PERSPECTIVE

# Oncogenic HMGA2: short or small?

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The High Mobility Group A (HMGA) family of proteins are architectural transcription factors that bind to DNA and introduce structural alterations in chromatin. The HMGA family consists of two members, HMGA1 and HMGA2, which are encoded by separate genes. As one of the major nonhistone chromosomal proteins, HMGA proteins are multifunctional and are involved in many fundamental cellular processes, including gene regulation, cell cycle, differentiation, and viral integration (Reeves 2001). Not surprisingly, therefore, HMGA mutations contribute to many common diseases, including benign and malignant tumors (Sgarra et al. 2004), obesity (Anand and Chada 2000), diabetes (Foti et al. 2005), and atherosclerosis (Schlueter et al. 2005). HMGA proteins are relatively abundant in the early embryo, where cells are proliferating rapidly, whereas they are undetectable in terminally differentiated cells (Sgarra et al. 2004). *hmga2*-deficient mouse embryonic fibroblasts (MEFs) grow more slowly than wild-type MEFs (Zhou et al. 1995), suggesting that HMGA2 confers a growth advantage. Consistent with this observation, HMGA is indeed oncogenic and is up-regulated in many tumors (see below). However, it was recently shown that HMGA proteins are also involved in cellular senescence, a state of "permanent" cell cycle arrest, adding further diversity to the many facets of the HMGA proteins (Narita et al. 2006).

HMGA proteins are primarily, but not exclusively, up-regulated in tumors of mesenchymal origin. Up-regulation of the *HMGA* gene products often results from genetic alterations such as gene amplification and translocation. Rearrangement of the *HMGA2* gene by reciprocal translocations in particular, is frequently observed in benign tumors such as lipomas, lung hamartomas, uterine leiomyomas, endothelial polyps, fibroadenomas, and adenolipomas of the breast (Ashar et al. 1995; Kazmierczak et al. 1995, 1996; Schoenmakers et al. 1995). HMGA is also involved in malignant tumors such as liposarcomas and osteosarcomas, acute lymphoblastic leukemia, as well as many lung carcinomas (Berner et al. 1997; Xu et al. 2004; Sarhadi et al. 2006). The *HMGA2* gene, which is located in the q13-15 segment of chromosome 12, consists of five exons. Each of the first three exons encodes for an AT-hook domain, so called because they bind to the minor groove of AT-rich stretches of DNA. Exons 4 and 5 encode the linker and acidic tail regions, respectively. In most *HMGA2* translocations, the breakpoint occurs within the ~140-kb third intron, giving rise to chimeric transcripts that are a fusion of HMGA2's three AT-hooks with various other genes (Goodwin 1998). It was therefore presumed that the fusion proteins themselves were the cause of the tumorigenicity, as exemplified by the classical oncogenic translocations PML-RARa and BCR-ABL. Surprisingly, however, a truncated form of HMGA2, containing only the three AT-hook domains, was sufficient for transformation in vitro. This finding raises the possibility that the loss of the acidic tail, rather than the generation of chimeric proteins, is the critical step in causing HMGA oncogenicity (Fedele et al. 1998). To date, multiple *hmga2* transgenic mouse models have been generated, which constitutively express either the full-length or the truncated form of the protein (Arlotta et al. 2000; Fedele et al. 2002). Although these mice all develop benign tumors, their tumor spectrum is slightly different; the truncated form of HMGA2 gives rise to gigantism associated with lipomatosis, while full-length HMGA2 leads to pituitary tumors with milder lipomatosis. Recently, new transgenic mouse models were generated, in which either a full-length or a truncated from of HMGA2 was expressed under a promoter specific for differentiated mesenchymal tissues (Zaidi et al. 2006). Both transgenic models developed various benign mesenchymal tumors, yet the severity of the tumor phenotype was not affected by the presence or absence of the C-terminal acidic tail. These findings, in contrast to the original *hmga2* transgenic models that ubiquitously and constitutively express HMGA2, suggest that the misexpression of HMGA2 itself is sufficient for tumorigenesis, at least in the mesenchymal lineage. Thus, how translocations in the *HMGA2* locus lead to tumor development is a matter of debate.

