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Lessons from the Crypt: HMGA1—Amping up Wnt for Stem Cells and Tumor Progression

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Abstract

High mobility group A1 (HMGA1) chromatin remodeling proteins are enriched in aggressive cancers and stem cells, although their common function in these settings has remained elusive until now. Recent work in murine intestinal stem cells (ISC) revealed a novel role for Hmga1 in enhancing self-renewal by amplifying Wnt signaling, both by inducing genes expressing Wnt agonist receptors and Wnt effectors. Surprisingly, Hmga1 also “builds” a stem cell niche by upregulating Sox9, a factor required for differentiation to Paneth cells; these cells constitute an epithelial niche by secreting Wnt and other factors to support ISCs. *HMGA1* is also highly upregulated in colon cancer compared with nonmalignant epithelium and SOX9 becomes overexpressed during colon carcinogenesis. Intriguingly, HMGA1 is overexpressed in diverse cancers with poor outcomes, where it regulates developmental genes. Similarly, *HMGA1* induces genes responsible for pluripotency and self-renewal in embryonic stem cells. These findings demonstrate that *HMGA1* maintains Wnt and other developmental transcriptional networks and suggest that *HMGA1* overexpression fosters carcinogenesis and tumor progression through dysregulation of these pathways. Studies are now needed to determine more precisely how *HMGA1* modulates chromatin structure to amplify developmental genes and how to disrupt this process in cancer therapy.

Chromatin and Cell Fate

Emerging evidence underscores the key role for chromatin binding proteins in maintaining nuclear organization critical for stem cell properties, both during development and oncogenesis. Indeed, nuclear structure is the most important feature that distinguishes a cancer cell from a normal cell histologically (1). Both stem cells and poorly differentiated cancer cells harbor enlarged nuclei with open, “poised” chromatin (2), which may endow

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them with plasticity or potential for multiple cell fate decisions. While the molecular underpinnings of chromatin structure and stem cell transcriptional programs are beginning to emerge, a better understanding of these networks promises to provide insight into cancer and development. Here, we focus on HMGA1 in “stemness” and carcinogenesis.

HMGA Proteins

Remarkably, eukaryotic DNA is condensed from >2 meters to <20 mm by association with nuclear proteins. Nucleoproteins and DNA comprise chromatin, and histones are the most abundant chromatin binding proteins. Histones compact DNA by creating positively charged octamer “spools” around which negatively charged DNA fibers wrap. HMG proteins are the next most abundant class of chromatin binding proteins (3–6), which were discovered in the 1970s in calf thymus using salt extraction and solubility in trichloroacetic acid (7–8). Ten years later, HMGA proteins were separated from other HMG proteins by their phosphorylation status in cancer cells (9–10). Intriguingly, histone H1 and HMGA share significant homology in plants and lower organisms, suggesting that they evolved from the same ancestral protein (11).

Today, HMG proteins are classified into 3 families: HMGB, HMGN, HMGA. All are basic, low-molecular-weight proteins that migrate rapidly through polyacrylamide gel, hence the name high mobility group. They all contain an acidic carboxyl terminus, although each family is defined by unique DNA or nucleosome binding motifs. All modify chromatin structure, but each has distinct functions.

HMGB

HMGB (HMGB1, HMGB2, HMGB3, and HMGB4) are the most abundant HMG proteins. They are distinguished by 2 HMG-box motifs that mediate binding to DNA without sequence specificity (5, 12–13). HMG boxes are formed by 3 alpha helices that fold into an L-shape that penetrates the minor groove of DNA, inducing a sharp bend. Unlike other HMG proteins, HMGB proteins function as cytokines mediating paracrine signaling (12–13). “HMG-box proteins” comprise a larger class of proteins that includes HMGB, and less abundant proteins with one or more HMG-boxes (SOX9, SRY, LEF1, TCF). In contrast to HMGB, proteins with only one HMG-box bind DNA with sequence specificity. The acidic carboxyl terminus modulates their affinity for different DNA structures. HMGB proteins participate in cell fate decisions, DNA damage responses, and senescence. Increasing evidence also implicates HMGB as key signaling molecules in cancer (13).

