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Review

High mobility group A1 and cancer: Potential biomarker and therapeutic target

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Summary. The *High Mobility Group A1* (*HMGA1*, formerly *HMG-I/Y*) gene is highly expressed during embryogenesis and in virtually all aggressive human cancers studied to date, although its role in these settings is only beginning to emerge. Moreover, high levels of expression portend a poor prognosis in some tumors. Increasing evidence suggests that the HMGA1 protein functions as a master regulator with a critical role in normal development and tumor progression in diverse malignancies. These proteins contain AT-hook DNA binding domains that mediate binding to AT-rich regions of chromatin. After binding to DNA, HMGA1 alters DNA structure, and orchestrates the assembly of a transcriptional complex or "enhanceosome" to regulate gene expression. Previous studies indicate that HMGA1 participates in regulating fundamental cellular processes, including transcription, cell cycle progression, embryonic development, neoplastic transformation, differentiation, senescence, viral integration, and DNA repair by virtue of its ability to interact with other proteins, bind to DNA, and modulate gene expression. Recent studies also link *HMGA1* expression to poor differentiation status and a refractory, stem cell-like state in aggressive cancers. Together, these findings suggest that HMGA1 could serve as a useful biomarker and therapeutic target in advanced malignancies. Here, we focus on prior studies implicating HMGA1 in the pathogenesis of refractory human tumors arising from diverse tissues and its potential role as a biomarker. We also review previous attempts to target HMGA1 pathways in cancer. Further study of HMGA1 promises to have a major impact on our ability to understand and treat cancer.

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Introduction

HMGA1 genes and proteins

High mobility group A1 (HMGA1) proteins are members of a superfamily of low molecular weight, nonhistone, chromatin binding proteins that were discovered almost 30 years ago in highly proliferative human cervical cancer (HeLa) cells (Lund et al., 1983). Since their initial discovery, an increasing body of literature has linked HMGA1 proteins to refractory or poorly differentiated human cancers with adverse outcomes (Reeves, 2001a; Pomeroy et al., 2002; Fusco and Fedele, 2007; Tesfaye et al., 2007; Ben-Porath et al., 2008; Hristov et al., 2010; Resar, 2010). The AT-hook DNA binding motif defines the HMGA family, which consists of the HMGA1 and HMGA2 proteins (Hock et al., 2007). Both HMGA1 and HMGA2 genes are highly expressed in cancer and stem cells (Chiappetta et al., 1996; Li et al., 2006, 2007; Ben-Porath et al., 2008; Di Cello et al., 2008a; Hristov et al., 2009; Hristov et al., 2010; Resar, 2010; Chou et al., 2011; Karp et al., 2011; Nelson et al., 2011; Resar and Brodsky, 2011). In addition to overexpression, *HMGA2* is also frequently involved in translocations in benign mesenchymal tumors, and to a lesser extent, in malignant mesenchymal tumors (Schoenmakers et al., 1995; Fusco and Fedele, 2007). The HMGA1 protein subfamily is the subject of this review and comprised of HMGA1a and HMGA1b protein isoforms (previously HMG-I and HMG-Y), which are encoded by the *HMGA1* (previously

Abbreviations: *HMGA1, high mobility group A1* gene; PCR, polymerase chain reaction

HMG-I/Y) gene. These protein isoforms result from alternative splicing of *HMGA1* mRNA and differ by 11 internal amino acids present only in HMGA1a (Johnson et al., 1988, 1992; Friedmann et al., 1993; Hock et al., 2007). The AT-hook DNA binding domains mediate binding to the minor groove of chromosomal DNA at AT-rich regions. After binding DNA, HMGA1 proteins orchestrate the assembly of additional transcription factors like the p50 and p65 subunits of NF-κB, forming a higher order transcriptional complex or "enhanceosome" that alters chromatin structure (Thanos and Maniatis, 1992, 1995; Thanos et al., 1993; Falvo et al., 1995; Munshi et al., 2001; Resar, 2010). In concert with other factors, HMGA1 modulates gene expression. Although first described in the context of the *interferon-β (IFN-β)* promoter, the enhanceosome function applies to other promoters and is likely to be a major mechanism through which HMGA1 proteins alter expression of specific target genes (Thanos and Maniatis, 1992, 1995; Thanos et al., 1993; Falvo et al., 1995; Munshi et al., 2001; Resar, 2010). HMGA1 proteins also globally activate gene expression by displacing histone H1 proteins bound to chromatin, thereby relieving histone H1-mediated repression of transcription (Mirkovitch et al., 1984; Zhao et al., 1993; Saitoh and Laemmli, 1994; Strick and Laemmli, 1995; Girard et al., 1998). Indeed, HMGA1 proteins share significant homology to histones, suggesting that they may have evolved from these proteins. Because HMGA1 proteins interact with other proteins to alter chromatin structure and gene expression, they have been termed "architectural transcription factors". As such, HMGA1 is involved in diverse cellular processes, such as cell cycle progression, embryologic development, neoplastic transformation, differentiation, apoptosis, cellular metabolism, and DNA repair.

