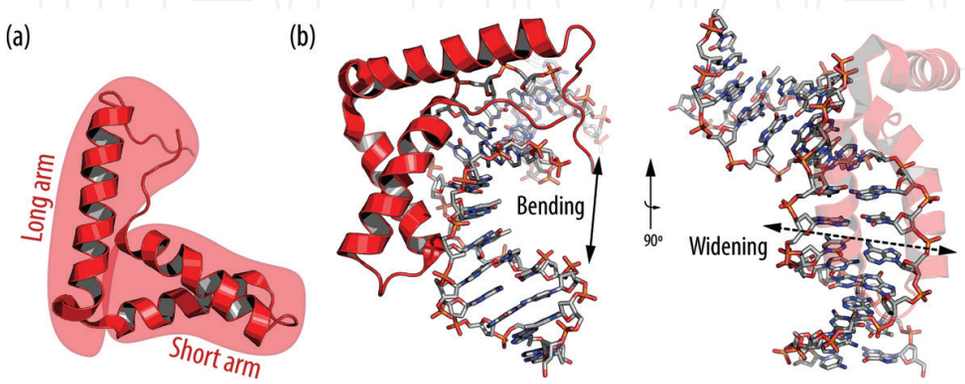

Figure 1. (a) Characteristic HMG-box fold (based on Sox17 protein structure; PDBID: 3F27). (b) Bending and widening produced in the double strand of DNA after protein binding.

play diverse roles in epigenetic control, since their interaction with chromatin affects the level of histone modifications [13]. In the light of recently opened research areas, in which HMGB proteins are involved, available knowledge is also discussed.

2. HMGB proteins from *Saccharomyces cerevisiae*

In *S. cerevisiae*, the genes *ABF2, HMO1, IXR1, NHP6A, NHP6B, NHP10*, and *ROX1* encode HMGB proteins [7]. The protein Spp41 also contains a HMG-like motif although homology searches reveal that it is far related to the others. The structural characteristics and functions of these yeast proteins are shown in **Table 1**. Only one HMG-box domain is present in most of them, but Abf2 and Ixr1 have two in tandem "HMG-box" motifs.

With the exception of Rox1 that behaves as a specific transcriptional regulator of the hypoxic yeast regulon [14] and Ixr1 that has a dual function as specific transcription factor and DNA-binding protein without sequence specificity, also participating in DNA repair [15], the other

Protein	Amino acids	Molecular weight (Da)	pI	Aliphatic index	Instability index	Domain position
Abf2	183	21,575	10.24	67.27	42.94	HMG: 42-112 HMG: 115-183 Coil 89-110
Hmo1	246	27,546	9.11	67.35	45.80	HMG: 105-180 PHHR13711: 22-185
Nhp6A	93	10,810	10.40	43.13	39.16	HMG: 20-90 PHHR13711: 7-93
Nhp6B	99	11,485	10.54	37.99	58.30	HMG: 26-96 PTHR13711: 6-99
Nhp10	203	23,858	8.15	68.12	51.57	Coil: 3-24 HMG: 93-159 PTHR13711: 74-182
Rox1	368	41,857	10.46	70.38	62.14	Coil: 90-118 HMG: 9-84
Ixr1	597	67,858	8.36	51.20	70.67	HMG: 360-430 HMG: 433-503 Poly-Q: 3 regions Coil: 292-313 PTHR13711: 1-594

Table 1. Characteristics of HMGB proteins in *Saccharomyces cerevisiae*.

HMGB proteins from *S. cerevisiae* might be considered as chromatin architectural proteins, but with wide influence on gene expression [16]. This is not a HMGB-exclusive mechanism since, in eukaryotes, many other chromatin components, such as histones [17], histone chaperones and modifiers [18], chromatin remodel complexes [19], and long noncoding RNAs [20], affect gene expression by different mechanisms.

Although Abf2 and Ixr1 are considered paralogs, resulting from the whole genome duplication in an ancestor of *Saccharomyces*, the function of Abf2 is not related to transcriptional regulation of hypoxic regulons. Abf2 is a mitochondrial DNA-binding protein involved in mitochondrial DNA replication and recombination [21, 22]. *In vivo*, PKA-mediated phosphorylation of Abf2 during glucose repression may regulate its functions on maintaining mitochondrial DNA content during the shift from gluconeogenic to fermentative growth [21].

Hmo1 is not considered a specific transcriptional factor either, although it regulates rDNA transcription from RNA polymerase I promoters and also regulates start site selection of ribosomal protein genes by RNA polymerase II [23–25].

Nhp10 (alias Hmo2) is a nonessential subunit of the INO80 chromatin remodeling complex, and it affects telomere maintenance via recombination [26, 27].

Nhp6a and Nhp6b are also paralogs and functionally redundant [28], they bind to and remodel nucleosomes [29, 30], and both are required for transcriptional initiation fidelity of some tRNA genes [31]. Their protein levels increase in response to DNA replication stress [32]. Besides, Nhp6a and Nhp6b acting on chromatin tightly repress histone expression; paradoxically, histone gene overexpression in the double *nhp6aΔ nhp6bΔ* mutant is compensated by downregulation of translation, finally determining a histone-decreased phenotype to avoid the toxic effect of histone overproduction [33].

Although few data are available about Ssp41 functions, it has been associated with chromatin remodeling [34], transcription, and RNA processing [35, 36]. Besides, overexpression causes chromosomal instability [36] and under hypoxia, it is rapidly exported to the cytosol [34].

