Critical role of the high mobility group A proteins in hematological malignancies

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Funding information
Open Access Funding provided by Consiglio Nazionale delle Ricerche within the CRUI-CARE Agreement.

Abstract
The high mobility group A (HMGA) protein family is composed of three non-histone chromatin remodeling proteins that act as architectural transcriptional factors. Indeed, although HMGA proteins lack transcriptional activity per se, they bind the minor groove of DNA at AT-rich sequences, and, interacting with the transcription machinery, are able to modify chromatin modeling, thus regulating the expression of several genes. HMGA proteins have been deeply involved in embryogenesis process, and a large volume of studies has pointed out their key role in human cancer. Here, we review the studies on the role of the HMGA proteins in human hematological malignancies: they are overexpressed in most of the cases and their expression correlates with a reduced survival. In some cases, such as in acute lymphoblastic leukemia and acute myelogenous leukemia, HMGA2 gene rearrangements have been also described. Finally, recent studies evidence a synergism between HMGA and EZH2 in diffuse B-cell lymphomas, suggesting an innovative therapy for this disease based on the inhibition of the function of both these proteins.

KEYWORDS
EZH2, hematological malignancies, HMGA1, HMGA1 pseudogenes, HMGA2

1 | INTRODUCTION

1.1 | The high mobility group A proteins in benign and malignant neoplasias

The high mobility group A (HMGA) protein group is composed of three proteins: HMGA1a and HMGA1b that are generated from the same gene via alternative splicing, and HMGA2 encoded by the homonym gene. The HMGA1 gene is located on the chromosome band 6p21, whereas HMGA2 lies on the chromosome band 12q13-15. HMGA are non-histone nuclear proteins able to bind AT-rich regions in the minor groove of DNA through their three basic AT-hook domains. Although HMGA proteins do not have an “intrinsic” transcriptional activity, they can regulate the expression of several genes, acting as architectural proteins.¹⁻³ These proteins exert their physiologic role mainly during the embryogenic development, where they are strongly expressed, whereas their expression is low or absent in normal adult tissues. However, HMGA are expressed at high levels in experimental and human malignancies.³,⁴ Indeed, their overexpression is mainly associated with a highly malignant phenotype, also representing a poor prognostic index since HMGA overexpression often correlates with the presence of metastases, and with a reduced survival in several neoplasias, such as colon, breast, thyroid, esophageal, and larynx carcinomas.³,⁵⁻⁷

Many studies indicate that high levels of HMGA expression have a causal relation to the development of a malignant phenotype. In
fact, the suppression of HMGA expression through the transfection of HMGA antisense cDNA constructs in thyroid cells prevents cell malignant transformation after infection of the same cells with murine transforming retroviruses. Consistently, HMGA1 silencing induces apoptotic cell death in human carcinoma cell lines, but not in normal ones. Noteworthy, HMGA are involved, even though with different mechanisms, in benign tumors. Indeed, HMGA2 gene rearrangements, following chromosomal translocations of the region 12q13–15, where the HMGA2 gene is located, have been often associated with benign tumors of mesenchymal origin, such as uterine leiomyomas, lipomas, and lung hamartomas. In the vast majority of the human benign tumors, chromosomal breaks are found in the third intron of this gene, giving rise to chimeric transcripts embracing the first three HMGA2 exons (encoding the AT-hook domains) and ectopic sequences from other genes. Consistently, the truncated form of HMGA2 is able to transform NIH3T3 cells, and transgenic mice overexpressing both truncated or wild type HMGA2 are characterized by the development of benign tumors.

Chromosomal alterations involving the 6p21.3 region, where the HMGA1 gene is located, have been also reported in benign neoplasias.

The HMGA overexpression contributes to cancer development through several mechanisms that include (a) regulation of genomic stability; (b) modulation of autophagy; (c) induction of AP-1 activity; (d) stemness regulation; (e) regulation of p53 expression and function; (f) cell cycle regulation; (g) induction of chemoresistance (Figure 1).

1.2 Modulation of HMGA expression: role of microRNAs and HMGA1 pseudogenes

Although several studies have assessed that HMGA overexpression is a feature of human cancer, the molecular mechanisms that control HMGA levels remain largely unexplored. In the last decade, a novel class of molecules, the microRNA (miRNAs), emerges as key regulator of gene expression at post-transcriptional level. miRNAs are small RNA fragments (19-25nt) that are able to bind the 3’ untranslated region (UTR) of several transcripts, leading to mRNA degradation or inhibition of protein translation. Interestingly, several studies reported that the HMGA expression levels are strongly regulated by miRNAs in human cancer, such as pituitary adenomas (mir-15, mir-16, mir-34b, mir-214, and mir-761), thyroid carcinomas, and seminomas (Let-7). Furthermore, chromosomal rearrangements that lead to the loss of HMGA2 3’UTR have been reported in mesenchymal benign tumors, thus abrogating the repression exerted by several miRNAs on this gene, and then inducing its overexpression.

