HMGA Proteins in Hematological Malignancies

Subjects: Oncology

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The high mobility group AT-Hook (HMGA) proteins are a family of nonhistone chromatin remodeling proteins known as “architectural transcriptional factors”. By binding the minor groove of AT-rich DNA sequences, they interact with the transcription apparatus, altering the chromatin modeling and regulating gene expression by either enhancing or suppressing the binding of the more usual transcriptional activators and repressors, although they do not themselves have any transcriptional activity. Their involvement in both benign and malignant neoplasias is well-known and supported by a large volume of studies.

Keywords: HMGA proteins ; hematologic malignancies ; molecular markers ; targeted therapy

1. Introduction

The high mobility group AT-Hook (HMGA) proteins are a family of nonhistone chromatin remodeling proteins regulating gene expression, known as “architectural transcriptional factors” [1][2][3][4]. The gene family comprises the *HMGA1* and *HMGA2* genes; the former is located on chromosome 6 (6p21), is about 10 kb large, and consists of eight exons [5]; the latter is located on chromosome 12 (12q14-15), is ≥160 kb in size, and consists of five exons [6]. Alternative splicing of the *HMGA1* gene produces three messenger RNA (mRNA) and three corresponding proteins, HMGA1a (formerly HMG-I), HMGA1b (formerly HMG-Y), and HMGA1c (formerly HMG-I/R) [7]. The HMGA1b isoform differs from the 1a isoform in that it lacks 11 amino acids; instead, the HMGA1c isoform is produced by alternative splicing of the *HMGA1* gene using noncanonical acceptor and donor sites. As regards HMGA2, recently, two isoforms (HMGA2-L and HMGA2-S*)* have been described for which expression seems to be confined to the hematopoietic compartment and to depend on the stage of development of the hematopoietic stem cell (HSC) (see below) [8].

Sequence alignment showed that HMGA2 has a homology of about 55% with HMGA1 (A and B isoforms), including AT-hooks that are located in separate exons [6]. The AT-hook motif is positively charged and consists of a stretch of nine amino acids, containing the Arg-Gly-Arg-Pro repetition. This motif allows the protein to recognize and bind the AT-rich sequences in the minor groove of B-form DNA, rendering it able to recognize a structure rather than a specific sequence [9], so that some data report the ability of the HMGA1 protein to bind DNA even in regions without a rich AT content [10][11][12]. Once bound to DNA, the AT-hook undergoes a conformational change [13], and simultaneous binding of two or more AT-hooks to different binding sites leads to an increase in the strength of HMGA interactions with DNA [14].

By binding the minor groove of AT-rich DNA sequences, HMGA proteins interact with the transcription apparatus, altering the chromatin modeling and regulating gene expression by either enhancing or suppressing the binding of the more usual transcriptional activators and repressors, although they do not themselves have any transcriptional activity [15][16][17][18]. Their function is critical for the formation of higher-order nucleoprotein complexes (called enhanceosomes) in the promoter region, allowing the efficient transcriptional activation of a gene [19] thanks to their multiple surfaces capable of protein–protein interactions. Through such interactions, HMGA proteins may directly or indirectly control transcription, inducing conformational changes in chromatin or in the transcription factors themselves. In such ways, HMGA proteins are able to influence a wide variety of normal biological processes, such as cell growth, proliferation, differentiation, and death. They show an active role in the division cycle, and data indicate that both histone H1 and HMGA1 are necessary for chromatin condensation [20][21][22][23][24].

HMGA1 and 2 display different target genes; for example, the *BRCA1* gene is negatively regulated by HMGA1 but not by HMGA2 [25]. Instead, HMGA2 has several other targets, including cycle regulators, one of which is the *CDKN2A* gene, encoding the two proteins p16INK4A and p14ARF. With the RNA-binding proteins LIN28A/B and the microRNA (miRNA) *let-7b*, HMGA2 and CDKN2A form an axis that controls stem cell aging in both normal and pathological conditions [22][23][24].

2. HMGA Proteins in Oncology

HMGA expression seems to be ubiquitous and high during embryogenesis and null or hardly detectable in adult differentiated tissues [26][27][28][29][30]. Several studies demonstrated the involvement of these proteins in embryonic development [31], adipocytes cell growth, and differentiation. Mice lacking the *HMGA2* gene showed a pygmy phenotype with a drastic reduction of fat tissue [32]; instead, HMGA2 overexpression results in giant, obese mice [33]. On the contrary, HMGA1 inhibits adipocytes cell growth and triggers differentiation [34].