While its role in transcription is well-established, the repertoire of genes regulated by HMGA1 is only beginning to emerge and includes genes involved in cell signaling, mobility, proliferation, and metastatic progression. Previous studies of gene expression profiles linked to HMGA1 suggest that the list of gene targets is extensive and this is the subject of another review (Sumter and Resar, 2012). Recent studies also suggest that AT-binding factors are important in regulating inflammatory pathways (Ma et al., 2011; Moliterno and Resar, 2011) and there are several genes involved in inflammation that are regulated by HMGA1. Here, we discuss previous studies linking aberrant *HMGA1* expression to diverse tumors and its role as a potential biomarker. We also outline what is known about its function in cancer. Finally, we describe previous efforts to target HMGA1 in cancer therapy as well as HMGA1 pathways that could be exploited in future studies.

Structural features of HMGA1 proteins

HMG proteins were originally named based on their rapid electrophoretic mobility (or high mobility group) in polyacrylamide gels (Hock et al., 2007). All HMG proteins share an acidic, carboxyl terminus and associate with chromatin, but are distinguished by unique functional motifs that confer distinct DNA binding motifs and biologic activities. The carboxyl-terminal tail is highly acidic, although it does not appear to function as a transcriptional activation domain like other acidic protein domains. Rather, mutational analysis suggests that the acidic tail is important in conferring sequence specific DNA binding (Yie et al., 1999). HMGA proteins also contain serine and threonine-rich domains, although the functional significance of these regions is unknown. The AT-hook DNA binding motif defines the HMGA family, which consists of the HMGA1 and HMGA2 proteins. The three basic, AT-hooks enable these proteins to bind to the minor groove of chromosomal DNA at AT-rich, B-form DNA by recognizing chromatin structure (Solomon et al., 1986; Geierstanger et al., 1994; Maher and Nathans, 1996; Banks et al., 1999; Bustin, 1999; Reeves, 2001). The HMGA1 subfamily includes HMGA1a and HMGA1b protein isoforms, which differ by 11 internal amino acids located upstream of the second AT hook in HMGA1a (Johnson et al., 1988, 1992; Friedmann et al., 1993; Hock et al., 2007). The functional significance of the different isoforms is not clear. While prior gene expression profile analyses show significant overlap in genes regulated by both HMGA1a and HMGA1b isoforms, a subset of target genes distinct to each isoform was identified in a prior study (Reeves, 2001). Functional studies, however, indicate that both isoforms behave similarly when overexpressed in cultured cells and transgenic mouse models (Wood et al., 2000a; Xu et al., 2004; Fedele et al., 2005). The list of protein partners that interact with HMGA1 proteins is extensive and probably incomplete to date. Nonetheless, most interactions have been mapped to the second AT-hook and the surrounding sequences (Chin et al., 1998; Yie et al., 1999; Pierantoni et al., 2005; Esposito et al., 2009). Protein-protein interactions are likely to be important modulators of HMGA1 function and are the subject of another review (Sgarra et al., 2005).

In addition to the ability to modulate chromatin structure and gene expression through DNA binding via AT-hook domains, an equally striking feature of HMGA1 is the lack of intrinsic structure and inherent flexibility (Reeves, 2001) when not bound to chromatin. Prior to binding to DNA, the AT-hook domains are thought to exist in an unstructured form, which transitions to a planar, crescent–shaped structure that interacts with about a half turn of the double helix. Likewise, the peptide backbone that flanks the AT-hooks is thought to be highly flexible and allows the AT-hook to associate with either long stretches of AT-rich DNA or two to three shorter stretches of AT rich sequence. A remaining challenge in the field will be to determine how these flexible motifs contribute to protein-DNA interactions and HMGA1 function. Further elucidation of the functions conferred by each domain could also identify additional molecular pathways that function in

embryonic development, cancer, and other diseases associated with aberrant *HMGA1* expression.