It has been recently found that HMGA1 expression levels are post-transcriptionally regulated by its pseudogenes. Indeed, eight HMGA1 pseudogenes have been identified in human genome. The most characterized HMGA1-pseudogenes are HMGA1P6 and HMGA1P7. They differ from HMGA1 just for few mismatches located in its coding and non-coding sequences (5’ and 3’UTRs of the HMGA1 gene). Consequently, they share target regions for miRNAs that have been already validated to target HMGA1 and other cancer-related genes, such as HMGA2, EZH2, and VEGF, then enhancing their expression through a competitive endogenous RNA (ceRNA) mechanism. Consistently, HMGA1P6 and HMGA1P7 overexpression increases cell migration, invasiveness, and proliferation. Interestingly, their expression has been found drastically upregulated in several human cancers types.

The HMGA1P1, HMGA1P2, and HMGA1P3, although classified as pseudogenes, may represent a sort of competitor proteins for HMGA1 wild-type with different post-translational modifications, since bioinformatic analyses revealed that no point mutations affect the translation capability. Moreover, another HMGA1-pseudogene,
Acute myelogenous leukemia (AML) and chronic myelogenous leukemia (CML) represent the main types of myelogenous leukemia. AML is the most frequent leukemia in adults, with about 30% of new diagnoses. Myeloid leukemia derives from the block of the differentiation and the accumulation of the granulocytic and monocytic blasts. The main treatment is based on Cytarabine and anthracyclines, but, unfortunately, the vast majority of patients relapses and long-term survival is very low. CML is a myeloproliferative disease that consists in the clonal expansion of hematological progenitor cells. CML occurrence is deeply associated with a peculiar chromosomal translocation t(9;22)–(q34;q11), the so-called Philadelphia chromosome, where a chimeric tyrosine-kinase (BCR-ABL) protein is generated, leading to the deregulation of cell growth pathways. Thus, the improved knowledge of CML molecular biology brought the development of the first targeted therapy for a human neoplasia, which specifically blocks the altered kinase activity of the chimeric BCR-ABL protein.

Several studies have underlined the role of HMG2 in myeloid malignancies. Indeed, Odero and colleagues reported several cytogenetic alterations of 12q13-15 chromosomal region in six myeloid neoplasia cases. In all the analyzed cases, the cytogenetic abnormalities induced HMG2 overexpression, suggesting the important function played by HMG2 in myeloid neoplasms.

Subsequently, the relation between HMG2 and homeobox A9 (HOXA9) genes in the regulation of myeloid leukemia cell differentiation has been investigated. Indeed, HOXA9 has been found upregulated in about 70% of AML patients and its role in the differentiation blockage of immature leukemic blasts has been also reported. Conversely, HMG2 silencing experiments led to monocytic–granulocytic differentiation of myeloid leukemia cell lines and also of primary cells, where the HMG2 knockdown increases CD11b positive population. Interestingly, it has been shown that HMG2 silencing decreases HOXA9 expression levels, thus suggesting its positive regulation by HMG2.

Intriguingly, it has been demonstrated that genomic mutations of the transcription factor Runx-related transcription factor 1 (RUNX1) increase self-renewal capability, halting granulocytic differentiation in human leukemia models by deregulating HMG2 expression. Moreover, mice knocked-out for the RUNX1 gene showed an accumulation of both myeloid and granulocyte-macrophage progenitors, and that this phenotype was reverted through the inactivation of Hmg2 gene, underlining that HMG2 is a transcriptional target of RUNX1 and critical regulator of differentiation and expansion of myeloid lineage.

