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The *High-Mobility Group A1* Gene: Transforming Inflammatory Signals into Cancer?

Linda M. S. Resar
The Johns Hopkins University School of Medicine, Baltimore, Maryland

Linda M. S. Resar: lresar@jhmi.edu

Abstract

HMGA1 is highly expressed during embryogenesis and in poorly differentiated cancers, and high levels portend a poor prognosis in some tumors. *HMGA1* induces oncogenic transformation in cultured cells and causes aggressive cancers in transgenic mice, while blocking it interferes with transformation in experimental models. These findings suggest a pivotal role for HMGA1 in cancer. This review focuses on two recently described HMGA1 transcriptional targets that mediate inflammatory signals and drive malignant transformation because they could serve as biomarkers or therapeutic targets. Further elucidation of HMGA1 function in transformation promises to have a major impact on our war on cancer.

Keywords

HMGA1; oncogene; transcription

Introduction

The High Mobility Group A1 (HMGA1, formerly HMG-I/Y) proteins participate in diverse, fundamental cellular processes, including transcriptional regulation, embryogenesis, transformation, cell cycle regulation, differentiation, senescence, viral integration, and DNA repair (1-22). They are members of a superfamily of nonhistone chromatin binding proteins whose name reflects their rapid electrophoretic mobility in polyacrilamide gels (high-mobility group). All HMG proteins share an acidic carboxyl-terminus and associate with chromatin, but are distinguished by unique functional motifs that confer distinct DNA binding domains and biologic activities (1-3). The AT-hook DNA binding motif defines the HMGA family, which consists of HMGA1 and HMGA2. Here, we focus on the HMGA1 subfamily, comprised of HMGA1a and HMGA1b protein isoforms. These isoforms result from alternatively spliced mRNA and differ by 11 internal amino acids present only in HMGA1a (4). Three AT-hook domains mediate binding to the minor groove of chromosomal DNA at AT-rich regions, which enables HMGA1 to recruit additional transcription factors and alter chromatin structure as an essential component of a higher order transcriptional complex or “enhanceosome” (3). In concert with other factors, HMGA1 modulates gene expression. Although first described in the context of the interferon-β promoter, the enhanceosome function likely applies to many promoters. HMGA1 proteins also displace histones and relieve histone-mediated repression of transcription, thereby globally facilitating transcription (5). Because HMGA1 proteins induce conformational changes and alter gene expression, they are called “architectural transcription factors”. While their role in transcription is well-established, the repertoire of genes targeted by HMGA1 is only beginning to emerge.

The first evidence linking HMGA1 proteins to cancer was their discovery in cervical carcinoma cells 25 years ago (1). Subsequent studies showed high *HMGA1* expression in rapidly dividing

cells, neoplastic cells (1-18), and during embryogenesis (6), but not in differentiated, adult tissues. Their evolutionary conservation and widespread occurrence in development suggested an important biologic function. *HMGA1* is induced in quiescent fibroblasts by serum or growth factors and displays delayed-early response kinetics (7). Increasing evidence demonstrates that *HMGA1* is widely overexpressed in aggressive malignancies arising from diverse tissues of different embryonic origins. Although the list is expanding, these include cancers of the thyroid, head and neck, colon, lung, breast, pancreas, hematopoietic system, cervix, uterine corpus, prostate, and central nervous system. Moreover, large scale gene expression studies show that high expression portends a poor prognosis in some tumors (8,18). *HMGA1* is also enriched in embryonic stem cells and high-grade (poorly differentiated) cancers, including breast, bladder, and brain cancers (18). Tissue microarray studies also demonstrate that increasing protein levels correlate with poor differentiation status and more advanced disease in diverse cancers. These findings indicate that *HMGA1* could be a useful biomarker and therapeutic target for high-grade cancers and suggest that HMGA1 orchestrates the molecular underpinnings of a more primitive, poorly differentiated state, both in cancer and development.