HMGN

HMGN proteins (HMGN1, HMGN2, HMGN3, HMGN4, and HMGN5) are found only in vertebrates. They lack an HMG-box, but contain a positively charged, nucleosome-binding “N” domain that mediates binding to nucleosomes (5). The acidic carboxyl terminus or “chromatin unfolding domain” alters DNA architecture, inducing changes in local organization and higher order structure. HMGN proteins “relax” DNA by competing for nucleosome binding with histone H1, which tends to compact DNA (14). HMGN proteins

also recruit active histone marks (histone 3 lysine 14 acetylation; H3K14Ac; ref. 15), deplete repressive marks (H3K17trimethylation; ref. 16), and oppose ATP-dependent remodeling proteins that restrict nucleosome motility (17). Recent work in Down syndrome leukemia found that triplication of chromosome 21 causes *HMGN1* overexpression, which contributes to leukemogenesis (16).

HMGA

HMGA proteins—the focus of this review—are distinguished from other HMG families by 3 AT-hook motifs that mediate binding to the minor groove of B-form DNA at AT-rich sequences (3–6, 18–20). This family includes HMGA1a/HMGA1b isoforms, encoded by the *HMGA1* gene (human chr 6p21) through alternatively spliced mRNA; HMGA1c, encoded by a rare splice variant found in testes; and (iii) HMGA2, an HMGA1 homolog encoded by *HMGA2* (human chr 12q14). Like HMGN, these proteins lack an HMG-box, but in contrast to HMGN or HMGB, they bind to DNA with sequence specificity (18–26). By NMR structural analysis, the AT-hooks are unstructured, although they transition to a highly ordered structure after binding DNA and/or protein partners (23). Like HMG boxes, AT-hooks penetrate the minor groove to induce bending. HMGA proteins also harbor an amino-terminal serine-, threonine-rich domain, although its function is unclear. The acidic carboxyl terminus mediates protein–protein interactions (5). Similar to HMGN, HMGA1 competes with histone H1 for DNA binding *in vitro* (21). After displacing histone H1, HMGA widens or “opens” the minor groove, facilitating recruitment of transcription factor complexes and chromatin modifiers to modulate gene expression (Fig. 1A; refs. 4–6, 27–35).

HMGA1 Portends Poor Outcomes

The first evidence linking *HMGA1/2* to cancer was their discovery in extraordinarily proliferative HeLa cervical cancer cells (10). Subsequent studies showed that *HMGA1/2* become overexpressed in diverse tumors arising from all three germ layers (18–20). While the list is expanding, *HMGA1* is overexpressed in cancers of the brain, head and neck, esophagus, thyroid, lung, breast, prostate, colon, rectum, pancreas, liver, uterine corpus, cervix, skin, and hematopoietic system (reviewed in ref. 19). *HMGA2* is also overexpressed in diverse cancers, although less broadly (18–20, 36–42). With the advent of microarray and RNAsequencing technology, it became clear that *HMGA1/2* overexpression correlates with poor differentiation and adverse clinical outcomes in diverse tumors (43–44). Indeed, the first study using mRNA microarrays revealed that *HMGA1* is among the genes associated with poor survival in medulloblastoma (43). High *HMGA1* also correlates with relapse in childhood leukemia (44). *HMGA1/2* are highly expressed during embryogenesis with low or undetectable levels in adult, differentiated tissues (45, 46). Similarly, *HMGA1/2* genes are enriched in ESCs (46–49) and many tissue-specific, adult stem cells (49–51). In fact, *HMGA1* was identified among a signature of 13 transcription factor genes most enriched in human ESCs (48). Strikingly, this signature predicts poor outcomes in breast, bladder, and brain cancer (48). Immunohistochemical analysis of HMGA proteins in primary tumors further validated gene expression studies, demonstrating high levels with poor differentiation and metastatic progression (52–53). To illustrate, HMGA1 immunoreactivity is present in >90% of pancreatic ductal adenocarcinomas (53–55) and correlates positively with poor