Consistently, HMG2 has been found deeply involved in several molecular pathways that drive leukemogenesis process and resistance to therapeutic approaches. Indeed, HMG2 was overexpressed in subsets of human AML samples mainly due to chromosomal rearrangements. Moreover, the HMG2 overexpression was especially high in patients without remission, and, noteworthy, the low HMG2- and high HMG2-expression levels significantly correlated with the remission rates after therapy. In agreement with these results, the silencing of HMG2 in several AML-derived cell lines led to increased cell viability and growth inhibition. Interestingly, Tan et al. reported that HMG2 silencing was also able to inhibit PI3K/Akt signaling pathway and cell proliferation by decreasing mTOR expression levels. Furthermore, it has been recently reported that HMG2 is able to modulate daunorubicin (DNR) sensitivity, an anthracycline-based chemotherapy drug used in the vast majority of first-line standard therapeutic protocols, in AML cells. Therefore, HMG2 silencing was able to increase the DNR effects on AML cells, whereas HMG2 overexpressing experiments gave opposite results. These findings are in agreement with previous studies reporting that the modulation of HMG2 is able to regulate chemoresistance in several cancer types.

The role of HMG protein overexpression in leukemia progression was also supported by the analysis of survival data of 430 AML patients correlated with HMG2 expression, indicating HMG2 overexpression as a powerful prognostic marker in AML. Indeed, increased HMG2 expression levels correlated with a lower rate of complete remission, a worse 3-year overall survival and relapse-free survival. Moreover, high HMG2 expression levels were
significantly correlated with the probability of the treatment failure of the primary anthracycline and cytarabine therapies. Notably, a HMGA2 test based on qRT-PCR analysis has been developed showing high reproducibility, specificity, and may represent also a potential cost reduction for AML diagnosis/prognosis processes. Therefore, the high expression of HMGA2 may represent an important novel prognostic marker, complementing the current AML clinical and genetic prognostic factors.

1.4.2 | HMGA genes in lymphocytic leukemias

Lymphocytic leukemias may be divided in two main groups: acute lymphoblastic leukemia (ALL) and chronic lymphocytic leukemia (CLL).

ALL derives from the lymphoid line of blood cells and is characterized by the hyperproduction of immature lymphocytes. ALL represents the most frequent form of childhood cancer, being responsible for 25% of all pediatric cancer cases. The most recurrent form of ALL is the B-lineage cell subtype (B-ALL), where a clonal expansion of precursor of B-cell lymphoblasts is found in bone marrow, blood or other tissues. Commonly, ALL is characterized by a rapid progression and a high mortality rate if not adequately treated.

CLL is the clonal expansion of CD5+ B cells that appear as small mature lymphocytes accumulating in blood, bone marrow and lymphoid tissues. CLL progression is characterized by a wide range of outcomes: from the patients that need a rapid treatment to live-long untreated cases. Unfortunately, in few patients, CLL may evolve rapidly in a more aggressive form of large cell lymphoma, thus representing the Richter’s syndrome (Rs).

Several evidence indicate a role of altered expression of the HMGA genes in these malignancies. Indeed, two independent studies reported high HMGA1 expression levels in all the analyzed ALL (6 and 28, respectively), whereas its expression was undetectable in normal cells from peripheral blood of healthy volunteers. Moreover, HMGA1 expression correlates with relapse in pediatric ALL, since gene expression profile of leukemic blasts from relapsed B-ALL children showed a significant increase of HMGA1 expression levels in leukemic blasts from patients with early and late relapses. Intriguingly, using the “Oncomine” database, HMGA1 was among the top 10% of the most overexpressed genes, with a fold change higher than 3 compared to normal bone marrow (Figure 2).

To better understand the involvement of HMGA1 overexpression in ALL development, transgenic mice bearing Hmgα1 gene under the control of the murine H-2K promoter and immunoglobulin μ enhancer were generated. Interestingly, these mice developed lymphoid tumors in 100% of cases with a mean age of death of 4.8 months. Pathological lymphoblasts were detected also in other body compartments such as spleen, lymph nodes, bone marrow, and peripheral blood, underlining the ongoing leukemia pathology. Moreover, the fluorescence-activated cell-sorting (FACS) analysis pointed out CD3+, CD4−, CD8+, and αβ TCR + T-cell markers.