An intriguing question is whether the *S. cerevisiae* HMGB proteins contribute altogether to regulate specific cell functions. An interesting perspective comes from the terms "environmental stress response" (ESR) or "common environmental response" (CER). These terms refer to adaptive yeast responses against acute changes in diverse environmental parameters (e.g., O_2, osmolarity, nutrients, pH, UV, etc.), which evoke a common transcriptional response, initially devoted to mitigate the deleterious effect of the specific stressor, but principally to balance cell energetics and to coordinate progression through the cell cycle [37]. We have summarized the information available in SGD about protein interactants of HMGB proteins from *S. cerevisiae* (http://www.yeastgenome.org/ as accessed date February 22, 2017) and used this information to construct a interactome network using STRING facilities (http://string-db.org/). **Figure 2** shows that this network statistically has significantly more interactions among HMG-box proteins and their previously reported partners than randomly expected, with a p-value < 0.01 according to STRING analysis. This result suggests that yeast HMGB proteins are related, not only structurally but also as a functional group. **Table 2** summarizes GOTerm enrichment analysis among the components of this network and their statistical significances evaluated by false discovery rate (FDR) according to STRING analysis [120].

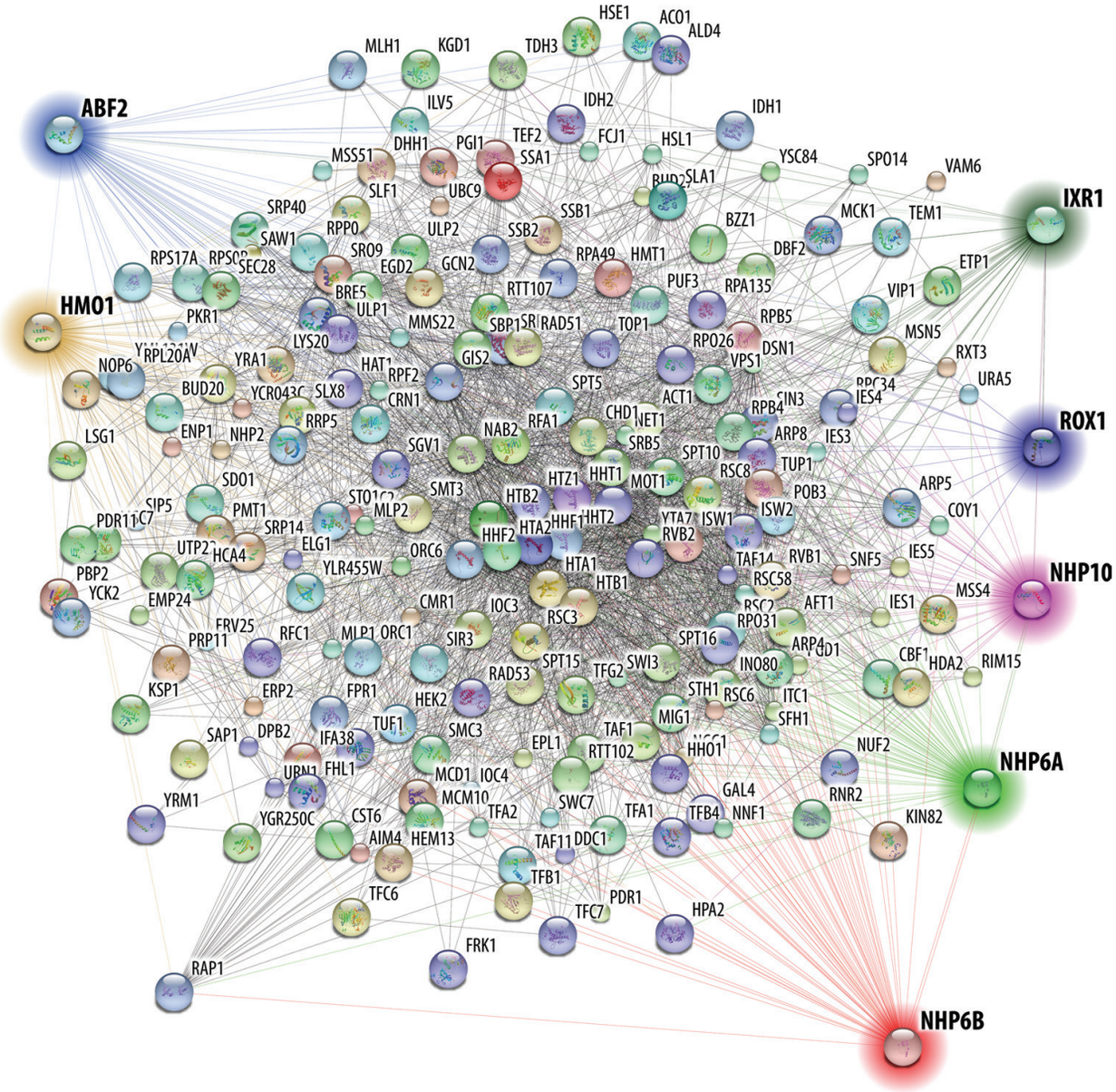

Figure 2. Network of yeast HMGB interactants according to STRING analysis.

References to the existence of interplay between the response to hypoxia, oxidative stress, and mitochondrial function have been reported, i.e., it is known that when cells experience hypoxia, up- or downregulation of an important number of oxygen-regulated genes in yeast depends on an active mitochondrial respiratory chain [38]. Treatment with antimycin A (respiration inhibitor) or oxygen deprivation cause downregulation of networks involved in the G1/S transition of the cell cycle as well as of those involved in energetically costly programs of ribosomal biogenesis and protein synthesis [37]. Similar regulation occurs in the response to DNA stress [39–41], and therefore, a wide gene-regulatory response might engage the functions of the HMGB proteins coordinately. **Figure 3** summarizes the participation of HMGB proteins from *S. cerevisiae* in functional responses against external (nutrient availability, oxidants, oxygen levels, DNA damaging agents) or internal (replicative stress) stressors.