Human cancers associated with HMGA1 overexpression

The first evidence linking HMGA1 proteins to cancer was their discovery in highly proliferative human cervical carcinoma cells (HeLa) as abundant chromatin binding proteins (Lund et al., 1983). In subsequent studies, HMGA1 proteins were identified in rat epithelial thyroid cells, but only after transformation by a murine sarcoma retrovirus, which enables the cells to grow in an anchorage-independent fashion in soft agar and form tumors in syngeneic mice (Giancotti et al., 1985). The same group also found that HMGA1 proteins are induced in rat thyroid epithelial cells (PC-13) after co-transformation by viral oncogenes (Giancotti et al., 1987). They also showed that mouse tumors initiated by different mechanisms, including carcinogens, viral oncogenes, or spontaneously occurring carcinomas, exhibit high levels of the HMGA1 proteins (Giancotti et al., 1989). Other investigators later demonstrated that HMGA1 proteins are expressed in rapidly dividing, undifferentiated tissues, and transformed human cancer cell lines (K562 leukemia cells), but not in differentiated, non-dividing cells (Johnson et al., 1988). The *HMGA1* gene was also identified as a growth factor induced gene with delayed-early kinetics (Lanahan et al., 1992). Following these initial observations, a plethora of reports were published demonstrating that HMGA1 proteins are undetectable in normal tissues, but expressed at high levels in diverse human cancer cells, including cancers of the thyroid (Chiappetta et al., 1998; Pomeroy et al., 2002), breast (Holth et al., 1997; Liu et al., 1999; Reeves et al., 2001; Dolde et al., 2002; Flohr et al., 2003; Chiappetta et al., 2010), cervix (Bandiera et al., 1998), gastric mucosa (Akaboshi et al., 2009), colon (Fedele et al., 1996; Kim et al., 1999; Balcerczak et al., 2004; Grade et al., 2007; Belton et al., 2012), liver (Chuma et al., 2004), pancreas (Liau et al., 2006, 2007; Liau and Whang, 2008; Hristov et al., 2010), hematopoietic system (Wood et al., 2000b; Pierantoni et al., 2003; Xu et al., 2004; Hillion et al., 2008), lung (Kettunen et al., 2004; Sarhadi et al., 2006), uterine corpus (Tesfaye et al., 2007) as well as in medulloblastoma (Pomeroy et al., 2002) and neuroblastoma (Giannini et al., 2000) of the central nervous system. These studies documented *HMGA1* mRNA and protein expression through a variety of methodologies, including high power liquid chromatography, immunohistochemical staining, Western analysis, Northern analysis, *in situ* hybridization, and, more recently, quantitative, reverse transcriptase, real-time polymerase chain reaction (PCR). The high level of expression at both the mRNA and protein level in cancers with absent expression in normal cells suggested that HMGA1 could serve as a target in diverse cancers arising from all three germ layers (Table 1). Additional studies began to link HMGA1 to metastatic progression. For example, high expression of *HMGA1* at the mRNA or protein level was reported by different groups in cultured cells derived from metastatic tumors compared to localized tumors, including breast (Holth et al. 1997; Reeves et al., 2001b; Dolde et al., 2002), colon (Fedele et al., 1996; Kim et al., 1999), prostate (Takaha et al., 2004), and pancreatic (Abe et al., 2000; Hristov et al., 2010) cancers.

Once it was established that high levels of HMGA1 proteins are found in cancer, several investigators sought to define a functional role for HMGA1 in neoplastic

Table 1. Cancers overexpressing *HMGA1*: Cultured cells and primary tumors.

Target protein/Disease	Main References
HMGA1 Expression & Functional Studies in Cultured Cells	
Lymphoid cancers Sarcomas	Wood et al., 2000a,b
Breast Cancer	Holth et al., 1997; Liu et al., 1999; Scala et al., 2000; Reeves et al., 2001; Dolde et al., 2002
Gastric Cancer	Akaboshi et al., 2009
Lung Cancer	Scala et al., 2000; Hillion et al., 2009
Thyroid Cancer	Scala et al., 2000
Colon Cancer	Scala et al., 2000; Belton et al., 2012
Pancreatic Cancer	Liau et al., 2006; Liau and Whang, 2008; Hristov et al., 2010
Prostate Cancer	Takaha, et. al., 2002
HMGA1 Expression & Functional Studies in Primary Tumors	
Thyroid cancer	Chiappetta et al., 1995, 1998
Medulloblastoma	Pomeroy et al., 2002
Breast cancer	Flohr et al., 2003; Ben-Porath et al., 2008; Chiappetta et al., 2010
Cervical cancer	Bandiera et al., 1998
Colorectal cancer	Fedele et al., 1996; Kim et al., 1999; Balcerczak et al., 2004; Grade et al., 2007; Belton et al., 2011
Gastric cancer	Akaboshi et al., 2009
Leukemia/lymphoma	Wood et al., 2000b; Pierantoni et al., 2003; Xu et al., 2004; Hillion et al., 2008; Karp et al., 2011; Nelson et al., 2011
Lung cancer	Kettunen et al., 2004 ; Sarhadi et al., 2006 ; Hillion et al. 2009
Neuroblastoma	Giannini et al., 2000
Pancreatic cancer	Abe et al., 2000, 2002; Liau et al., 2007; Hristov et al., 2010

transformation. Using cell-based approaches, our group was the first to discover that HMGA1 proteins have potent oncogenic properties in cultured mammalian cells (Wood et al., 2000a,b). Forced overexpression of HMGA1a or HMGA1b leads to a transformed phenotype with anchorage-independent cell growth in rat fibroblasts (Rat1a cells) and human EBV-transformed lymphoblastoid cells derived from normal cord blood (CB33 cells). While parental Rat1a or EBV-transformed CB33 cells are not clonogenic in soft agar, cells engineered to overexpress HMGA1a or HMGA1b proteins exhibit colony formation in soft agar similar to cells with forced overexpression of the c-Myc oncoprotein (Dang et al., 1999). These studies provided early functional evidence that HMGA1 induces a transformed phenotype in human cells. We also found that inhibiting HMGA1 expression using an RNA interference approach in Burkitt's lymphoma cells blocks both cellular proliferation and anchorage-independent growth in soft agar (Wood et al., 2000b). In addition, HMGA1a or HMGA1b are tumorigenic in Rat 1a cells, resulting in fibrosarcomas following subcutaneous injection into nude mice (Wood et al., 2000a,b). Moreover, a subset of tumors metastasized to the lungs. Subsequent studies also showed that overexpression of HMGA1a or HMGA1b enhanced anchorage-independent cell growth in MCF-7 human breast cancer cells (Reeves et al., 2001) in addition to orthotopic tumors with metastatic progression in immunocompromised mice. Interestingly, the MCF-7 tumors also developed mesenchymal features suggesting that the epithelial breast cells underwent an epithelial-mesenchymal transition. This group also found that interfering with HMGA1 function through an antisense or dominant-negative approach blocked proliferation and colony formation in soft agar in human breast cancer cells (Reeves et al., 2001). A subsequent study showed that HMGA1 expression in pancreatic adenocarcinoma cells reduces anoikis, or the susceptibility of cells to undergo apoptosis when grown in suspension (Liau et al., 2007). This group also showed that knock-down of HMGA1 in pancreatic cancer cells blocked metastatic progression following implantation in the pancreas in a murine model (Liau et al., 2006). Another group reported that adenovirus-mediated antisense knock-down of HMGA1 causes apoptotic cell death in cultured human thyroid, colon, lung, and breast cancer cells, but not in cells derived from normal tissue, further substantiating a functional role for HMGA1 in transformation (Scala et al., 2000). Our group found that forced expression of HMGA1a led to anchorage-independent cell growth in cultured cells derived from normal breast tissue (Dolde et al., 2002). Taken together, these functional studies provided further evidence that HMGA1 proteins contribute to neoplastic transformation in diverse human cancers (Wood et al., 2000a,b; Scala et al., 2000; Reeves et al., 2001; Dolde et al., 2002).