Overexpression of both genes is observed in most human malignant neoplasias, linking their alteration to carcinogenesis [35][36][37][38][39], while blocking their expression prevents thyroid cell transformation and triggers the death of malignant cells [40][41][42][43][44][45][46][47][48][49]. Various in vitro and in vivo studies have demonstrated the oncogenic potential of HMGA proteins; their overexpression transforms mouse and rat fibroblasts [50][51], and in transgenic mice, the development of natural killer T-cell lymphomas and pituitary adenomas has been observed [52][53][54][55]. There are high expression levels of *HMGA* transcripts in embryonic stem (ES) cells [56][57], HSCs [58][59][60], leukemic stem cells, and poorly differentiated or refractory tumors [61][62][63][64][65][66]. In cultured human lymphoid cells, the ectopic expression of HMGA1a triggers leukemic transformation [67] and, in transgenic mice, the development of an aggressive T-cell lymphoid neoplasia [68][69]. In particular, *HMGA1* is overexpressed in several high-grade or refractory neoplasias, including hematologic malignancies and solid tumors [70]. Indeed, HMGA1 proteins are the most abundant nonhistone, chromatin-binding proteins in tumor cells .

romosomal duplications or translocations cause HMGA1 overexpression in rare cases; more frequently, the translocations involve *HMGA2* (chromosomal region 12q14-15) in benign tumors, such as lipomas [71] and uterine fibroids [72][73][74]. With Fluorescent in Situ Hybridization (FISH) analysis, it has been observed that, in most cases, the breakpoint in the *HMGA2* locus involves exons 1-2 or 1-3, leading to the loss of the C-terminal tail [75], separating the DNA-binding domains from the acid tails, and merging them with ectopic sequences. This seems to be sufficient for tumor development. Further studies revealed the presence of multiple binding sites for miRNA *let-7* in the 3'-Untranslated Region (3'-UTR) of *HMGA2* [76]. This evidence corroborates the observation that, in tumors with rearrangements destroying 3'-UTR of *HMGA2*, there were increased levels of the intact protein [77][78]; this suggests the presence of functional sites for the binding of miRNAs (such as *let-7*, *mir-98*, and *miR-33*) [79][65][66][78][79][65][66][80][81][82][83][84][85][86] that are important in regulating the gene expression.

A large volume of data demonstrates that miRNA dysregulation may intervene in tumor development [87][88]. Cancers exhibit distinctive miRNA expression signatures, raising the speculation that a dysregulation of specific pathways intervenes in tumorigenesis mechanisms in a specific tissue [89][90][91].

The repression of *let-7* is necessary to enhance cell proliferation; in fact, *let-7* expression is inversely related to the expression of HMGA2. This finding supports the hypothesis that *let-7* can act as a repressor of HMGA2 [92].

3. HMGA Proteins in Hematopoiesis

In the hematologic field, HMGA proteins seem to play a pivotal role in both physiological and pathogenic conditions.

The loss of HMGA2 in HSCs does not allow a correct fetal hematopoietic process, causing slower self-renewal and proliferation rates, while it seems not to be indispensable in adult hematopoiesis [93]. Indeed, in 2013, in mouse models, Copley et al. demonstrated that the fine equilibrium between levels of the RNA-binding protein LIN28B and *let-7* strikingly influence HSC developmentally timed changes, observing that HSC self-renewal potentials reduced when LIN28B decreased and *let-7* increased [93]. As *HMGA2* expression is high during embryogenesis, being particularly upregulated in fetal HSCs and gradually decreasing during the transition to adult hematopoiesis, experiments in transplanted irradiated hosts to define the role of HMGA2 and LIN28 in HSC functions showed that both LIN28- and HMGA2-induced overexpression increased the self-renewal activity of adult HSCs. However, HMGA2 overexpression in adult HSCs did not seem sufficient to mimic all the effects of elevated LIN28B that triggers a fetal lymphoid differentiation program. Accordingly, *HMGA2* seems to be a downstream modulator of the HSC self-renewal ability; its function is regulated by LIN28B, that acts as a master regulator of developmentally timed changes of HSC [93]. However, this regulatory mechanism seems to be even finer tuned. In a recent work, Cesana et al. employed high-throughput genomic approaches to profile miRNAs, long intergenic non coding RNAs (lincRNAs), and mRNAs in HSCs during development in order to characterize transcriptional and posttranscriptional changes. These analyses highlighted distinct alternative splicing patterns of HSCs in various key hematopoietic regulators, one of which is HMGA2, for which an alternative isoform, escaping miRNA-mediated control, was identified. It seems that the splicing kinase CLK3 conserves HMGA2 function in response to an increase of *let-7* miRNA levels by regulating HMGA2 splicing. These data delineate a CLK3/HMGA2