Pathway ID	Biological function; pathway description	Observed gene count	False discovery rate
GO.0006325	Chromatin organization	50	4.50E-27
GO.0010468	Regulation of gene expression	81	5.85E-25
GO.0051171	Regulation of nitrogen compound metabolic process	84	5.85E-25
GO.0051276	Chromosome organization	63	5.85E-25
GO.0006355	Regulation of transcription, DNA-templated	71	3.30E-24
GO.0051252	Regulation of RNA metabolic process	72	3.30E-24
GO.0071824	Protein-DNA complex subunit organization	39	1.27E-22
GO.0043933	Macromolecular complex subunit organization	78	1.24E-21
GO.0090304	Nucleic acid metabolic process	95	1.53E-21
GO.0034728	Nucleosome organization	27	3.55E-21
GO.0006338	Chromatin remodeling	26	3.00E-20
GO.0006351	Transcription, DNA-templated	61	3.69E-19
GO.0006974	Cellular response to DNA damage stimulus	43	5.34E-19
GO.0006333	Chromatin assembly or disassembly	24	7.13E-19
GO.0006281	DNA repair	39	2.21E-18
GO.0016568	Chromatin modification	36	3.02E-18
GO.0006259	DNA metabolic process	47	1.11E-17
GO.0010467	Gene expression	82	1.39E-15
GO.0016070	RNA metabolic process	78	1.73E-15
GO.0006357	Regulation of transcription from RNA polymerase II promoter	45	8.94E-14
GO.0006323	DNA packaging	16	1.73E-11
GO.0006366	Transcription from RNA polymerase II promoter	29	1.99E-11
GO.0043044	ATP-dependent chromatin remodeling	14	5.72E-11
GO.0006950	Response to stress	54	6.10E-10
GO.0016458	Gene silencing	22	1.12E-09

Pathway ID	Biological function; pathway description	Observed gene count	False discovery rate
GO.0006354	DNA-templated transcription, elongation	16	1.21E-09
GO.0040029	Regulation of gene expression, epigenetic	23	1.75E-09
GO.0050896	Response to stimulus	67	3.76E-09
GO.0006342	Chromatin silencing	21	4.01E-09
GO.0071103	DNA conformation change	16	9.65E-08
GO.0016584	Nucleosome positioning	7	1.67E-07
GO.0007049	Cell cycle	49	2.67E-07
GO.0018193	Peptidyl-amino acid modification	18	5.44E-07
GO.0022607	Cellular component assembly	47	7.03E-07
GO.0065004	Protein-DNA complex assembly	17	9.19E-07
GO.1902589	Single-organism organelle organization	58	9.77E-07
GO.0042766	Nucleosome mobilization	7	9.81E-07
GO.0018205	Peptidyl-lysine modification	15	1.06E-06
GO.0022402	Cell cycle process	43	2.30E-06
GO.0006337	Nucleosome disassembly	8	2.35E-06
GO.0031498	Chromatin disassembly	8	2.35E-06
GO.0006368	Transcription elongation from RNA polymerase II promoter	12	2.40E-06
GO.0006302	Double-strand break repair	16	2.65E-06
GO.0098781	ncRNA transcription	12	4.52E-06
GO.0000122	Negative regulation of transcription from RNA polymerase II	19	7.75E-06
GO.0006383	Transcription from RNA polymerase III promoter	9	9.65E-06
GO.0000723	Telomere maintenance	12	4.18E-05
GO.0006360	Transcription from RNA polymerase I promoter	9	6.50E-05
GO.0009303	rRNA transcription	8	0.000151
GO.0016570	Histone modification	13	0.000222

Table 2. GOTerm enrichment in the interactome network depicted in **Figure 2**.