Genetically engineered mouse model systems and functional studies

To further investigate the role of HMGA1 in cancer, transgenic mouse models were subsequently developed (Table 2; Xu et al., 2004; Fedele et al., 2005; Tesfaye et al., 2007). We first reported that *HMGA1* transgenic mice succumb to aggressive T-cell lymphoid malignancy by 2-10 months with 100% penetrance. In this model, the murine *hmga1a* transgene is driven by the H-2K promoter and immunoglobulin μ enhancer, which results in *hmga1a* expression in B and T lymphoid cells, with highest levels documented in T-cells. The transgene is expressed at levels ranging from 2 to 10-fold above that observed in normal murine lymphocytes (Xu et al., 2004). Similarly, *HMGA1*α expression was found to be increased in primary human B- and T-cell acute lymphoblastic leukemia cells by 2 to 10-fold above that observed in normal human T and B cells (Xu et al., 2004). The female mice also develop uterine sarcomas and *HMGA1a* mRNA and protein levels were increased in the uteri by 5 to 15-fold compared to control uteri (Tesfaye et al., 2007). Similar to the mouse model, levels of *HMGA1a* mRNA were found to be 2 to 20-fold higher in high-grade uterine cancers compared to normal uterine tissue (Tesfaye et al., 2007). Preliminary studies also demonstrate that these mice develop proliferative changes in the intestines and polyps (Belton et al., 2012). Another *HMGA1* transgenic mouse bearing the *HMGA1b* transgene driven by the CMV promoter was also reported (Fedele et al., 2005). These mice also develop T cell lymphomas, although with a lower

Table 2. Genetically engineered murine models misexpressing or deficient in *HMGA1*.

Target protein/Disease	Main Ref/Source
HMGA1 misexpression mouse model systems	
T-cell ALL	Xu et al., 2004/Resar Laboratory
NK lymphoma	Fedele et al., 2005/Fusco laboratory
Uterine sarcomas	Tesfaye et al., 2007/Resar laboratory
Pituitary adenoma	Fedele et al., 2005/Fusco laboratory
Intestinal polyps	Belton et al., 2012/Resar laboratory
HMGA1 deficient mouse models	
Adult-onset diabetes	Foti et al., 2005/Fusco laboratory
Cardiomyopathy lymphoproliferative disorder	Fedele et al., 2006/Fusco laboratory

penetrance and at a later age. The T cells express NK cell markers. Females in this model develop pituitary adenomas with a penetrance of 80% by 16 months; 15% of males have pituitary adenomas by 22 months. The alternate isoform (hmga1b) or a lower level of transgene expression could account for decreased tumor penetrance in this model (Fedele et al., 2005). Nonetheless, the two independent mouse models provided the most compelling evidence that *HMGA1* functions as an oncogene i*n vivo* (Xu et al., 2004; Fedele et al., 2005; Tesfaye et al., 2007).

Shortly after the *HMGA1* transgenic mice were reported, a knock-out mouse model was generated (Foti et al., 2005; Fedele et al., 2006). Prior to the development of the mouse model, a murine embryonic stem cell (mESC) line (Battista et al., 2003) null for *hmga1* were engineered. When induced to differentiate into hematopoietic cells, the *hmga1* knock-out mESCs preferentially formed B-cells, erythroid progenitors, and megakaryocytes with a decrease in T-cell precursors and the monocyte/macrophage compartment (Battista et al., 2003). Similarly, the knock-out mouse model had a paucity of T-cells coupled with an increase in B-cells (Fedele et al., 2006). In addition to B-cell hyperplasia, these mice also have an increase in erythroid progenitors and granulocytes, a phenotype described as lympho-myeloproliferative disease. In fact, some of these mice go on to develop frank malignancy, which raised the possibility that HMGA1 could also function as a tumor suppressor (Fedele et al., 2006). Alternatively, the T cell deficiency could be the cause of the proliferative disease, which resembles features of lymphoproliferative disorders observed in humans with T cell immuno-deficiency. Regardless of the mechanism for the lymphoprolifereative disease, both the transgenic and null mice indicate that HMGA1 plays an important role in T cell development and further studies are needed to dissect its role in this process.