differentiation and decreased survival (53). While HMGA1 was undetectable in normal tissue and early precursor lesions, immunoreactivity occurs in late precursor lesions and invasive tumors, suggesting a role in tumor progression (53). In contrast, HMGA2 immunoreactivity is present in 30% of tumors, where it associated with lymph node metastases and poor survival (41). In general, tumors with high HMGA1 lacked HMGA2 and vice versa. In contrast, studies in lung (39–40, 52), breast (42, 56), colon (42, 57–59), and other malignancies showed overexpression of both *HMGA1/2* genes and proteins, suggesting that they collaborate in these settings. Together, these studies highlight HMGA1/2 as potential biomarkers and therapeutic targets in diverse tumors.

While *HMGA1/2* genes are overexpressed in cancer, the mechanisms that mediate their expression are only beginning to emerge. Both *Hmga1/2* are robustly induced by serum or growth factors (FGF, EGF, and PDGF) in murine fibroblasts rendered quiescent by serum deprivation (60). Similarly, *HMGA1/Hmga1* is upregulated by EGF or phorbol esters in MCF-7 breast cancer cells (61) or by IL2 in mouse T cells (CTLL; ref. 60). In fibroblasts, *Hmga1/2* display delayed-early kinetics with maximal induction within 5 to 10 hours following growth factor stimulation (60). Their transcription requires new protein synthesis, suggesting that immediate-early transcription factors induce *HMGA1/2* expression. In fact, *HMGA1* is a direct transcriptional target of MYC oncoproteins, and *HMGA1* is overexpressed in tumors driven by MYC (Burkitt lymphoma, neuroblastoma; refs. 62–63). AP1 transcription factors also induce *HMGA1* (64, 65) and *HMGA1* is upregulated in tumors linked to inflammation (colon, refs. 57–59, 66; esophageal, ref. 67; cervical carcinomas, ref. 68) as well as experimental models of viral infection (27–34). Following viral infection, HMGA1 recruits NF- κ B to enhancer complexes, where it transactivates *IFN β* (27–34). HMGA1 also upregulates other proinflammatory genes, including *STAT3* (69, 70) and *COX-2* (71, 72). STAT3 may induce *HMGA1*, providing a feed-forward loop to maintain *HMGA1* (69–70). Hypoxia also induces *HMGA1* in vascular endothelial cells, which promotes angiogenesis through COX-2 (73). In rare cases, chromosomal duplication or translocations cause *HMGA1* overexpression, although translocations and fusion genes involve *HMGA2* more commonly (36, 74). Loss of tumor suppressor microRNAs, such as *Let-7*, induces *HMGA2* (75–76). *APC* mutations, common early events in colorectal cancer, repress *mir-26*, resulting in overexpression of *Hmga1* in murine intestinal epithelium (77). Together, these findings suggest a model whereby hyperactive growth factor signaling, mutations, infection, and inflammation converge on *HMGA1/2* to upregulate their expression.

Cancer and Embryogenesis

Following their discovery, functional studies of *HMGA1/2* revealed potent oncogenic and stem cell properties. Forced expression of *Hmga1a*, *Hmga1b*, or *Hmga2* induces oncogenic transformation (62, 78–80), recapitulating *cMYC* phenotypes in immortalized cells, including anchorage-independent cell growth and xenograft tumorigenesis in immunosuppressed mice. Transgenic mice overexpressing murine *Hmga1a* from the H-2K promoter and m enhancer develop aggressive lymphoid tumors (80). During tumorigenesis, *Hmga1* upregulates genes involved in proliferation, inflammation, and hematologic development (81). Female transgenics also develop uterine sarcomas that depend, at least in