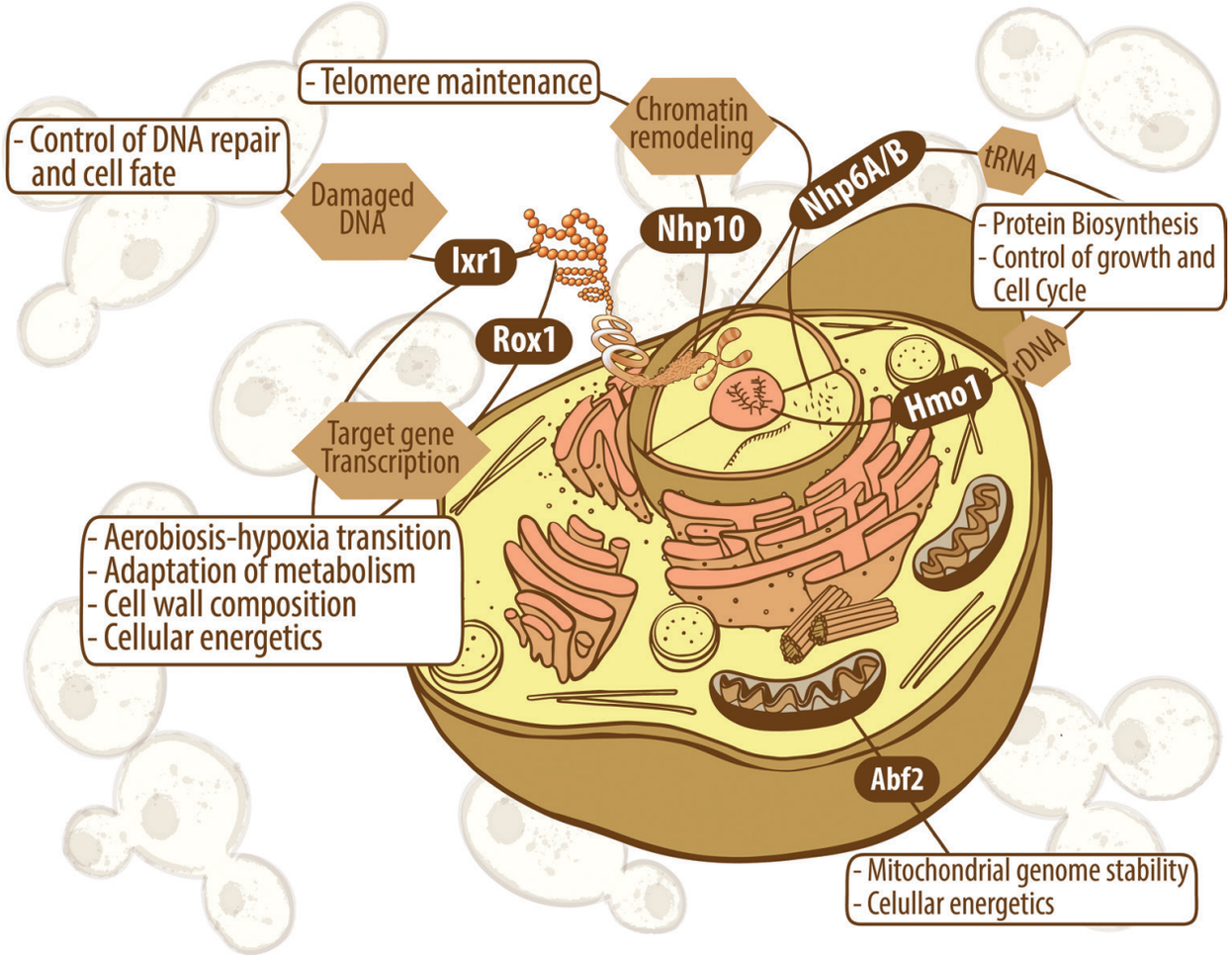

Figure 3. Orchestrated action of *S. cerevisiae* HMGB proteins in cellular responses to stress.

3. HMGB proteins from other yeasts

Although the complete sequences of a huge number of genomes from yeast and fungi are available, functional studies of HMGB proteins are not very frequent and only a few HMGB homologs have been characterized so far.

In *Yarrowia lipolytica*, YlMhb1, the homologous of Abf2 from *S. cerevisiae*, compacts mitochondrial DNA *in vitro*. Phenotypic analysis of a *mhb1Δ* strain reveals a large decrease in the mitochondrial DNA copy number and also shows that the protein protects the mitochondrial genome against mutagenic events. Like Abf2, YlMhb1 has two HMG-box domains [42]. In *Candida parapsilosis*, the homologous of Abf2 has been named Gcf1 and diverse experimental data support its role in the maintenance of the *C. parapsilosis* mitochondrial genome; in contrast to Abf2 and YlMhb1, Gcf1contains a coiled-coil domain and a single high-mobility HMG-box domain [43]. A similar structure is observed in *Candida albicans* [44].

In *C. albicans*, proteins with DNA-binding activity and high similarity to Nhp6 promote changes in chromatin structure, which are involved in hypha-specific gene regulation [45].

Regarding the Rox1 homolog in *Kluyveromyces lactis*, its molecular function, synteny, and HMG-box structural features were shown to be different from that of *S. cerevisiae* [46, 47]. The *KlROX1* gene from *K. lactis* does not regulate the hypoxic response in this yeast neither interacts with the components of the general corepressor factor (Tup1-Ssn6) that mediates the transcriptional repression exerted by Rox1 in *S. cerevisiae*. However, KlRox1 mediates the response to metals [47].

Although a low number of functional data is available, we may speculate that in yeasts the functions of "architectural" HMGB proteins are probably more conserved than those with functions as specific transcriptional factors. This is also predictable considering that transcriptional factors are among the proteins more strongly diverged between yeasts [48].

4. HMGB proteins in multicellular organisms

In multicellular eukaryotes, a large number of proteins contain HMG boxes, most of which are transcription factors that contain a single HMG-box [49], although some may have up to 6 HMG-box domains, like Ubf1 [50]. According to the classification from Bustin [7], "canonical" chromatin HMGB proteins represent a subgroup that invariably contains two in tandem HMG boxes. A model for the phylogenesis of HMGB genes in metazoan suggests that these two HMG boxes have their origin in the duplication of an ancient single HMG-box; even those which are part of HMG-box transcription factors might evolve from this ancestral ProtoBox [51].

Transcription factors (including SOX factors) are the most divergent group of HMG-box proteins in humans, whereas in plants the chromosomal HMGB-type proteins are most variable [52]. In plants, HMG-box proteins classify into four groups: HMGB-type proteins, structure-specific recognition protein 1 (SSRP1), proteins containing 3 HMG-box domains (3xHMG-box), and proteins that contain both an AT-rich interaction domain (ARID) and an HMG-box domain (ARID/HMG). These latter two groups are apparently specific for plants [52]. Conversely, HMG-box containing transcription factors such as Sry, a sex-determining factor that is necessary for testes development [53], Lef-1, which regulates gene expression during cell differentiation [54], and the SOX family are presumably not present in plants [52].

Table 3 resumes the homologies found between *S. cerevisiae* and human HMGB groups using the YeastMine facility "Yeast gene-human homolog(s)-Disease" (http://yeastmine.yeastgenome.org/yeastmine/begin.do accessed on date February 25, 2017) and completed with functional data from SGD (http://www.yeastgenome.org/) and associated human diseases. **Figure 4** summarizes the structural and phylogenetic relationships between several HMGB proteins from *S. cerevisiae* and their human homologs.

Yeast	*H. sapiens*	Associated human diseases
Rox1	Sox1	
	Sox10	Peripheral demyelinating neuropathy, central dysmyelination, Waardenburg syndrome, and Hirschsprung disease
	Sox11	Mental retardation, autosomal dominant 27
	Sox12	
	Sox13	
	Sox14	
	Sox15	
	Sox17	Vesicoureteral reflux
	Sox18	Hypotrichosis-lymphedema-telangiectasia-renal defect syndrome
	Sox2	Microphthalmia, syndromic 3
	Sox21	
	Sox3	Mental retardation, X-linked
	Sox30	
	Sox4	
	Sox5	
	Sox6	
	Sox7	
	Sox8	
	Sox9	Campomelic dysplasia
	Sry	46,Xx sex reversal 1
Ixr1	Hmg20a	
	Hmg20b	
	Smarce1	Susceptibility to familial meningioma
	Sp110	Susceptibility to *Mycobacterium tuberculosis*
	Sp140	
	Tfam	
	Ubtf	
	Ubtfl1	
Abf2	Tfam	
Hmo1	Hmg20a	
	Hmg20b	
	Smarce1	Susceptibility to familial meningioma
	Sp110	Susceptibility to *Mycobacterium tuberculosis*
	Sp140	
	Tfam	
	Ubtf	
	Ubtfl1	
Nhp6a/b	Hmg20a	
	Hmg20b	
	Hmgb1	
	Hmgb3	Microphthalmia, syndromic 13
	Smarce1	Susceptibility to familial meningioma
	Sp110	Susceptibility to *Mycobacterium tuberculosis*
	Sp140	
	Tfam	
	Ubtf	
	Ubtfl1	

Table 3. Human homologs to HMGB yeast proteins and associated diseases.