The knock-out mice also develop decreased insulin receptor expression, insulin resistance, and a type 2 diabetes-like phenotype (Foti et al., 2005). Interestingly, mutations that result in decreased expression of *HMGA1* were also found in four patients from a screen of 148 patients with type 2 diabetes. Two cases were from the same family and both individuals had a hemizygous deletion of the *HMGA1* gene locus. The remaining two cases had a single nucleotide deletion in the 3' untranslated regions and functional studies in genetically engineered cell lines showed that the nucleotide deletion decreased *HMGA1* gene expression. The human correlates indicate that decreased *HMGA1* expression could contribute to the development of type 2 diabetes in a subset of patients. The *hmga1* deficient mice also develop cardiac hypertrophy, although there are no studies to date to link HMGA1 to cardiac hypertrophy in humans (Fedele et al., 2006).

Table 3. Compounds that target HMGA1 in preclinical studies.

Compound	Putative Mechanism	Potential Limitations	Model System†	Main Ref/Source
FR900482	Crosslinking agent	Not specific for HMGA1, Toxicity, with vascular leak syndrome	Jurkat cells, Phase II trials	Beckerbauer et al., 2000, 2002
FK317	Crosslinking agent	Not specific for HMGA1	Jurkat cells, Phase II trials	Beckerbauer et al., 2002
NOX-A50	Direct HMGA1 binding	Unknown	Xengrafts with pancreatic cancer cells	Maasch et al., 2010
Actinomycin-D‡	AT-rich DNA binding	Not specific for HMGA1	*In vitro* biochemical studies	Wadkins et al., 2000
Distamycin	Minor groove binding	Not specific for HMGA1	Mouse model of endotoxemia	Baron et al., 2010
Netropsin	Minor groove binding	Not specific for HMGA1	Mouse model of endotoxemia	Grant et al., 2009
Antisense technology (antisense or RNA interference with siRNA or shRNA)	HMGA1 knock-down	Clinical delivery	Adenovirus delivery of antisense cDNA into lung, colon, breast, thyroid, pancreatic cells Antisense RNA delivery into Burkitt's lymphoma, breast cell si/shRNA delivery into pancreatic, uterine and lung cancer cells	Scala et al., 2000; Wood et al., 2000b; Dolde et al., 2002; Trapasso et al., 2004; Liau et al., 2006; Tesfaye et al., 2007; Hillion et al., 2009
COX-2 inhibitors	Blocking downstream target of HMGA1	Cardiovascular toxicity. Does not block other HMGA1 pathways	HMGA1a transgenic mice. Murine xenografts with uterine cancer cells	Tesfaye, et al., 2007; Di Cello et al., 2008b; Hillion et al., 2010
STAT3 inhibitors	Blocking downstream target of HMGA1	Does not block other HMGA1 pathways	HMGA1 transgenic mice tumor cells. Cultured leukemia and Burkitts leukemia/lymphoma cells	Hillion et al., 2008
MMP inhibitors	Blocking downstream target of HMGA1	Not specific for single MMP, toxicity. Does not block other HMGA1 pathways	Lung cancer cells	Hillion et al., 2009

†: Studies where HMGA1 was targeted; ‡: Actinomycin-D may compete with HMGA1, although this has not been directly tested.

Potential role as a biomarker

With the advent of global gene expression profiling and tissue microarrays came studies identifying HMGA1 as a marker for metastatic progression or adverse outcomes. The first such study was an investigation of 34 medulloblastomas by gene expression profile analysis, which demonstrated that *HMGA1*, among other genes, correlates with poor prognosis (Pomeroy et al., 2002). Another study of HMGA1 in squamous cell carcinoma and adenocarcinoma lung cancers found that more intense staining for HMGA1 protein by immunohistochemical analysis correlates inversely with survival (Sarhadi et al., 2006). In colorectal cancer, HMGA1 expression was associated with more advanced tumors and lymph node metastases (Balcerczak et al., 2004). Higher *HMGA1α* mRNA and protein levels were found in hepatocellular carcinoma with intrahepatic metastases compared to those without intrahepatic metastases (Chuma et al., 2004). In breast cancer, an immunohistochemical analysis showed that HMGA1 protein levels correlate with high grade (Flohr et al., 2003). Another group found that HMGA1 immunohistochemical staining correlates with ErbB2 expression, which is amplified in poor prognosis breast cancer (Chiappetta et al., 2004). There was no correlation with clinical stage, pathologic grade, or lymph node metastases in this study. A later study of familial breast cancer patients showed no correlation between HMGA1 and survival, although this investigation focused on patients with mutations in BRCA1 or BRCA2. In a small study or uterine tumors, *HMGA1* mRNA levels were found to correlate with higher grade (Tesfaye et al., 2007). More recently, our group found a positive correlation was observed between HMGA1 and poor differentiation status in pancreatic cancer (Hristov et al., 2010). This study also showed that high levels of HMGA1 protein correlate with poor survival. Another study comparing gene expression profiles also found that HMGA1 is among a list of 9 core transcription factors enriched in embryonic stem cells and high-grade/poorly differentiated solid tumors, including breast, bladder and brain tumors (Ben-Porath et al., 2008). Importantly, overexpression of this signature was associated with poor survival in patients with breast, bladder, and brain cancer (Ben-Porath et al., 2008). Taken together, these studies suggest that HMGA1 could promote tumor progression and serve as a biomarker and potential target for more advanced disease in some tumors. Prospective studies are needed to determine if *HMGA1* mRNA or protein expression at diagnosis will predict poor outcomes or could be useful to stratify patients by risk for different therapeutic options in cancers with high expression.