part, on *COX-2* upregulation (71). Transgenics overexpressing human *HMGA1b* from the CMV promoter develop lymphoid tumors and pituitary adenomas (82), while those overexpressing a truncated *HMGA2* develop lipomatosis and gigantism (83–84). Functional studies demonstrated that blocking *HMGA1* expression profoundly disrupts cancer phenotypes. For example, silencing *HMGA1* in breast cancer cells halts proliferation and reprograms invasive, mesenchymal cells into noninvasive, epithelial-like cells (56). Both orthotopic tumorigenesis and metastatic progression to the lungs were disrupted. *HMGA1* silencing also depletes tumor initiator/ cancer stem cells in limiting dilution tumor assays and prevents three-dimensional (3D) sphere formation (56). Similar results were observed in cancer cells from colon (57), pancreas (54), lung (52), and others. In some cancer cells (breast, colon, and pancreatic), tumor progression, epithelial–mesenchymal transition (EMT), and cancer stem cell properties depend upon *HMGA2* (42, 58, 75, 85). These studies showed that *HMGA1/2* genes promote tumor progression, at least in part, by hijacking EMT and other stem cell pathways (Fig. 1B and C).

Studies in human ESCs revealed that *HMGA1* decreases with differentiation and parallels that of the pluripotency factors, while forced *Hmga1* expression blocks differentiation (46). When included with the Yamanaka reprogramming cocktail, *HMGA1* enhances the derivation of induced pluripotent stem cells (iPSC), resulting in larger, more abundant colonies (46). Mechanistic studies showed that *HMGA1* occupies promoters of pluripotency genes and induces their expression. Intriguingly, another group showed that *HMGA2* slightly decreases reprogramming efficiency to iPSCs by the Yamanaka factors (47). Mice lacking *Hmga2* exhibit a pygmy phenotype with decreased fat tissue (86). Hematopoietic stem cells lacking *Hmga2* have defective fetal hematopoiesis with slower proliferation and self-renewal rates, whereas *Hmga2* is dispensable for adult hematopoiesis (87). Mice deficient in *Hmga1* have been described, with decreased spermatogenesis and infertility in one model (88), and a diabetes-like phenotype (89) with cardiomegaly and aberrant hematopoiesis (90), in another. In preliminary studies, our group found premature aging and partial embryonic lethality in *Hmga1*-deficient mice (91). Further research is needed to better understand the function of *HMGA1/2* during embryogenesis and aging.

Hmga1 Amplifies Wnt and Self-Renewal

Recent work uncovered a unique role for *Hmga1* in maintaining both stem cells and the niche compartment in intestinal epithelium (Fig. 2; ref. 51). *Hmga1a* transgenic mice develop hyperproliferation, aberrant crypt formation, and polyposis involving small and large intestines (51). To determine how this occurs, crypt cultures from *Hmga1* mice were compared with those from wild-type controls, revealing a marked increase in organoid formation, organoid and bud size, and bud number from *Hmga1* cells (51). Because ISCs localize to bud tips recapitulating *in vivo* crypt organization, bud number is a surrogate for ISC number and/or function (92). To enumerate ISCs, *Hmga1* mice were crossed to EGFP-*Lgr5*⁺ mice, which mark crypt basilar *Lgr5*⁺ ISCs with green fluorescent protein (GFP; ref. 92). ISC frequency was increased in all regions of small intestine in *Hmga1* mice compared with controls. In both controls and transgenic mice, *Hmga1* mRNA and protein are enriched in *Lgr5*⁺ ISCs, but with higher levels in the transgenic model (51). To determine whether *Hmga1* regulates self-renewal, purified *Lgr5*⁺ ISC cultures were followed using time-lapsed