functional axis regulating HSC functions during development. In humans, *HMGA2* presents alternative splicing isoforms, *HMGA2-L*, which is sensitive to degradation by *let-7*, being the dominant isoform in fetal HSCs, whereas newborn HSCs express the *HMGA2-S* isoform, that is resistant to degradation by *let-7* (Figure 1). In support of the crucial role of HMGA2 in regulating HSCs properties, it has been found in gene therapy experiments that a deliberate overexpression of *HMGA2*, in parallel with that of the transgene of interest, might be needed to obtain the therapeutic effect [94][95], particularly in cases where a large fraction of corrected HSCs must be obtained to gain the benefit. In the case reported in 2010 by Cavazzana et al. of an adult patient with severe βE/β0-thalassaemia treated with gene therapy, the presence of a dominant, myeloid-biased cell clone was demonstrated, in which the integrated vector transferring the β-globin gene caused the transcriptional activation of *HMGA2* in erythroid cells and further increased the expression of a truncated *HMGA2* mRNA insensitive to degradation by *let-7* miRNAs [94].

There is evidence in mice that Hmga2 is also a regulator of gamma-globin mRNA, and that it moderately increased HbF levels in human adult erythroblasts in vitro [96]. Targeted inhibition of *let-7* is sufficient for specific developmental changes to occur in gamma-globin transcription and HbF levels through increased *HMGA2* levels [97].

As regards the LIN28B-*let7*-HMGA2 axis, it is also involved in the megakaryocyte and platelet lineage. LIN28B expression in fetal myelo-erythroid progenitors suggests that it could have a role in the prenatal platelet-forming lineages; indeed, megakaryocytes derived from human ES cells express higher levels of LIN28B as compared to adult controls [98]. This implies that LIN28B may also have an active function in megakaryocyte development and thus platelet function [99].

In vitro experiments on ES cells lacking one or both *HMGA1* alleles showed that these cells showed a lesser differentiation in T-cell precursors than Wild Type (WT) ES cells and preferentially in B cells, maybe because of an increased interleukin 6 and decreased interleukin 2 expression [100]. Furthermore, there was evidence of an aberrant hemopoietic differentiation, with a reduction of the monocyte/macrophage population and an increase in megakaryocyte precursors, erythropoiesis, and globin gene expression. The restoration of *HMGA1* expression reestablished the WT phenotype. These studies highlighted that HMGA1 proteins directly control the transcription of GATA-1, a key transcription factor which regulates red blood cell differentiation, that is overexpressed in *HMGA1*−/− ES cells. This could offer an explanation, at least in part, of the alteration of the lineages of megakaryocytes/erythrocytes [100]. These observations add weight to those of Pierantoni et al., who observed that the induction of HMGA1 protein synthesis appears to play a role in the differentiation of megakaryocytes while its inhibition may be necessary in the differentiation of erythrocytes or macrophages [101].

Regarding lymphoid compartment, animal experiments showed HMGA2 involvement in mouse thymopoiesis, as it is highly expressed in fetal and neonatal early T cell progenitors (ETP), the most intrathymic precursors, while it results almost undetectable 5 weeks after birth [102]. In the same way, the number of thymic cells increases during the first two weeks after birth, stabilizes, and then declines by seven weeks of age. In fact, HMGA2-deficient mice showed deficient ETPs after birth, and also the total thymocyte number was fewer as compared to WT. Bearing in mind that, also in human fetal thymic progenitors, HMGA2 expression is high and decreases during growth, it is possible that a similar mechanism takes place [102].