Drugs and biotherapeutics

Although the widespread overexpression of *HMGA1* in human cancer with little or no expression in most normal tissues makes it an attractive target for cancer therapy, there are few published studies investigating the use of drugs or other compounds to directly interfere with the function of this protein (Table 3). A previous study identified FR antibiotic/anti-tumor agents, including FR900482 and FK317 as potential inhibitors to HMGA1 function (Beckerbauer et al., 2000, 2002). Similar to the DNA cross-linking agent, mitomycin C, the FR family of antibiotics cross-link DNA preferentially at 5'CpG'3 sequence after undergoing reductive activation to form reactive mitosene derivatives. FR900482 was shown to covalently cross-link HMGA1 to the minor groove of DNA. In human T-cell acute lymphoblastic leukemia cells (Jurkat), FR900482 also covalently cross-links other minor-groove binding proteins to DNA, such as HMGB1 and HMGB2. Such agents were originally thought to function non-selectively, although FR900482 does not cross-link the major groove binding proteins Elf-1 and NF-κB. While this drug induced apoptotic death in Jurkat cells, it caused life-threatening vascular leak syndrome with pulmonary and cardiac failure in clinical trials and was therefore withdrawn from further clinical investigations (Beckerbauer et al., 2002). FR900482 was later shown to induce expression of both *IL-2* and *IL2Ra* in addition to causing cellular necrosis, which could contribute to vascular leak syndrome. It is possible that FR900482 also interfered with other AT-binding proteins, such as AKNA (Ma et al., 2011; Moliterno and Resar, 2011), which could cause generalized inflammation and pulmonary toxicity. A subsequent study found that the related compound, FK317, covalently cross-links HMGA1 and other minor groove binding proteins to DNA, although without significant vascular leak syndrome. *In vitro* studies with Jurkat cells showed that FK317 caused apoptosis. In contrast to the more toxic agent, FR900482, there was no induction in expression of *IL-2* and *IL2Ra* (Beckerbauer et al., 2002; Nelson et al., 2004). There have been no subsequent published clinical or preclinical trials evaluating its efficacy, however. Actinomycin-D, another antibiotic/anti-tumor agent, selectively binds to and stabilizes DNA at AT-rich regions, and could potentially interfere with HMGA1 binding, although it has not been studied in this context (Wadkins et al., 2000). The minor-groove binding drug Distamycin was recently shown to interfere with HMGA1 binding to the *P-selectin* promoter, but not the *E-selectin* promoter. In addition, Distamycin A caused decreased lung and liver inflammation in a murine endotoxemia model (Baron et al., 2010). Similarly, Netropsin, another small, minor grove binder that selectively targets AT-rich DNA sequences, can interfere with transcription factor binding (Grant et al., 2009). Treatment with this agent also improved survival in mice with experimentally-induced endotoxemia. Notably, there was no benefit in *nitric oxide synthase-2* (*NOS2*) null mice, suggesting that HMGA1 activation of the *NOS2* gene was attenuated by netropsin. *In vitro* studies demonstrated that netropsin interfered with HMGA1 binding to the *NOS2* promoter (Grant et al., 2009), indicating that this is an important

transcriptional target of HMGA1. More recently, a study was published using stable L-RNA oligonucleotides (or Spiegelmers) that were designed to bind to HMGA1 and compete with HMGA1 binding to AT-rich DNA (Maasch et al., 2010). One such compound, NOX-A50, was shown to bind HMGA1 *in vitro* and interfered with xenograft tumor growth from human pancreatic cancer cells following subcutaneous injections near the xenograft tumor (Maasch et al., 2010). This study showed significant levels of NOX-A50 within the tumors, with little accumulation in the liver or kidney tissues. Although further studies are needed, these preclinical studies suggest that small molecules to target HMGA1 could be effective in cancer therapy.

As outlined briefly under functional studies, several groups have used antisense gene targeting or silencing with short-hairpin RNA to block HMGA1 function in cancer cells (Scala et al., 2000; Wood et al., 2000a; Trapasso et al., 2004; Tesfaye et al., 2007; Liau and Whang, 2008, Hillion et al., 2009, 2010; Belton et al., 2012). These studies showed that blocking *HMGA1* expression interferes with multiple cancer phenotypes, such as proliferation, anchorage-independent cell growth, migration, invasion, xenograft tumorigenesis, and even metastatic progression in some cases. Although this approach presents the challenge of effective delivery in the clinic, the results further underscore the potential benefit of blocking HMGA1 function as a therapeutic modality. Given the diversity of cancers overexpressing *HMGA1*, this strategy is likely to have anti-tumor effects in a broad range of aggressive human malignancies.