HMGA1 Function in Cancer

Following the discovery that *HMGA1a* is linked to cancer, investigators began to look for its function in transformation. Our laboratory provided early evidence that *HMGA1* contributes directly to neoplastic transformation (9-11). Forced overexpression of *HMGA1a* or *HMGA1b* induces a transformed phenotype with anchorage-independent cell growth and xenograft tumorigenesis in immortalized cells. *HMGA1a* is also directly activated by the c-Myc proto-oncoprotein and up-regulated in Burkitt's lymphoma, an aggressive tumor with constitutive *c-myc* expression. Moreover, inhibiting *HMGA1* expression in Burkitt's and other cancer cells blocks anchorage-independent cell growth and proliferation. Knock-down of *HMGA1* also causes apoptosis in lung, breast, and thyroid cancer cells, indicating its central role in diverse malignancies (12). In MCF-7 breast cancer cells, HMGA1b induces an epithelial-to-mesenchymal transition (13), further linking these proteins to a primitive, de-differentiated state in cancer.

The subsequent development of mouse models misexpressing *HMGA1* provided the most compelling evidence that *HMGA1* causes cancer. As reported here 5 years ago, *HMGA1a* transgenic mice succumb to aggressive T-cell lymphoid malignancy by 2-10 months (11). The females also develop uterine sarcomas (15). In this model, murine *HMGA1a* is driven by the H2K promoter and immunoglobulin μ enhancer with expression in MHC class I expressing cells and B-cells (11). Another group reported a transgenic model with murine *HMGA1b* driven by a CMV promoter, and these mice develop NK-lymphomas and pituitary adenomas (14). These tumors occur later and with a decreased penetrance compared to the *HMGA1a* mouse model. The variation in phenotypes could relate to the different isoforms expressed or to different levels of tissue-specific transgene expression. More recently, *HMGA1* knock-out mice were made and both homozygous and heterozygous null mice develop a decrease in T-cells with a relative increase in B cells, erythroid cells, and myeloid cells, and a phenotype described as lympho-myeloproliferative disease (19). The proliferative disease progresses to frank malignancy in some cases, which led to the speculation that HMGA1 has tumor suppressor activity. The hematologic findings also resemble lymphoproliferative disease seen in humans with T-cell immunosuppression, suggesting that T-cell deficiency is the cause of the hematologic abnormalities.

Despite recent progress, the molecular mechanisms that mediate HMGA1 function are only beginning to emerge. Its diverse activities have been attributed to its role as a chromatin remodeling transcription factor, which could lead to induction of different molecular pathways depending on the cellular context. Accordingly, promoter analyses and gene expression profile

studies have uncovered downstream gene targets and an HMGA1 "oncogenic transcriptome" is emerging. These studies suggest that HMGA1 orchestrates diverse cellular processes through modulating gene expression, including pathways involved in inflammation, proliferation, transformation, metastatic progression, angiogenesis, and DNA repair. Although only about 50 HMGA1 transcriptional targets have been reported, most include Nuclear Factor-κB (NF-κB) regulatory elements in their promoter regions and many participate in mediating inflammatory pathways. Given the increasing evidence that inflammation is a precursor lesion in some cancers, the link between HMGA1 and NF-κB suggests that these proteins cooperate to induce inflammatory signals and drive transformation. Here, we highlight two recently identified gene targets related to inflammation and oncogenesis because their functions could be blocked in cancer therapy.

HMGA1a in Cancer - New Insights

Cyclooxygenase-2 (COX-2)

COX-2 was originally identified as a putative HMGA1 target gene in hypoxic vascular endothelial cells (20). Under low oxygen tension, HMGA1 binds to an AT-rich region near an NF-κB binding site in the *COX-2* promoter *in vitro* and up-regulates *COX-2* expression in transfection experiments. We also found that HMGA1 activates *COX-2* expression during tumorigenesis (15-16). Uterine sarcomas from the *HMGA1a* transgenics have increased *COX-2* expression and treatment with sulindac (a COX-1/COX-2 inhibitor) inhibits tumor growth (15). Both *HMGA1* and *COX-2* are also overexpressed in leiomyosarcomas, a highly lethal, human uterine sarcoma. Sulindac or celecoxib (a more selective COX-2 inhibitor) results in blockade of anchorage-independent cell growth and xenograft tumorigenesis in human uterine sarcoma cells, but only in cells with high *HMGA1a* levels (16). This indicates that targeting COX-2 is effective in selected tumors with dysregulation of the HMGA1-COX-2 pathway. *COX-2* is induced by inflammatory signals, and, like *HMGA1*, is thought to elicit a number of cellular pathways involved in neoplastic transformation, including proliferation, angiogenesis, metastasis, and inhibition of apoptosis. It is not clear if hypoxia is a prerequisite for *COX-2* induction by HMGA1 and further studies are needed to elucidate the role of this pathway in other cancers.