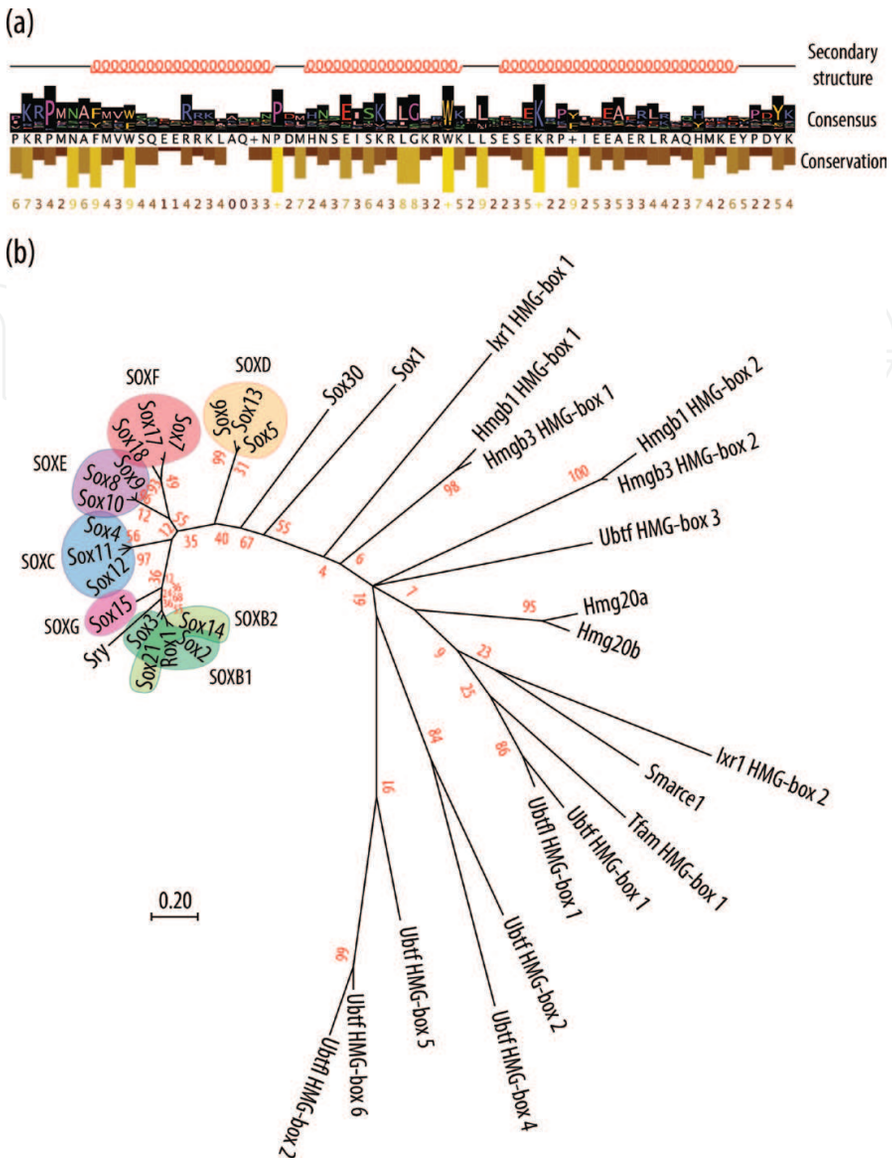

Figure 4. Molecular phylogenetic analysis of HMG-box domains by maximum likelihood method. (a) Characteristic HMG-box conservation. The evolutionary history was inferred by using the maximum likelihood method based on the JTT matrix-based model [118]. (b) The tree with the highest log likelihood (−3421.5683) is shown. Initial tree(s) for the heuristic search were obtained automatically by applying Neighbor-Join and BioNJ algorithms to a matrix of pairwise distances estimated using a JTT model, and then selecting the topology with superior log likelihood value. The tree is drawn to scale, with branch lengths measured in the number of substitutions per site. The analysis involved 39 amino acid sequences. All positions containing gaps and missing data were eliminated. There were a total of 63 positions in the final dataset. Evolutionary analyses were conducted in MEGA7 [119].

5. Mechanisms of transcriptional regulation mediated by HMGB proteins

5.1. Direct binding to target promoters

In *S. cerevisiae*, Rox1 is a DNA-binding protein with an HMG-box domain that binds to the consensus sequence YYYATTGTTCTC present in the promoter regions of genes related to hypoxia, causing a DNA bending of 90° in the double strand [55, 56]. Up to one-third of the *S. cerevisiae* hypoxic genes are transcriptionally repressed during aerobic growth by Rox1,

through the recruitment of the general corepressor complex Ssn6/Tup1 [14, 57]. In several promoters, this repression is synergic with the caused by regulator Mot3 [58]. *ROX1* expression is dependent of oxygen and heme levels in the cell, since its transcription is under the control of Hap1 [59], and therefore, it is induced aerobically [60]. In addition to aerobic upregulation produced by Hap1, the *ROX1* expression is counterbalanced by self-repression, to avoid cell toxic effects produced by an eventual overexpression. At low oxygen levels, the Rox1 protein levels rapidly decay by degradation, since it is labile in these conditions, and because the *ROX1* gene is no longer transcribed. Under normoxic (aerobic) conditions, the heme-activated Hap1 complex increases *ROX1* expression, allowing in turn Rox1 repression of hypoxic genes. In hypoxia, the situation is reversed, since the low levels of Rox1 allow derepression. The genes that are under the control of Rox1, either directly by the protein binding to their promoter regions, or indirectly through signal transduction pathways, are those related to efficient metabolism under low oxygen levels, ergosterol and heme synthesis, cell wall maintenance, or electron chain transport [61]. The genes repressed simultaneously by Mot3 and Rox1 preferentially encode proteins of the cell wall and plasma membrane; cell conjugation-related genes are negatively regulated by both factors and by osmotic stress [62]. During anaerobiosis, the histone deacetylase and global repressor complex Rpd3 act at the promoter of the anaerobic gene *DAN1* to antagonize the chromatin-mediated repression caused by Mot3 and Rox1 and chromatin remodeling by Swi/Snf is necessary for expression [63].