Now, Lee and Dutta (2007) in this issue of *Genes & Development*, together with others (Hebert et al. 2007; Lee and Dutta 2007; Mayr et al. 2007; Wang et al. 2007), provide new insight into this long-standing debate, indicating that the chromosomal translocations within *HMGA2* may contribute to tumorigenesis by removing *HMGA2*'s 3′ untranslated region (UTR). These reports identify *HMGA2* as a target of the *let-7* family of microRNAs (miRNAs). miRNAs encode a class of small, regulatory noncoding RNAs, which have come to prominence as a key mechanism of post-transcriptional regu-

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lation within the last decade (Ambros 2004; Bartel 2004; Zamore and Haley 2005). Primary transcripts of miRNA genes (pri-miRNAs) undergo sequential processing to yield mature miRNAs, 18–25 nucleotides in length. The biogenesis of miRNAs involves two RNase III enzymes, Drosha and Dicer. pri-miRNAs are processed by Drosha into precursor miRNAs (pre-miRNAs), which are subsequently processed by Dicer into the mature miRNAs. The mature miRNAs typically bind, with imperfect base pairing, to the 3′UTRs of specific mRNA targets and repress their expression at the post-transcriptional level (Fig. 1A).

Lee and Dutta (2007) identify that the *HMGA2* transcript can be regulated by miRNA through a screen for candidates based on Dicer knockdown in HeLa cells. They subsequently confirm that the *HMGA2* mRNA is destabilized only in the cytoplasmic fraction, consistent with the cytosol being the primary site of miRNA function. Computational searches identified multiple putative *let-7*-binding sites in the 3′UTR of the *HMGA2* mRNA (Hebert et al. 2007; Lee and Dutta 2007; Mayr et al. 2007; Wang et al. 2007). *Let-7* was one of the first miRNA genes to be discovered in *Caenorhabditis elegans*, a heterochronic gene regulating the developmental timing of the larvae. The *let-7* family's expression is also developmentally regulated in mice (Schulman et al. 2005) and humans (Pasquinelli et al. 2000). The expression of *let-7* during development is inversely correlated with that of *HMGA2*. This observation lead Lee and Dutta (2007) to focus on *let-7*, and *let-7b* and *let-7e* more specifically, and carry out detailed structural and functional analyses of the 3′UTR of the *HMGA2* transcript, showing in luciferase reporter assays that six of the eight putative *let-7*-binding sites are responsible for *HMGA2* repression. Mayr et al. (2007) perform a similar analysis, yielding consistent results. Furthermore, disruption of the *let-7* repression of *HMGA2* enhances cell proliferation in H1299 cells (Lee and Dutta 2007) and causes transformation in NIH-3T3 cells (Mayr et al. 2007). These results suggest an intriguing possibility: that the "translocation-associated loss of miRNA-mediated repression" may contribute to tumorigenesis (Fig. 1B).

Genomic rearrangement may not be the only thing that affects the miRNA-mediated regulation of *HMGA2*. Herbert et al. (2007) show in primary human oral squamous carcinoma cells (SCCs) that levels of *miR-98* (a miRNA highly related to *let-7*) increase in hypoxic conditions, characteristic of the microenvironment found in many tumor tissues. The authors also show the up-regulation of *let-7* in the same hypoxic context, although to a lesser extent. Interestingly, the hypoxia-induced up-regulation of *miR-98* correlated with the down-regulation of *HMGA2*, which causes SCCs chemoresistance. Indeed, Herbert et al. (2007) verify that *miR-98* can target *HMGA2* in these cells. Although the data are correlative, the study suggests that a hypoxic microenvironment could potentially modulate the characteristics of a tumor through the alteration of its miRNA profile.

Approximately 80% of the conserved vertebrate miRNAs that are expressed during embryonic development are tissue specific (Wienholds and Plasterk 2005). This tissue specificity is not restricted to only a few major organs, even individual cell types within tissues have specific expression of one or a few miRNAs (Wienholds and Plasterk 2005). The distinct expression profile of miRNAs may also be important in cellular transformation and tumorigenesis. Aberrant expression of some miRNAs is associated with certain types of tumors such as leukemias, lung cancer, and breast cancers (Calin et al. 2004; Cimmino et al. 2005; Iorio et al. 2005; Johnson et al. 2005; Volinia et al. 2006; Yanaihara et al. 2006). Wang et al. (2007) analyze the global miRNA expression pattern of 55 samples of human uterine leiomyomas (ULMs), a tumor in which a *HMGA2* translocation is commonly found, and show a homogenous and specific miRNA signature in these tumors. In this study, *let-7* is one of the top five deregulated miRNAs in ULMs and, indeed, *let-7* is up-regulated in tumors compared with