F I G U R E 2  High mobility group A protein roles in myeloid and lymphoid neoplasms. Created with BioRender.com
whereas cells were negative for natural killer 1.1, thus suggesting a mature T-cell phenotype and T-ALL diagnosis.63

Since the abrogation of the CDKN2A tumor suppressor locus is a feature of almost all T-ALL cases, inducing the leukemic transformation, a mouse strain transgenic for Hmga1 and null for Cdkn2a (HMGA1a/Cdkn2a−/−) was generated providing an important model of human T-ALL, a neoplasia of thymocytes characterized by the rapid accumulation of T lymphocytes precursors. Indeed HMGA1a overexpression enhanced the T-ALL malignant phenotype in these mice.65

Interestingly, HMGA proteins seem to be involved also in CLL pathology. Indeed, Santulli and colleagues reported a case of Richter transformation with a 12q13 translocation t(12; 14) (q13; q32h), the chromosomal region where HMGA2 locus is located. Fluorescence in situ hybridization (FISH) analysis confirmed that HMGA2 gene was involved in the 12q chromosomal translocation, revealing also that the chromosomal breakpoint occurred in HMGA2 intron 3, which was transferred to a derivative chromosome 6. Furthermore, through immunohistochemistry (IHC) experiments performed on bone marrow smear, HMGA2 has been found specifically overexpressed in the blasts. Interestingly, further analyses revealed that HMGA2 translocation has been associated with chromosomal abnormalities of 13q14 region, where Rb1 gene is located, suggesting that the cooperation between inappropriate HMGA2 expression with impairment of Rb functions may have a role in the progression of this disease66 (Figure 2). Consistently, this hypothesis would be in line with reported data showing a synergistic effect of HMGA overexpression and cell cycle alterations in the development of pituitary adenoma21,67 and T-cell lymphoma.65

Notably, the most recurrent chromosomal anomaly in atypical CLL is represented by the trisomy of the chromosome 12, which is associated with the amplification of 12q13–15 region and this chromosomal alteration is a feature of most aggressive CLL, indicating its association with cancer progression.68 Moreover, in a case of ALL, a t(9; 12) (p22; q14) chromosomal translocation, involving the HMGA2 locus has been reported. Interestingly, by using specific probes, FISH analyses revealed the absence of the most common HMGA2 breakpoints described so far and occurring in third intron. Further experiments pointed out that HMGA2 transcript overexpressed in blast cells do not have the carboxy-terminal tail, corresponding to exons 3 and 4.69 Consistently, two cases of AML with a chromosome 12 anomaly where new HMGA2 splice variants have been found. Intriguingly, these variants did not have the linker region and the acidic carboxy-terminal domain.70

In order to better understand the HMGA2 role in ALL and CLL, an engineered mouse strain bearing the human HMGA2 gene under control of the VH promoter/Em enhancer was created. About 90% of Em-HMGA2 transgenic mice showed abnormal lymph nodes and spleens, and immunophenotype analyses reported the hyperproliferation of CD5+CD4+, CD5+CD8+, or CD5+CD8+CD4+ T-cell populations in these organs. These altered populations may be comparable to those that characterize the human T-ALL.71

The 12q14.3 locus was also analyzed by microsatellite (MST) markers showing submicroscopic deletions in 20 of the 78 ALL cases (26%), with the highest frequency in Ph-negative B-cell ALL (13 of 27, 48%). Interestingly, the analysis of deletion frequencies of MST markers along this locus underlines that the targeted gene of deletion is likely located within a 170-kb region starting about 65 kb upstream of HMGA2 and ending in the intron 3 of HMGA2.72 These data strongly suggest that the submicroscopic deletions may deregulate HMGA2 expression, likely having a role in ALL pathogenesis, particularly in Ph-negative B-cell ALL.

Moreover, it is remarkable to note that 12q13 chromosomal translocations have been found in a subset of acute non-lymphoblastic leukemia with a poor prognosis. Indeed, Brynes and colleagues reported that the totality of these patients presented blasts immaturity, suggesting a deregulation of early hematopoiesis72,73

### 1.5 | HMGA1 overexpression in human B-cell lymphomas: correlation with Enhancer of Zeste Homolog 2 (EZH2) expression

Recently, an increased expression of HMGA1 has been detected in a panel of hematological neoplasias including a selection of human follicular lymphomas, mantle cell lymphomas, and diffuse large B-cell lymphomas. Intriguingly, also EZH2 was overexpressed in the same tissue samples with a significant correlation with HMGA1 levels. These data were also confirmed by the analysis of other DLBCL cases reported in the Cancer Genome Atlas (TCGA) database. EZH2 is an E2F-regulated gene necessary for cell cycle progression since it regulates G2/M transition.74,75 Several human malignancies such as lymphoma, melanoma, prostate, breast, colon, bladder, and liver cancer are characterized by EZH2 protein overexpression.76–78 In these tumors, EZH2 expression was related with tumor cell proliferation, an aggressive clinical behavior, and poor outcome. Many studies report that EZH2 upregulation has a significant role in the progress of some hematological malignancies.79–81