As regards HMGA1, studies using HMGA1-green fluorescent protein fusion explored HMGA1 expression in undifferentiated and differentiated populations of hematopoietic cells, demonstrating that HMGA1 is highly expressed in CD4/CD8-double negative (DN) cells and transiently downregulated in CD4⁄CD8-double positive (DP) cells during early T cell development in the thymus [103]. Indeed, HMGA1 binds directly to cis-regulatory elements in the *CD4*⁄*CD8* loci in DN cells but not in DP cells. Moreover, in DN leukemic cells, CD4⁄CD8 expression is induced by the inhibition of HMGA1, and T leukemic cells lacking HMGA1 showed a markedly decreased proliferation [103].

HMGA1 indirectly controls *μ* enhancer activity during B lymphocyte development, acting on the combinatorial activity of transcription factors [104][105][106][107]. Various studies revealed that HMGA1 interacts with both PU.1 and ETS proto-oncogene 1 transcription factor 1 (Ets-1) in solution [108][109]; MGA1 interaction with PU.1 likely induces a change in PU.1 structure, increasing PU.1/*μ* enhancer binding. This augmented binding renders HMGA1 able to boost PU.1/Ets-1 functional synergy on the *μ* enhancer [110].

In view of the role of HMGA proteins in driving both benign and malignant tumors and the evidence regarding their main functions in various hematopoietic physiological mechanisms, various research studies have explored their involvement in hematological malignancies.

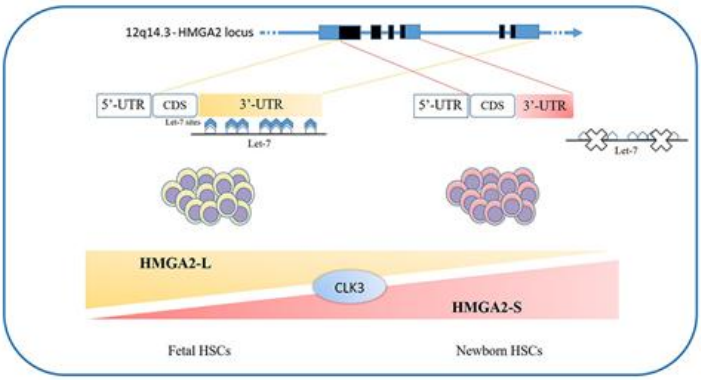

Figure 1. *HMGA2* development-specific isoforms: HSCs feature distinct alternative splicing patterns in various key hematopoietic regulators, one of which is HMGA2. In humans, two alternative splicing isoforms have recently been discovered: the *HMGA2-L* isoform, which is sensitive to degradation by *let-7* and is dominant in fetal HSCs, and the *HMGA2-S* isoform, that is resistant to degradation by *let-7* and is prevalent in newborn HSCs. The two isoforms reveal alternative 3'UTR usage; they share the first three exons and differ in their terminal exon usage (including C-terminal domains and 3'UTRs). The *HMGA2-S* 3'UTR is one third the length of the *HMGA2-L* 3'UTR and lacks the seven *let-7* sites as well as the other most conserved miRNA sites. The balance between alternative isoforms and the escape from miRNA-mediated control seems to depend on the activity of the splicing kinase CLK3, which promotes exon skipping and thus influences the *HMGA2* splicing pattern. HSCs - hematopoietic stem cells; 3'UTR - 3'-Untranslated Region.[111]

4. HMGA Proteins as Targetable Markers

In view of their role in carcinogenesis, HMGA proteins could be suitable candidates for molecular therapy against HMGA-overexpressing cancers. As they bind AT-specific minor grooves of DNA, their binding could be inhibited by other DNA minor groove binders/ligands, such as distamycin and netropsin [112], that have been studied as potential new therapies for several types of human cancer [113].

The search for HMGA1 inhibitors is ongoing. Despite toxicity issues that still need to be addressed, promising preliminary data have been obtained for flavopiridol and FR900482 [114].