imaging and demonstrated an increase in self-renewal rates. Colony formation and replating efficiency were also increased, further demonstrating enhanced stem cell function (51). In contrast, silencing *Hmga1* in crypt cultures disrupts organization of 3D organoids and bud formation, while overexpressing *Hmga1* in wild-type crypt cells phenocopies the organoids from *Hmga1* mice. Intriguingly, *Hmga1*-overexpressing organoids exposed to Wnt exhibit exaggerated responses, forming larger cystic structures with more Lgr5⁺ ISC compared with controls (51). Conversely, *Hmga1* crypts are relatively impervious to Wnt inhibitors, suggesting that Hmga1 amplifies Wnt signals, possibly by upregulating Wnt signaling genes. To test this, canonical Wnt pathway gene expression was interrogated in Lgr5⁺ ISCs. Strikingly, Hmga1 upregulated genes encoding *both* Wnt agonist receptors and downstream Wnt effectors (51). While the mechanisms are not yet known, Hmga1 could directly transactivate Wnt effector gene expression or indirectly upregulate their expression through changes in chromatin architecture.

HMGA1 “Builds” a Niche

Surprisingly, Hmga1 also helps “build” a Paneth cell niche by upregulating *Sox9*, a Wnt target gene that is essential for Paneth cell differentiation (51, 93, 94). This was unexpected because Paneth cells are terminally differentiated; they also provide an epithelial-specific niche for ISCs by secreting Wnt. Additionally, Paneth cell granules protect the intestinal epithelium from bacteria and other pathogens by releasing lysozyme and other enzymes. Hmga1 binds directly to the *Sox9* promoter to induce its expression (51). Accordingly, both *Sox9* mRNA and protein are upregulated in *Hmga1* transgenic intestinal epithelium and organoid cultures. Further, *Sox9* overexpression in organoids is sufficient for Paneth cell expansion in this model (51). This was the first example of Hmga1 promoting terminal differentiation to establish a stem cell niche.

Hmga1/2 in Colorectal Carcinogenesis

In human colonic epithelium, *HMGA1* and *SOX9* are positively correlated and both become markedly upregulated during colorectal carcinogenesis [data from The Cancer Genome Atlas (TCGA); ref. 51]. In cancer, however, their correlation is lost, which likely occurs because colonic epithelium acquires multiple mutations during carcinogenesis, some of which enhance *SOX9* or *HMGA1* independently (95). Prior studies identified *HMGA1* among the genes most upregulated in colon cancer compared with nonmalignant epithelium (66). These data support a model whereby tightly regulated *HMGA1* and *SOX9* collaborate in intestinal homeostasis, whereas both become deregulated and overexpressed in cancer.

Intriguingly, transgenic mice overexpressing *Lin28* in the intestinal epithelium develop *Hmga2* overexpression and findings similar to *Hmga1* mice with intestinal hyperproliferation and polyps (58). Accelerated adenomas and adenocarcinomas also form and these phenotypes depend upon repression in *Let-7b/c* by knockout of the *mirLet7c2/mirLet7b* locus in the intestinal epithelium in concert with *Lin28* overexpression (59). In contrast to *Hmga1* mice, Paneth cells are depleted, both in *Lin28* mice and in *Let-7b/c*-deficient mice, suggesting that a threshold level of *Let-7b/c* is needed for Paneth cell development (58–59). Wnt signaling and stem cell genes are upregulated in intestinal

epithelium in both *Lin28*-overexpressing and *Let-7*-deficient models. In addition to *Hmga2*, *Igf2bp1*, and to a lesser extent, *Hmga1*, are induced in intestinal crypts from both models (58–59). *Hmga2* overexpression in organoids phenocopies the *Lin28* organoids whereas heterozygous loss of *Hmga2* decreases tumorigenesis in *Lin28* transgenic mice (59). Human colorectal tumors overexpress *HMGA1* or *HMGA2*, and *HMGA1/2* overexpression associates with poor survival in a subset of tumors (TCGA data; ref. 59). Together, these findings indicate that *Hmga2* or *Hmga1* confer proliferative and stem-like programs when overexpressed in mouse intestinal epithelium, while human tumor data further implicate *HMGA1/2* as potential therapeutic targets in colorectal cancer.