Consistently with the correlated HMGA1 and EZH2 expression, HMGA1 is able to bind to EZH2 promoter regions enhancing its transcription. As expected, inhibition of HMGA1 expression leads to the reduction of the EZH2 levels resulting in an inhibition of human lymphoma cell lines proliferation and migration rate. Finally, these studies recognize HMGA1 as an EZH2 activator, revealing a new molecular mechanism sustaining EZH2 overexpression in human cancers and a synergy of these two proteins in tumor progression (Figure 3). Intriguingly, by analyzing the data available on TCGA database, it has been pointed out a strong correlation between the HMGA1P1 and EZH2 levels, suggesting a role also for this HMGA1 pseudogene in the lymphomagenesis process by upregulating EZH2 expression.82

Therefore, these studies propose a novel approach for the therapy of human lymphoma based on the combined impairment of EZH2 and HMGA functions.82
1.6 | HMGA overexpressing mice develop lymphomas

The role of HMGA protein overexpression in lymphomas is supported by animal models overexpressing the HMGA genes. Indeed, mice carrying the wild-type or truncated form of Hmga2 gene under the CMV promoter developed lymphomas at 1 year of age.\textsuperscript{83} These tumors were classified as natural killer–T/natural killer cell lymphomas. The mechanism underlying their development is based on the ability of HMGA2 to transcriptionally activate interleukin-2 (IL2), interleukin-15 (IL15), and their receptors.\textsuperscript{83,84} Similar results were obtained analyzing mice overexpressing the wild-type form of Hmga1 gene.\textsuperscript{83} Moreover, a form of aggressive lymphoma, compatible with a mature T-cell phenotype, developed between 1 and 8.5 months of age also in transgenic mice carrying Hmga1a flanked by the H-2K promoter and immunoglobulin intronic enhancer.\textsuperscript{64}

Recently, transgenic HMGA1P6- and HMGA1P7- overexpressing mouse models have been also generated.\textsuperscript{82,85,86} At 12 months of age, about 50% of these mice were affected by splenomegaly and different mouse anatomical districts were invaded by lymphoid cells. Indeed, the pathological spleens revealed disseminate and monotonous lymphoid cells destroying the splenic parenchyma with the loss of the characteristic structures and germinal centers. These neoplastic cells were characterized as B cells, suggesting the diagnosis of B-cell lymphomas for the HMGA1P7 mouse model.\textsuperscript{85}

The mRNA profile of the neoplastic spleens, compared with the normal ones, showed that the genes blocked by B-cell receptor inhibitors in diffuse large B-cell lymphoma (DLBCL) were notably enhanced in the mouse pathological spleens. Indeed, the decreased genes were enriched of transcripts downregulated in post-Germinatal Center (GC) of BCL 6 dependent B-cell lymphomas, and expressed in the GC B-cell-type DLBCL signature. Therefore, the lymphoproliferative lesions developed in these mice match with DLBCL of the non-GCB type.\textsuperscript{85}

2 | CONCLUSIONS

Numerous studies have confirmed that the inhibition of HMGA protein expression and/or function has an adverse consequence on proliferation and metastatic ability of tumor cells. Then, the focus of the next years will be to use all this data in order to discover new therapeutic approaches that will help patients affected by HMGA1-overexpressing tumors. It is worth note that a HMGA-based therapy could have a wide range of applications representing an excellent tool for hematological malignancies and cancers of different origins overexpressing these proteins. Then, the development of cancer therapies based on the inhibition of HMGA proteins has been the subject of several studies. It has been reported that trabectedin, already used for the therapy of human ovary cancer, exerts its cytotoxic properties on tumor cells through its ability to impair HMGA protein functions. However, the antitumoral effects of trabectedin treatment in HMGA positive cancer patients have to be better evaluated by further studies.

Moreover, several miRNAs able to target the HMGA genes have been identified: then, a miRNA treatment of patients affected by hematological malignancies could also be taken in consideration.

ACKNOWLEDGMENT
This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

Open Access Funding provided by Consiglio Nazionale delle Ricerche within the CRUI-CARE Agreement.

CONFLICT OF INTEREST
The authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT
The data that support the findings of this study are available from the corresponding author upon reasonable request.

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TRANSPARENT PEER REVIEW
The peer review history for this article is available at https://publons.com/publon/10.1002/hon.2934.

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How to cite this article: De Martino M, Esposito F, Fusco A. Critical role of the high mobility group A proteins in hematological malignancies. Hematol Oncol. 2022;40(1):3-11. https://doi.org/10.1002/hon.2934