The first report about the participation of Ixr1 in the yeast hypoxic response was the aerobic repression of the *COX5B* gene, which encodes the hypoxic isoform of the subunit Vb of the mitochondrial complex cytochrome c oxidase [64]. Ixr1 also regulates other hypoxic genes like *TIR1*, a cell wall mannoprotein of the serine-alanine-rich protein family [65] and *HEM13*, which encodes the enzyme coproporphyrinogen III oxidase in the heme biosynthetic pathway [66]. The whole set of genes that are regulated by Ixr1 during the hypoxic response was determined in a genome-wide approach [67]. Hypoxic genes are also regulated by oxidative stress. Indeed, reactive oxygen species (ROS) induce expression of *CYC7* and *COX5B* through an Ixr1-independent mechanism that diminishes the access of Rox1 to its promoter targets [68].

A cross-regulation between Rox1 and Ixr1 in the yeast hypoxic response has been reported [66]. In aerobiosis, low levels of *IXR1* expression are maintained by Rox1 repression and during hypoxia Ixr1 auto-enhances *IXR1* expression [66]. Ixr1 is also required for hypoxic repression of *ROX1*. Binding to specific regions of the *ROX1, IXR1, HEM13*, and *TIR1* promoters were probed *in vitro* and *in vivo* [66, 69]. Ixr1 is also known by binding to cisplatin-DNA adducts with high affinity [70]. We have recently evidenced that functional specialization of the 2 HMG boxes, which are present in Ixr1, may explain its dual function. Regulation of transcription and DNA repair is achieved through differential recognition of specific regulatory sequences in the target promoters, or DNA disturbances caused by cisplatin treatment [15].

Rox1 from *S. cerevisiae* is homologous to the SOX family of transcriptional factors from human (**Table 2**) and other metazoan, from which SRY was the founding member. In vertebrates, there are more than 20 SOX genes characterized, which originate through a process of duplication and divergence [71], and they play important roles in tissue homeostasis, organogenesis, and cell fate decision during developmental processes (thoroughly reviewed by Ref. [72]).

For most mammals, SRY is the only member of the SOXA group [73]. SOXB1 group (SOX1, SOX2, and SOX3) participates in neural, lens, and ear development; SOXB2 group (SOX14 and SOX21) in neuronal differentiation SOXC group (SOX4, SOX11, and SOX12) in nervous system development and retinal differentiation; and SOXD group (SOX5, SOX6, and SOX13) in chondrocyte differentiation, cartilage formation, and neural development. SOXE group (SOX8, SOX9, and SOX10) is involved in primary sex determination and neural development, and SOXF group (SOX7, SOX17, and SOX18) in cardiac, vascular, and lymphatic development [72]. The SOXG group has only one member in mammals, and SOX15 involved in skeletal muscle regeneration [72, 74]. Besides, SOX4 and SOX11 are involved in tumorigenesis, and SOX7, SOX17, and SOX18 in endoderm development [72]. **Figure 5** summarizes the functions of these human SOX factors.