Because HMGA1 functions by modulating expression of specific genes, interrupting downstream pathways provides an alternative approach to target HMGA1 function in cancer. Our group showed previously that HMGA1 induces expression of the *signal transducer and activator of transcription 3* (*STAT3*) gene, which encodes a central regulator in diverse tumors (Yu and Jove, 2004; Hillion et al., 2008; Yu et al., 2009). Similar to the HMGA1 protein, STAT3 is known to regulate diverse pathways involved in tumor initiation and progression, including angiogenesis, metastatic progression, immune evasion, and inhibition of apoptosis (Yu and Jove, 2004; Yu et al., 2009). Prior studies have used multiple approaches to target transcriptionally active STAT3-STAT3 dimers (Yue and Turkson, 2009; Haftchenary et al., 2011). In the *HMGA1* transgenic leukemia cells, our group found that blocking DNA binding by STAT3 with a platinum-based small molecule (CPA-7; Turkson et al., 2004) resulted in apoptosis in the leukemic cells, but not the normal lymphoid cells. *In vitro* studies in myeloid leukemia or lymphoma cell lines showed that blocking STAT3 function with a dominant-negative protein resulted in decreased mobility and colony formation (Hillion et al., 2008). More recently, we used a small molecule GQ-oligonucleotide inhibitor to STAT3 binding (Jing et al., 2004; Weerasinghe et al., 2007) and found decreased tumor burdens in mice transgenic for *HMGA1* and null for the *CDKN2A* tumor suppressor locus (Hillion, Shah, and Resar, unpublished data) These promising preclinical studies suggest that targeting STAT3 could interfere with tumors driven, at least in part, by HMGA1.

Genes encoding *matrix metalloproteinases* were also identified as transcriptional targets of HMGA1 proteins (Reeves et al., 2001; Takaha et al., 2004; Liau et al., 2006; Hillion et al., 2009). In both lung and prostate cancer cell lines, HMGA1 was found to induce *MMP-2* expression (Takaha et al., 2004; Hillion et al., 2009), while in pancreatic cancer cell lines, HMGA1 up-regulates expression of *MMP-9* (Liau et al., 2006). Inhibiting *MMP-2* expression in lung cancer cells blocks transformation phenotypes *in vitro*, including migration, invasion, and anchorage-independent cell growth. More recently, *HMGA1* transgenic mice were crossed with mice null for MMP-2 and these mice had significantly smaller uterine sarcomas, although the lymphoid tumors appeared to be unaffected (Hillion and Resar, unpublished results, 2011). Although these intriguing preclinical studies suggest that targeting MMPs could be effective cancer therapy for tumors overexpressing *HMGA1*, clinical studies with MMP inhibitors have been disappointing, which could relate to the lack of specificity of many of these agents (Zucker and Cao, 2009). Future work is needed to determine if more effective and specific MMP inhibitors could be used to prevent tumor progression in tumors overexpressing *HMGA1*.

HMGA1 was also found to induce expression of *cyclooxygenase-2* (*COX-2*), first in vascular endothelium (Ji et al., 1998), and more recently, in uterine sarcomas (Tesfaye et al., 2007). Moreover, COX-2 inhibitors have been shown to have efficacy in preventing gastrointestinal cancers (Menter et al., 2010). Increasing evidence also indicates that individuals who take COX-2 inhibitors have a decreased incidence of diverse tumors, suggesting that this could be an effective pathway to target in the prevention of diverse cancers overexpressing *HMGA1* (Menter et al., 2010). In preclinical studies, our group showed that sulindac, a COX-1/2 inhibitor, blocked uterine sarcoma growth in the HMGA1 transgenic model at early time points (Di Cello et al., 2008b). In addition, the growth of tumor xenografts from poorly differentiated uterine sarcomas with high endogenous levels of *HMGA1* was blocked by COX-1/2 inhibitors, but not more differentiated uterine cancer cells with low levels of *HMGA1* expression. Unfortunately, the lymphoid tumors were not significantly affected by therapy with *COX-2* inhibitors, which could reflect an inconsistent up-regulation of *COX-2* in these tumors (Di Cello et al., 2008b). In preliminary studies, we also have evidence that blocking COX-2 is effective in pancreatic cancer xenografts that overexpress HMGA1 (Hillion et al., 2010). Taken together, these studies suggest that targeting the COX-2 pathway could be used to treat, or even prevent, cancers with dysregulation in the HMGA1-COX-2 pathway.

Next Frontiers

Despite recent advances in our understanding of HMGA1 function in cancer, diabetes, and normal development, the precise molecular mechanisms that mediate the biologic activities of HMGA1 are only beginning to emerge. Although several studies have mapped the domains required for DNA binding and identified regions involved in protein-protein interactions (Yie et al., 1999), a more detailed molecular dissection of the functional domains of the protein should provide insight into HMGA1 function in normal and disease processes. As outlined above, gene expression profile analyses have led to the discovery of downstream gene targets activated by HMGA1 (Reeves et al., 2001; Martinez Hoyos et al., 2004; Treff et al., 2004a,b; Takaha et al., 2004; Hillion et al., 2008; Schuldenfrei et al., 2011). These studies, however, likely provide only a snapshot of HMGA1 transcriptional regulatory activities. Candidate sequences with high affinity for HMGA1 have been proposed, and some of the identified genes containing these sequences have been previously validated as HMGA1 targets (Manabe et al., 2009). With the advent of more comprehensive gene expression and chromatin immunoprecipitation arrays that represent the entire human "transcriptome", investigations are needed to globally identify the classes of genes and specific targets regulated by HMGA1 during development, neoplastic transformation, and other biologic settings.