Implications and Future Directions

The recent work highlighted here revealed for the first time that intestinal overexpression of *Hmga1* or *Hmga2* amplifies Wnt signaling, causing hyperproliferation and polyposis. *Hmga1* drives ISC expansion by enhancing self-renewal, although it is not yet known whether *Hmga2* alters the ISC number or function (52). *Hmga1* also upregulates Wnt agonist receptors. Recent work also uncovered an unexpected role for *Hmga1* in “building a niche” by fostering Paneth cell differentiation through *Sox9*. In contrast, mice overexpressing *Lin28* repress *Let-7b/c* and deplete Paneth cells, despite an upregulation in *Hmga1/2* and other stem cell genes, indicating that Paneth cell development may require *Let-7*. *HMGA1/2* genes are enriched in human ISCs (50–51) and other tissue-specific stem cells, including hematopoietic (49) and mesenchymal (96); they may be critical regulators in diverse adult stem cells. Prior studies showed declining *Hmga1/HMGA1* in murine and human hematopoietic stem cells with aging (97, 98), which could contribute to decreasing regenerative function with age. Our knockout mouse model also suggests that *Hmga1* deficiency causes aging phenotypes, possibly through attrition in stem cell number or function (91). Because HMG proteins foster “open” chromatin, it is plausible that *HMGA1/2* promote epigenetic alterations and a chromatin state that permits multiple cell fate decisions, plasticity, and regenerative function, not only in adult stem cells but also in aggressive, stem-like cancers.

Overexpression of *HMGA1/2* and *SOX9* in colonic epithelium could also collaborate in tumor initiation and progression. Multiple genetic lesions are acquired during colon carcinogenesis, such as *APC* mutations and other genes in this pathway, including *SOX9* (95). *APC* mutations generally occur early and may upregulate *HMGA1* by repressing *miR-26* as demonstrated in murine models (77). Functional studies show that *HMGA1* is required for metastatic progression and stem cell properties in colorectal cancer models (57). Thus, mutant *APC* could induce both *HMGA1* and *SOX9* during tumor progression. These data, together with results showing that *Tcf4* binds to the *HMGA1* promoter in colorectal cancer cells (99), suggest that *HMGA1* orchestrates a “feed-forward” loop whereby Wnt/*Tcf4*/b-catenin induces *HMGA1*, and *HMGA1*, in turn, amplifies Wnt and other developmental pathways to drive tumor progression. Wnt signaling also upregulates *HMGA1* in gastric cancer (100), and there are likely to be many developmental pathways linked to *HMGA1* during tumorigenesis. *HMGA2* also promotes tumor progression and stem cell properties (40, 58–59, 75–76).

While Paneth cells are absent in normal colon, Paneth cell “metaplasia” occurs with inflammatory bowel disease, adenomas, and in a subset of colon cancers (101), and HMGA1 could foster their development. Although their function is unknown, colonic Paneth-like cells could provide a “cancer niche” to support and nurture malignant cells. Disrupting this pathway may provide a unique opportunity to target stem-like cancer cells, although further work is needed to test this.

As Siddhartha Mukherjee so eloquently wrote in the *Emperor of all Maladies* (102), “cancer cells are distortions of our normal selves.” Indeed, cancer cells distort normal development and HMGA proteins could represent fundamental “distorters” where signals converge, but become amplified and warped to foster hyperactive Wnt signaling, stem-like networks, niche development, and tumor progression. During normal development, HMGA1 also serves as a discriminating conductor, precisely orchestrating Wnt and stem cell pathways. Studies are now needed to dissect mechanisms that distinguish normal regeneration from distorted processes manifest in cancer cells and their microenvironment. Through this work, we will hopefully gain the capacity to slay this malevolent emperor and harness the regenerative potential of tissue-specific stem cells.