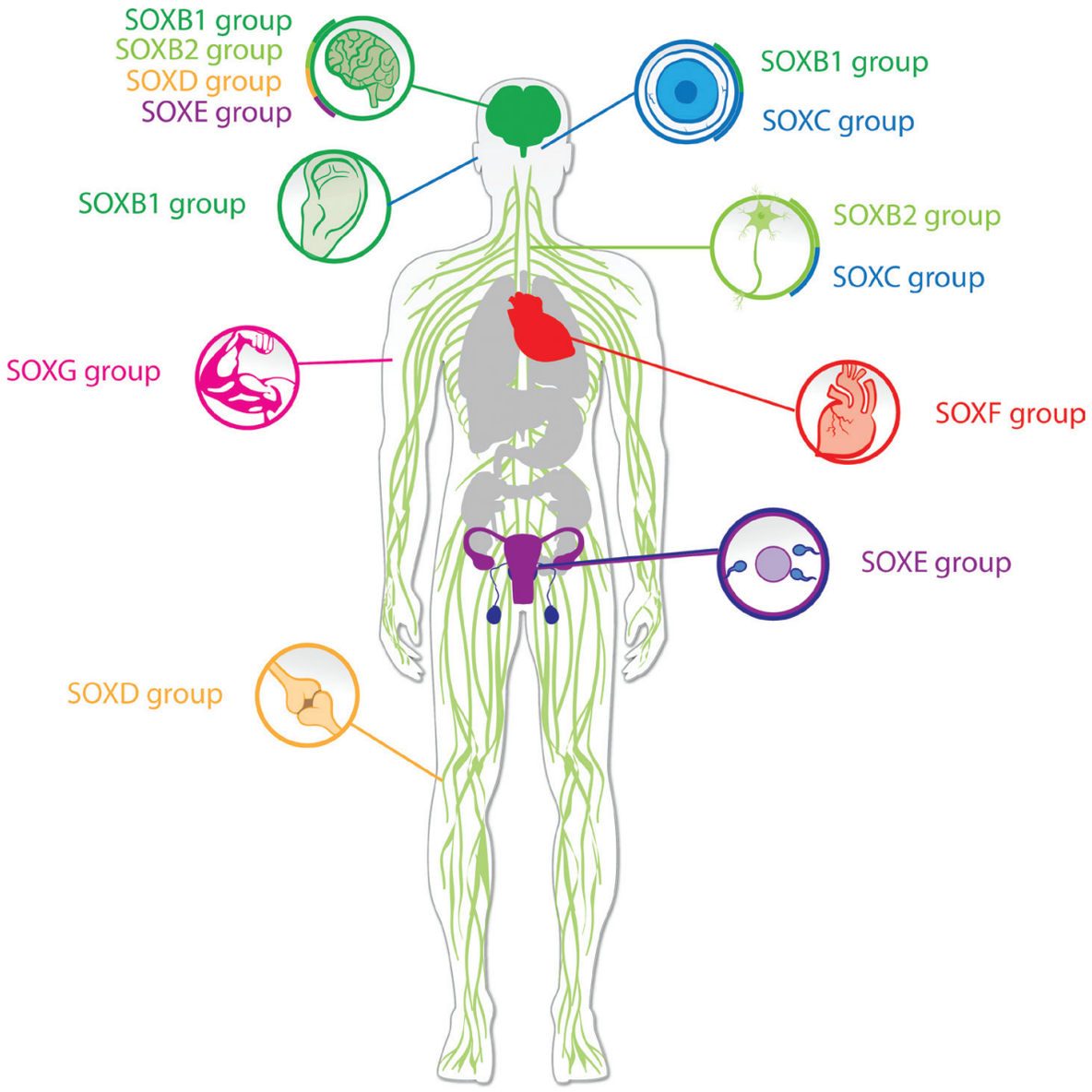

Figure 5. Functional groups of human SOX factors.

SOX proteins are highly dynamic regulators of cell functions due to their nucleocytoplasmic shuttling properties [75]. However, because of their low affinity for DNA binding, and despite SOX proteins usually have their own C-terminal activation/repression domain, they are committed to recruit partner proteins to fulfill their transcriptional regulatory task [76]. Homo- and heterodimerization of SOX proteins is also a mechanism used for the formation of these regulatory complexes [77]. SOX proteins also interact with signaling effectors, Wnt/β-catenin being one of the most studied signaling pathways [78]. Different molecular complexes of SOX factors and their partner proteins are formed along developmental processes. Besides, these specific interactions are usually dependent on posttranslational modifications of SOX proteins like phosphorylation, acetylation, SUMOylation, and ubiquitination [72].

5.2. Other mechanisms for transcriptional regulation

The HMGB proteins that are not classified as transcriptional factors also influence transcription by different mechanisms, which affect chromatin. Since these HMGB proteins are very dynamic in their interactions and have no DNA sequence specificity, they usually help transcription factors or cofactors to bind to their cognate sites by bending the DNA molecule, but are rarely retained within the formed complexes [79].

In plants, HMGB proteins contribute to transcriptional regulation by functional interaction with certain transcription factors like Dof2 [80]. In mammals, Hmgb1 alters the structure and stability of the canonical nucleosome in a nonenzymatic, ATP-independent way to facilitate strong binding of estrogen receptor to their regulatory elements [81].

HMGB proteins also interact with nucleosomes to promote their sliding or other chromatin remodeling processes [79]. Yeast Nhp6a, Nhp6b, and Hmo1 proteins stimulate the sliding activity of the yeast remodeler complex SWI/SNF, while octamer transfer and transient exposure of nucleosomal DNA catalyzed by this complex are only stimulated by Hmo1. Hmo1 also favors the sliding activity of the ISW1a complex [82].

Hmo1 in yeasts and the upstream binding factor (Ubf) in mammals function as cofactors in RNA polymerase I transcription and therefore are essential for transcription of the rRNA genes *in vivo*, but also have more generalized roles in chromatin structure. Binding of Ubf to human rRNA genes is accompanied by a reduction in core histone binding at the same sequences [83, 84], and a similar mechanism has been described for its ortholog Hmo1 in yeast [25]. Similarly, mammalian cells lacking Hmgb1 and yeast *nhp6* mutants contain a reduced amount of core, linker, and variant histones [85]. Consequently, the reduced number of nucleosomes produces a global increment of transcription and affects the relative expression of about 10% of genes [85].

Finally, HMGB proteins have been involved in the selection of modified histone variants. Studies carried out in mouse showed that conditional inactivation of Ubf is also accompanied by recruitment of H3K9me3, which reveals its function in the epigenetic control of gene expression [86].

6. Mechanisms of DNA repair mediated by HMGB proteins

The three HMG families (A, B, N) are involved in the four major DNA repair pathways. HMGB proteins contribute to nucleotide excision repair (NER), base excision repair (BER), double-strand break repair (DSBR), and mismatch repair (MMR), but with specific particularities (reviewed in Ref. [87]). The first report about participation of HMGB proteins in DNA repair was the identification of Hmgb1 binding to the major DNA lesions formed in cells treated with cisplatin, which are repaired by the NER pathway [88]. In general, the effects of HMGB proteins on DNA repair are achieved by different mechanisms. First, they contribute to modulate chromatin compaction and nucleosome occupancy; through interactions with chromatin-modifying enzymes and energy-dependent remodeling complexes, HMGB proteins favor or avoid the access of the repair machinery to altered DNA. Second, HMGB proteins can also regulate repair by direct modulation of the enzymatic activities and/or mechanistic steps implied in the diverse repair pathways. Third, acting as transcriptional regulators, HMGB proteins may change the expression levels of genes involved in DNA repair processes.

Hmgb1 and many other HMGB proteins (e.g., Ubf, Lef-1, Sry, and human mtTFA) inhibit NER [87]. If Hmgb1 binds first to a cisplatin adduct, the replication protein A (hRPA), necessary for NER repair, cannot displace it, thus potentially inhibiting repair [89]. On the contrary, Hmgb1 stimulates *in vitro* NER of triplex DNA interstrand crosslinks, caused by psoralen, by facilitating the interaction with components of this pathway [83, 90].

Hmgb1 coimmunoprecipitates with proteins from the BER pathway, including Ape1, Fen-1, and Pol-beta, and *in vitro*, modulates the deoxyribose phosphate lyase activity of Pol-beta [91].