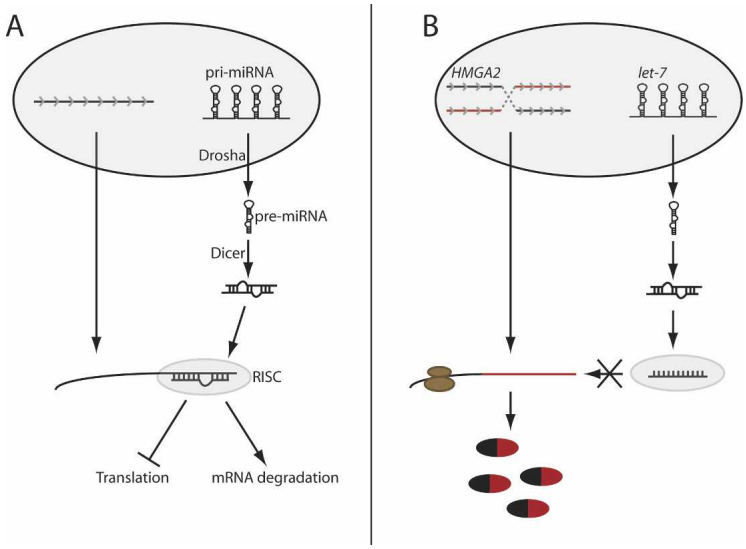


**Figure 1.** Translocation-associated loss of miRNA-mediated repression. (*A*) miRNAs are sequentially processed after transcription in both the nucleus and cytoplasm. miRNAs regulate mRNA expression by inhibiting translation and/or causing the degradation of the mRNA. (*B*) As suggested by a series of new studies, upon translocation within a gene locus, in this case *HMGA2*, the sites previously recognized by the corresponding miRNA, *let-7*, can be removed with the result that the mRNA is aberrantly expressed. Conceivably, any translocation within a gene locus may result in the loss of the miRNA-mediated regulation of a gene's expression. This might also be true even for the cases where chimeric gene products have aberrant functions that would be further modified quantitatively by the exchange of the post-transcriptional regulation. Here, HMGA2 is in black and its fusion partner is in red.

the matched myometrium samples. More careful analysis revealed a correlation between tumor size and *let-7*/*HMGA2* expression levels; the small tumors tending to exhibit higher *let-7* and lower HMGA2 expression, while the large ULMs tend to show the opposite pattern. Although no functional analysis is provided, one tempting interpretation of this data is that, during tumor development, up-regulation of *let-7* is triggered, which inhibits the tumor's growth by repressing the expression of *HMGA2* and probably other targets. This, then, might be an example where *let-7* exhibits an active tumor suppressor function in vivo.

Are miRNAs the only method of post-transcriptional regulation of *HMGA2* mRNA? Post-transcriptional repression of genes involves several events, including translational repression and mRNA decay (for review, see Eulalio et al. 2007). It was recently shown that translational repression and mRNA decay are not only functionally, but also physically associated, and miRNAs can be a link between them (Eulalio et al. 2007). The AU-rich element (ARE)-mediated mRNA decay (AMD) pathway, for example, is one of the most studied mechanisms of post-transcriptional regulation. The ARE motif is a *cis*-acting RNA element and the presence of an ARE motif in mRNAs is associated with the rapid turnover of unstable mRNAs in mammalian cells. Recently, a specific miRNA, *miR-16*, was shown to be involved in the degradation of at least some ARE-containing mRNAs (Jing et al. 2005), although it is not clear whether *miR-16* is the sole link between the miRNA and AMD pathways. Similar to miRNA, ARE target sites are often located in the 3′UTR of mRNAs. Interestingly, the post-transcriptional regulation of *HMGA2* through its 3′UTR was originally implied 10 yr ago (Geurts et al. 1997). It was shown that the *HMGA2* transcript contains 10 ARE motifs (AUUUA) in its 3′UTR (Geurts et al. 1997; Borrmann et al. 2001). Borrmann et al. (2001) performed reporter assays using several 3′ deletion mutants of the *HMGA2* mRNA, and showed that *HMGA2* expression is negatively regulated by its 3′UTR. Since they used a series of large truncations, it is not possible to say whether the effects of the deletion mutants reflect the loss of the *let-7* targeting sites in the 3′UTR. Thus, a dual regulation of *HMGA2* expression by AMD and *let-7* is still a possibility. It remains to be shown whether *HMGA2* expression is negatively regulated by these two mechanisms independently or whether they cooperatively contribute to the repression of *HMGA2* and, as a consequence, in tumor suppressor function.