Based on studies with other oncogenic transcription factors, it is likely that HMGA will modulate expression of microRNAs (miRNA) involved in neoplastic transformation (Calin and Croce, 2006). Studies have also shown an inverse relationship between the expression of the tumor suppressor miRNA, *let-7*, and *HMGA1* in retinoblastoma and gastroenteropancreatic neuroendocrine tumors (Mu et al., 2009; Rahman et al., 2009). This suggests that HMGA1 could repress *let-7* expression, or alternatively, *let-7* could repress *HMGA1*. Identification of miRNAs dysregulated by *HMGA1* should complement our knowledge of its role in tumorigenesis. In addition, it is likely that tumor suppressor miRNAs repress *HMGA1* expression. Identification of miRNAs that repress *HMGA1* could lead to novel therapeutic approaches with miRNA replacement as cancer therapy. Indeed, recent preclinical studies with miRNA replacement therapy have demonstrated efficacy with murine models of cancer (Pramanik et al., 2011).

Further study of coding genes that regulate *HMGA1* expression in cancer should also uncover additional pathways that could be manipulated in cancer therapy. For example, *HMGA1* is a transcriptional target of c-Myc, and AP1 family members (Dang et al. 1999; Wood et al., 2000b; Pedulla et al., 2001; Dhar et al., 2004; Takaha et al., 2004; Resar, 2010) and interrupting the function of these transcription factors should also interrupt *HMGA1* expression in cancers dependent upon these pathways. Thus, additional investigation of both coding and noncoding RNAs that regulate HMGA1 should shed light on HMGA1 expression in malignancy as well as identify pathways to target in cancer therapy.

Similarly, a more comprehensive investigation of proteins regulated by HMGA using a proteomics approach may help to elucidate additional biologic functions. While previous research has identified interacting proteins that are important in HMGA1 function (Sgarra et al., 2005; Pierantoni et al., 2007), the discovery of additional protein-protein interactions should advance our understanding of HMGA in cancer, development, and other cellular processes. Previous studies also implicate HMGA1 in genomic instability (Takaha et al., 2002), with a potential role in mediating unbalanced chromosomal rearrangements, and nucleotide excision repair (Adair et al., 2007; Maloney et al., 2007). Further investigations of the role HMGA1 in chromosomal instability are likely to yield insight relevant to HMGA1 in cancer.

The recent interest in stem cell biology has led to the identification of multiple proteins with dual roles, including a role in: 1) normal stem cell function during embryogenesis, and, 2) oncogenic transformation or tumor progression when misexpressed postnatally. Emerging evidence indicates that HMGA1 is such a protein, with important roles in both development and tumorigenesis. Numerous previous studies identified HMGA1 as a factor enriched in normal stem cell populations. For example, studies showed that *HMGA1* is highly expressed in hematopoietic stem cells (Zhou et al., 2001; Karp et al. 2011; Nelson et al., 2011), normal embryonic stem cells (Ben-Porath et al., 2008) and poorly differentiated solid tumors with poor outcomes (Tesfaye et al., 2007; Ben-Porath et al., 2008; Di Cello et al., 2008b; Hristov et al., 2010). Further elucidation of its function in normal stem cells is likely to uncover potential activities that could be targeted in cancer. Similarly, oncoproteins have also been shown to induce senescence in primary cells, a phenomenon known as "oncogene-induced senescence" (Serrano et al., 1997). Recent studies indicate that both HMGA1 and HMGA2 proteins contribute to senescence (Satou et al., 2004; Narita et al., 2006) and a better understanding of this process may identify therapeutic targets that could be manipulated in human cancers associated with HMGA1.

In summary, substantial evidence links HMGA1 proteins to high-grade, aggressive cancers, from its initial discovery in the extraordinarily proliferative HeLa human cervical cancer cells (Lund et al., 1983) to the more recent identification of HMGA1 as a key transcription factor enriched in poorly differentiated cancers with poor outcomes (Pomeroy et al., 2002; Ben-Porath et al., 2008; Hristov et al., 2010). The recent discoveries of transcriptional networks shared by normal embryonic stem cells and cancer in addition to rapidly advancing technology to globally investigate the normal and cancer genome provides unprecedented opportunities to investigate HMGA1 in cancer and

development. These strategies should also uncover novel approaches to target its activity in cancer therapy. The identification of genes, miRNAs, and proteins that are either dysregulated by HMGA or regulate HMGA1 function during transformation promises to have a major impact in our ability to understand and treat cancer. These insights may also have relevance to diabetes, cardiac hypertrophy, and other, as yet undiscovered, diseases linked to HMGA1 proteins.

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