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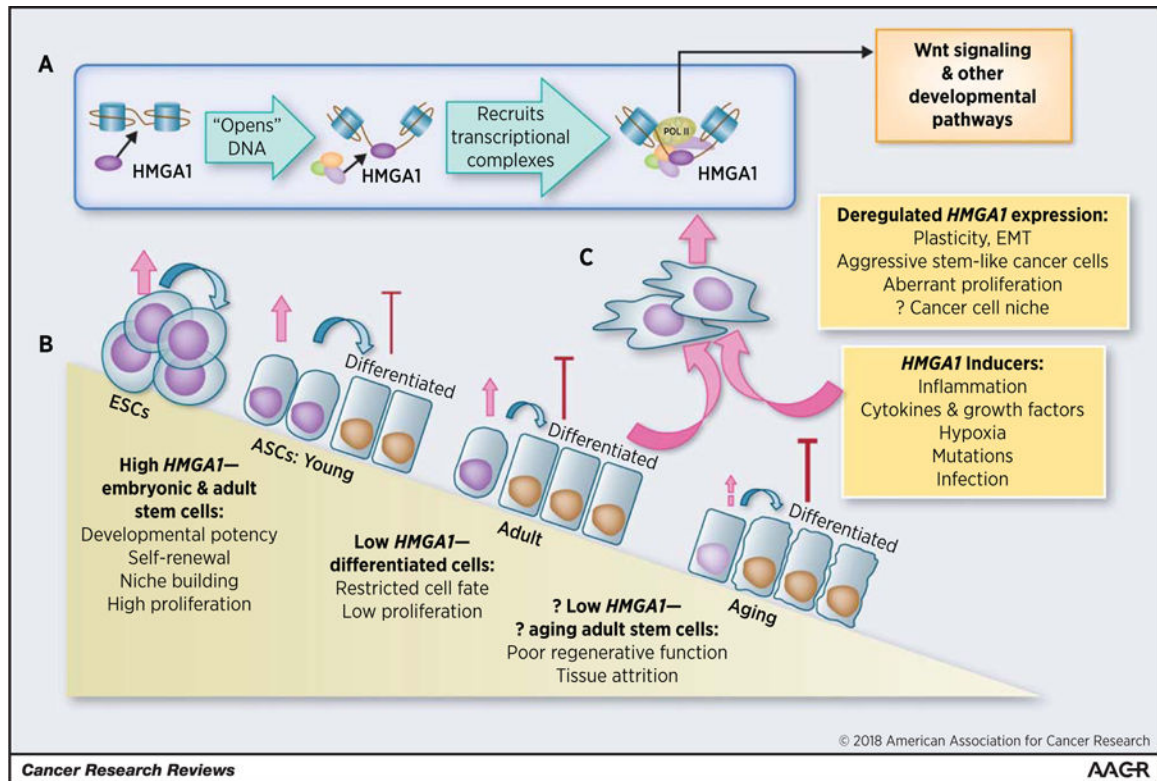


Figure 1.

HMGAI remodels chromatin to drive developmental transcriptional networks in cancer and stem cells. **A**, HMGAI binds to DNA, “opens” chromatin, and recruits transcriptional complexes to activate Wnt genes and other developmental transcriptional networks. **B**, In ESCs and adult stem cells, *HMGAI* is highly expressed, where it fosters plasticity, regenerative function, self-renewal, niche building, and proliferation, whereas *HMGAI* is low or silenced in differentiated cells. Data in murine and human adult stem cells suggest that *HMGAI/Hmgal* levels decline with aging, which could contribute to decreased regenerative function and tissue attrition. **C**, In contrast, *HMGAI* is induced by many factors, which, in the setting of an aged and/or mutated genome, could drive plasticity, EMT, neoplastic transformation, and cancer stem cell properties. It may also help to establish a “cancer cell niche.” This model predicts that tightly regulated *HMGAI* is essential for normal regenerative function, and possibly “normal” aging, whereas deregulated overexpression fosters tumor initiation and progression.