Signal transducer and activator of transcription 3 (STAT3)

Recent studies also uncovered *STAT3* as a critical downstream target of HMGA1 (17). *STAT3* is up-regulated in cells and transgenic mice engineered to overexpress *HMGA1a*. Similar to the *COX-2* promoter, HMGA1 binds to an AT-rich region near an NF-κB binding site and activates *STAT3* expression. HMGA1 occupies this promoter in cultured cells from hematopoietic malignancies. Moreover, a STAT3 small molecule inhibitor induces apoptosis in leukemic cells from *HMGA1* transgenics, but not in normal lymphoid cells, indicating that this pathway could be a rational therapeutic target in some malignancies. In ongoing studies, we are testing additional STAT3 small molecule inhibitors in our transgenic models *in vivo*, and preliminary data show decreases in the tumor burdens (unpublished data). The HMGA1-STAT3 pathway is of interest because *STAT3* is a key mediator of inflammatory signals and molecular pathways that contribute to cancer initiation and progression, including proliferation, angiogenesis, metastatic progression, survival, and immune evasion.

Future Directions—Although recent studies have identified downstream gene targets, it is likely that these results provide only a glimpse of HMGA1 transcriptional networks in cancer. A global investigation of both genes and microRNAs should lead to the discovery of rational therapeutic targets relevant to diverse cancers. Interestingly, both *COX-2* and *STAT3* are important transducers of inflammatory signals with NF-κB regulatory elements in their promoter regions near the HMGA1 binding sites. The presence of NF-κB sites in HMGA1

transcriptional targets suggests that these proteins function together as reported in the regulation of *interferon-β* expression. Although not directly proven, HMGA1, together with NF-κB and other transcription factors, could form an enhanceosome that constitutes a major "hub" activated by inflammation. This hub, in turn, could induce cellular pathways that lead to cancer initiation and progression. In some settings, overexpression of *HMGA1* could activate inflammatory pathways and circumvent the need for inflammation to promote oncogenic transformation. Our preliminary data from gene expression analysis support the role of HMGA1 in inducing multiple inflammatory pathways in transformation (data not shown). Further dissection of these pathways will reveal how HMGA1 promotes transformation and tumor progression, and could identify rational interventions to treat, or even prevent, cancer. Our studies have focused on pathways downstream of HMGA1 because the ability to target nuclear oncogenes therapeutically is only emerging. Additional studies to identify molecular circuitry induced by HMGA1 as well as functional analysis in preclinical mouse models are needed before these findings can be translated to the clinic.

While it is clear that growth factor signaling, oncogenic transcription factors, viruses, hypoxia, and inflammatory signals induce *HMGA1* expression, the molecular mechanisms mediating *HMGA1* overexpression in most tumors is unknown. Amplification has not been detected to date. Epigenetic changes or microRNA alterations could play a role and studies to uncover the molecular mechanisms inducing *HMGA1* should advance our ability to block its activity in cancer therapy. Recent studies also implicate *HMGA1* in maintaining "stemness" and understanding its role in this setting should elucidate therapeutic targets relevant to cancer and cancer stem cells (18). Emerging evidence also indicate that HMGA proteins participate in cellular senescence (21), and this activity could potentially be exploited in therapy. Finally, its activity in DNA repair could play a central role in transformation and is worthy of further study (22). Given their importance in embryogenesis and cancer, it is likely that there are, as yet, undiscovered HMGA1 cellular activities that will provide insight for novel therapeutic approaches in cancer. Further investigation of HMGA1 proteins in development and malignant transformation promises to bolster our war on cancer - *clearly a war worth waging*.