Also *in vitro*, purified Hmgb1 binds to the ends of the double-strand breaks, similarly to the Ku proteins, and stimulates kinase and ligase activities required for DBSR of these lesions [92, 93]. Oppositely, in yeast, the HMGB protein Hmo1 must be evicted, along with core histones, for efficient DSBR [94].

Hmgb1 and Hmgb2 form part of a pentameric "damage-sensing" complex (also including heat shock protein 70, protein disulfide-isomerase Erp60, and glyceraldehyde3-phosphate dehydrogenase) specifically recruited to nonnatural nucleosides *in vivo* as part of the MMR pathway [95]. *In vitro*, Hmgb1 also interacts with the MMR proteins Msh2 and Mlh1 and cooperates with the replication protein A to mediate the exonuclease I activity that creates a gap, which is filled in by DNA polymerase, and finally, the broken strands are sealed by DNA ligase [96]. In yeast, following Nhp6a interaction to DNA, the mismatch repair complex Msh2-Msh6 is excluded from binding, unless a mismatch is present. *In vitro* the complex Msh2-Msh6-Nhp6a is stable and responsive to ATP on mismatched substrates [97].

Other important connection between Hmgb1 and DNA repair comes from the observation that this protein interacts with p53 *in vitro* and *in vivo*, stimulating p53 binding to sequence-specific recognition sites as well as to cisplatin-modified DNA [98, 99]. p53 directly impacts the activity of various DNA-repair systems, and besides, it halts cell cycle, thus allowing the repair machineries to restore genome stability [100].

7. HMGB proteins at the forefront of cutting-edge research

Recent publications on HMGB proteins reveal that these proteins are becoming a focus of interest due to their participation in cellular processes of great importance for humankind like epigenetic control of gene expression, aging, disease, or regenerative cellular therapies.

An interesting research field concerning HMGB proteins is their function replacing histones under specific conditions. In eukaryotic chromatin, histone H1 associates with the linker DNA in the nucleosome core particle to stabilize the higher-order chromatin structure and to modulate the ability of specific regulatory factors to access their final targets. It has been demonstrated that in *S. cerevisiae* Hmo1 might replace histone H1 and protect linker DNA from nuclease digestion, creating a less dynamic chromatin environment that depends on its lysine-rich domain. This lysine-rich extension is unusual in other HMGB proteins, which have an acidic domain instead [101, 102].

Environmental changes, sensed through signaling cascades, regulate chromatin organization, thus contributing to gene expression and, ultimately, cell adaptation to external stimulus. These responses are related to cell fate and aging. In yeast, the nutrient-dependent target-of-rapamycin complex 1 (TORC1) pathway and histone H3 collaborate to retain HMGB proteins within the nucleus, and in this way, they increase longevity [103].

The role of HMGB proteins remodeling chromatin on a genome-wide scale relates to the onset of several human diseases. Two chromatin structural proteins, CCCTC-binding factor (Ctcf) and high mobility group protein B2 (Hmgb2), regulate pathologic transcription in myocytes during heart disease [104]. The response of macrophages to inflammation starts by nucleosome loss and cell lacking Hmgb1 contains 20% less nucleosomes and has a specific transcription pattern. In a mouse model, unstimulated Hmgb1-/- macrophages activate transcriptional pathways associated with cell migration and chemotaxis. Wild-type macrophages, under lipopolysaccharide (LPS)/interferon (IFN)-γ exposure, rapidly secrete Hmgb1 and reduce their histone content [105].

Hmgb1 is overexpressed in many types of cancer, including those of etiology based on oxidative damage [8], and frequently, Hmgb1 expression increases with tumor stage and metastasis. In the pediatric acute lymphoblastic leukemia, autophagy is regarded as a mechanism that underlies chemoresistance. Since autophagy depends on the Hmgb1 translocation from nucleus to cytoplasm, this protein is a good target of study in order to overcome the problem [106]. It has been found that Hmgb1 expression is inversely correlated with semaphorin 3A expression, a suppressor of angiogenesis and cell migration. The epigenetic mechanism causing semaphorin 3A repression by Hmgb1 implies that it promotes heterochromatin formation and decreased occupancy of acetylated histones at the semaphorin 3A locus [107].

Other remarkable function of HMGB proteins, yet not fully understood, is their participation in telomere maintenance, studied in yeast [108] plants [109] and notoriously in animals [110], because of their implications in cancer development. The telomerase that conserves telomere structures is formed by a catalytic protein subunit (telomerase reverse transcriptase (TERT))

and an RNA subunit (telomerase RNA, TR), and both physically interact with Hmgb1 *in vitro*. Knockout of the HMGB1 gene in mouse embryonic fibroblasts (MEFs) causes chromosomal abnormalities, enhanced localization of γ-H2AX at telomeres, moderate shortening of telomere lengths, and lower telomerase activity compared to the wild-type cells. Oppositely, knockout of the HMGB2 gene elevates telomerase activity, which reveals the intricate interplay of these proteins in chromosome stability and cancer [110].

Evidences linking HMGB proteins with stem cell biology and cellular reprograming are also found. Sox factors participate in embryonic pluripotent cell differentiation; Oct4 interacts with Sox2 to maintain pluripotency or with Sox17 to promote endoderm commitment [111]. Expression of Hmgb2 changes notably at different time points during embryogenesis [112] and controls the differentiation of neural stem cells into neurons, astrocytes, and oligodendrocytes. Besides, several Sox factors [113, 114] and also chromatin HMGB proteins [115] are involved in back-reprograming differentiated cells into stem cells. Hmgb1 was also proposed as an efficient stem cell recruiter with tissue-regenerating roles; it was able to induce stem cell transmigration through an endothelial barrier or to capture in muscle the stem cells injected into the general circulation [116]. In murine and human mammary cancer stem cells, Hmgb1 promotes self-renewal of these cells [117], which are responsible for tumor progression, metastases, resistance to therapy, and tumor recurrence. Therefore, HMGB proteins are clues in the search of more effective cancer therapies and cellular regenerative treatments.

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