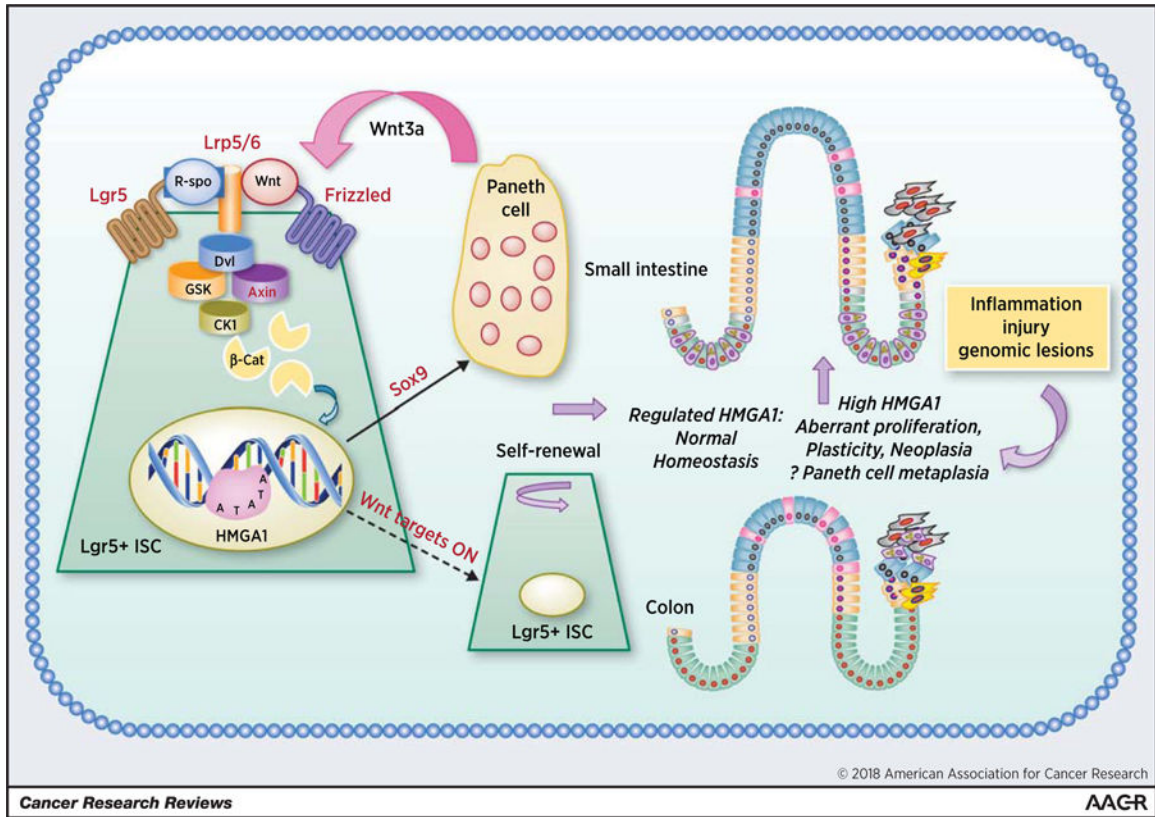


Figure 2. Tightly regulated *HMGA1* fosters balanced self-renewal and “builds a niche” in normal intestinal homeostasis (left). In contrast, deregulated, overexpressed *HMGA1* drives aberrant plasticity, EMT, cancer stem cell properties, proliferation/polyposis, and may also “build” a “cancer stem cell niche” through Paneth cell metaplasia in the colon (right). Proteins encoded by genes that are upregulated in *Hmg1a* transgenic *Lgr5*⁺ ISCs are indicated by red text. (Figure adapted from reference 51).