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Abbreviations

HMGA1	*high-mobility group A1* gene

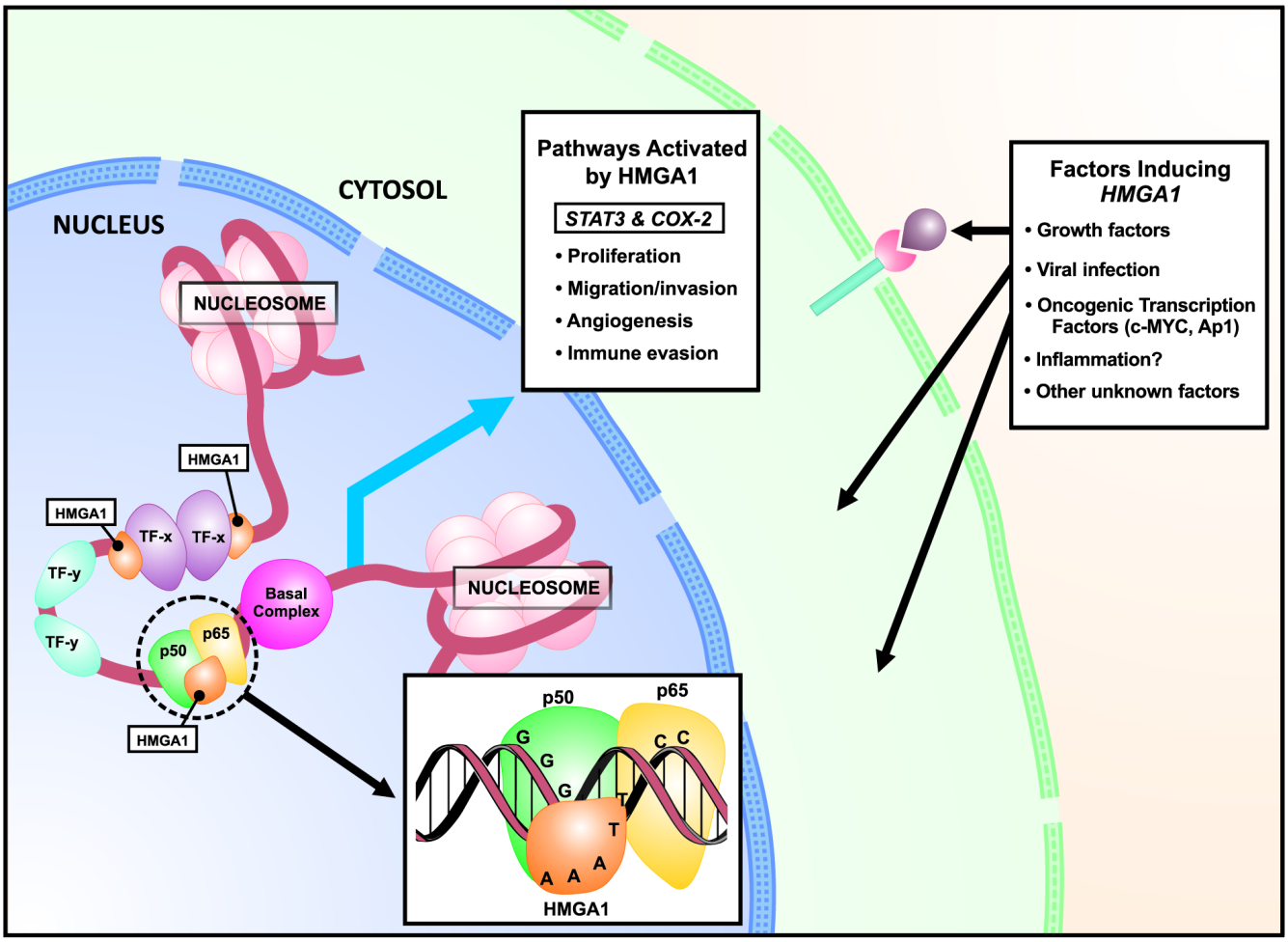

Figure 1.

Induction of *HMGA1* results in binding to the minor groove at AT-rich regions in chromatin and recruitment of transcriptional regulators. NF-κB (p65/p50) and other transcription factors (TF-x, TF-y) are shown, which leads to the formation of the enhanceosome and activation of oncogenic pathways.