A series of studies explored the use of STAT3 as a targetable marker in aggressive lymphoid malignancies overexpressing HMGA1. Nanoparticle delivery of STAT3 with G-quartet oligodeoxynucleotides that specifically inhibit STAT3 binding to DNA has been shown to have antileukemia effects in an HMGA1 transgenic model of aggressive T-ALL [115]. Indeed, BP-1-102, a salicylic acid-based inhibitor, was tested in preclinical models of ALL and Burkitts lymphoma with STAT3 activation [116], demonstrating that BP-1-102 inhibits STAT3 phosphorylation at tyrosine 705, preventing STAT3 dimerization, DNA binding, and the activation of downstream genes. It also decreases nuclear and cytoplasmic phosphorylated STAT3. Further treatment of cultured cells derived from B-lymphoid tumors previously shown to express high levels of HMGA1 and STAT3, including B-ALL, Burkitts leukemia, and T-ALL cells, showed a decreased proliferation [117]. However, there was no antitumor efficacy in murine xenograft models; the reason for this is still uncertain and may lie either in the limited exposure to the drug or in the induction of oncogenic pathways alternative to the one inhibited by BP-1-102[117]. These experiments also helped to show that BP-1-102 treatment represses HMGA1, highlighting that not only does HMGA1 induce STAT3 expression but even STAT3 feeds forward to upregulate HMGA1, leading to an enhanced expression of both genes during tumor progression. In fact, a putative STAT3 consensus DNA binding site (TTN5AA) was found in the *HMGA1* promoter region; it is conserved in humans and mice and could mediate STAT3 dimer binding and transactivation. In conjunction with direct transactivation, STAT3 could induce downstream factors that upregulate *HMGA1* expression [117].

Furthermore, Bortezomib (BTZ) also seems to influence HMGA1 levels. This is a proteasome inhibitor used to suppress Diffuse large B-cell lymphoma (DLBCL) progression [118][119][120]. DLBCL is the most frequent non-Hodgkin lymphoma, showing variable clinical presentations as well as variable therapy responses [121][122][123]. In vitro studies on DLBCL CRL-2630 cells showed that BTZ treatment significantly inhibited the proliferation of DLBCL CRL-2630 cells [124]. After studies showing that exposure to BTZ induced an upregulation of *miRNA 198* (*miR-198*) while depletion of the miR significantly reversed the inhibitory effect of BTZ on cell proliferation [125], further studies on *miR-198* revealed the 3'-UTR of *HMGA1* as a downstream target of *miR-198*, suppressing the expression of *HMGA1* in DLBCL cells. This evidence links HMGA1 to BTZ treatment that decreased the level of HMAG1 and inhibited the migration of DLBCL cells [126][127][128].

Indeed, a recent screening of about 36,000 compounds indicated a class of phosphodiesterase inhibitors that help to suppress *let-7* targets [129]. These potential drugs augment cAMP levels and elevate *let-7* levels, inhibiting *let-7* target genes such as *HMGA2* and *MYC* and decreasing growth in multiple cancer cell lines [129].

In the treatment of CML patients, the introduction of specific tyrosine kinase inhibitors (TKI) has promoted great progress in patient management [130][131]. Several TKIs are currently enrolled in common practice (such as imatinib, nilotinib, and dasatinib), the use of which is strictly related to adverse events and to the observation of resistance phenomena developing during therapy [132][133]. These issues increase the need to devise alternative therapies; in recent years, studies on the use of epigenetic therapy associated with other therapies have seemed to offer valid therapeutic tools[134]. In this regard, the Vitkeviciene team investigated the potential role of two epigenetic modulators, EGCG (epigallocatechin-3-gallate) and BIX-01294 (1-benzylpiperidin-4-yl)-6,7-dimethoxy-2-(4-methyl-1,4-diazepan-1-yl) quinazolin-4-amine) in two AML and CML cell lines [135].

EGCG is a naturally occurring catechin in green tea. This molecule is known to have many functions, including antibacterial, antioxidant, and anti-inflammatory actions, but it also seems to have a potential antineoplastic role, inhibiting proliferation and inducing apoptosis in different tumors [136][137]. BIX-01294 is a synthetic molecule that allows the specific inhibition of EHMT2/G9a histone methyltransferase. EHMT2/G9a is an important protagonist of gene silencing mechanisms[138] [139]. A study in vitro showed that EGCG and BIX-01294, acting as epigenetic modulators, cause cell cycle arrest in the G0/G1 phase; the lines treated with EGCG also showed an increased level of ATM, HMGA2, phosphorylation of ATM, and Senescence-associated (SA)-β-galactosidase staining, for which concerted action favors the cellular senescence phenomenon [135]. Although apoptosis as compared to the induction of senescence is believed to be more effective in the treatment of cancer, the use of substances capable of inducing senescence offers a great advantage in terms of therapy planning [140].

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