Whichever is the case, altogether these new studies convincingly show that *HMGA2* is a *let-7* target (Hebert et al. 2007; Lee and Dutta 2007; Mayr et al. 2007; Wang et al. 2007) and imply that the tumor-suppressive activity of *let-7* relies on HMGA2 repression (Lee and Dutta 2007; Mayr et al. 2007), reinforcing the important roles of miRNA in cancer biology (Caldas and Brenton 2005). Furthermore, these studies provide a new view on why *HMGA2* translocation leads to so many tumors. Thus, these studies, in conjunction with the unique history of the studies of HMGA2 oncogenicity, raise an important question: Is the "translocation-associated loss of miRNA-mediated repression" a general mechanism in tumor development? Conceivably, any cancer-related translocation may result in the loss, or more precisely speaking, exchange, of the miRNA-mediated regulation of a gene's expression (Fig. 1B). This might also be true even for the cases where chimeric gene products have aberrant functions, which would be further modified quantitatively by the exchange of the post-transcriptional regulation. In addition, how commonly does the *let-7* defect contribute to *HMGA2* up-regulation and tumorigenesis without any genomic alteration of the *HMGA2* locus. Finally, how does HMGA2 confer a growth advantage to cells? Although there is not much insight into the molecular basis for the oncogenic activity of HMGA proteins, a potential role of its C-terminal acidic tail in tumorigenesis has been suggested, and an enhanced transformation activity of such a truncation of HMGA2 has been shown in vitro and in xenograft systems (Fedele et al. 1998). In addition, truncated HMGA1 was also shown to dramatically increase the growth rate of 3T3-L1 cells, a model of adipogenisis in vitro (Pierantoni et al. 2003). HMGA proteins participate in the regulation of many genes through their physical association with DNA, as well as with a large number of proteins. The acidic tail is thought to have an influence on HMGA's protein–DNA or protein–protein binding and, indeed, it has been shown that the acidic tail can modify the "architectural transcription" activity of HMGA proteins for certain specific target genes (Yie et al. 1997; Borrmann et al. 2003). In addition, the rearrangement in the *HMGA2* locus in malignant tumors is very complicated, and this can involve not only *HMGA2* breakpoints, but also the status of its neighboring genes, *MDM2* and *CDK4*, both of which are often coamplified with *HMGA2* in tumors (Berner et al. 1997). Interestingly, ectopic expression of *MDM2* and *CDK4* can mask the ability of HMGA2 to enhance the senescence phenotype of human diploid fibroblasts (HDFs) (Narita et al. 2006). Also, full-length HMGA2 can contribute to the malignant transformation of the HDFs cooperatively with oncogenic *ras*, only when the senescence pathway is completely blocked (Narita et al. 2006). Therefore, full-length HMGA2 function is largely context dependent, which might in part be attributable to its acidic tail. Thus, the discovery of the post-transcriptional regulation of *HMGA2* through the 3′UTR does not necessarily detract from the importance of the potential role of the acidic tail in the oncogenic properties of HMGA proteins in some cellular contexts. Perhaps more physiological settings will be required to tackle the precise role of the acidic tail in malignant transformation.

The series of new studies discussed here (Hebert et al. 2007; Lee and Dutta 2007; Mayr et al. 2007; Wang et al. 2007) provide convincing evidence of the link between *let-7* and *HMGA2* using cultured cells. However, the clinical and in vivo significance of the *let-7*/*HMGA2* connection remains to be addressed. Both the up-regulation of HMGA2 and the down-regulation of *let-7* have been reported in independent studies of lung cancer, for

example. Indeed, both are associated with poor prognosis (Takamizawa et al. 2004; Sarhadi et al. 2006). This inverse correlation between *HMGA2* and *let-7* expression is very interesting, but the analysis of the direct link between these two transcripts in the same tumor tissues still remains to be determined. Does the deficiency of the *let-7* cluster contribute to cancer development and is HMGA2 required for this phenotype in vivo? Is *HMGA2* the sole target for the *let-7* phenotype in cancer? Given the flexibility of the target specificity of each miRNA and the diversity of the highly related miRNAs, it would be necessary to view the relation between mRNA targets and miRNAs as a network. In this sense, for example, what is the role of *ras*, another important oncogene in lung cancer, which has also been shown to be a target of *let-7* (Johnson et al. 2005)? Do *HMGA2* and *ras* cooperate in certain lung cancers and, also, is *let-7* a key element for the cooperative action between them? Paradoxically, both the *HMGA2* and *ras* oncogenes contribute to the cellular senescence phenotype. What is a role of *let-7* in senescence, if any, both in vitro and in vivo? Currently, there are few mouse models available to study the roles of miRNAs in cancer (He et al. 2005); genetically modified mouse models for specific miRNAs, the *let-7* cluster in this case, in conjunction with the *hmga2* transgenic and knockout mice will be necessary to address these questions. An important note is that the transgenes of the existing *hmga2* transgenic mice apparently only contain the open reading frames and, consequently, are free of *let-7* regulation. Cancer is a complicated disease and the miRNA regulation of cancer-related genes certainly adds another layer of complexity, but understanding its in vivo significance will extend our outlook and increase our chances of finding targets for cancer therapy.

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