PERSPECTIVE

Unraveling the crucial roles of *Meis1* in leukemogenesis and normal hematopoiesis

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The “cancer stem cell” hypothesis has emerged as the leading paradigm in how we view the origin and perpetuation of neoplastic-initiating cells in leukemia and solid tumors (for review, see Buzzeo et al. 2007). Central to this model is the concept that only a rare subpopulation of cells in the malignant clone retains or acquires the ability to self-renew and proliferate to initiate and maintain the disease. Although hematopoietic stem cells (HSC) with inherent self-renewal properties are generally believed to be the initiating cells for malignant transformation in acute leukemias, it is now evident that the target stem cell of origin for select oncogenic mutations includes committed hematopoietic progenitors. While substantial evidence supports a leukemic stem cell (LSC) model in both acute myeloid and chronic leukemias, details of the molecular processes regulating LSC properties remain poorly resolved. Insights into these processes have recently emerged from recognition that many key regulators of HSCs and LSCs are transcription factors, as evidenced by their obligatory expression in normal primitive hematopoietic cells and/or their involvement in leukemia-specific translocations.

Chromosomal translocations involving the *Mixed Lineage Leukemia (MLL)* gene (11q23) fuse N-terminal sequences of *MLL* to one of >40 functionally diverse group of C-terminal fusion partners (Daser and Rabbitts 2005) and constitute 5% of all acute myeloid leukemia (AML) cases and 22% of those with acute lymphoblastic leukemia (ALL) (De Braekeleer et al. 2005). Leukemias associated with *MLL* rearrangements generally have a poor prognosis and are associated with poor response to chemotherapy (Eguchi et al. 2005). Gene expression analyses of all types of *MLL* fusion-associated leukemias revealed *HOX* gene dysregulation (Rozovskaia et al. 2001; Armstrong et al. 2002; Yeoh et al. 2002; Ferrando et al. 2003), implicating *HOX* genes as integral factors in *MLL* fusion-associated leukemias. This is not surprising, as both wild-type *MLL* and *MLL* oncogenic fusions directly bind

to regulatory regions within *Hox* gene clusters and maintain the active transcription state of these genes (Yu et al. 1995, 1998; Milne et al. 2005; Caslini et al. 2007). Furthermore, coactivation of *HOXA9* with the *HOX* co-factor *MEIS1* is a frequent occurrence in leukemias associated with *MLL* rearrangements (Yeoh et al. 2002; Kohlmann et al. 2003; Tsutsumi et al. 2003; Fine et al. 2004), and may represent a common molecular pathway that unifies the oncogenic potential of these diverse *MLL* fusion genes. Indeed, *Meis1* is also a transcriptional target of select *MLL* oncoproteins (Milne et al. 2005) and co-overexpression of *HoxA9* and *Meis1* in murine bone marrow (BM) can recapitulate *MLL-ENL*-induced immortalization of myeloid progenitor cells (Zeisig et al. 2004).

The crucial role of *Meis1* in *MLL*-induced leukemia

In the previous issue of *Genes & Development*, Wong et al. (2007) used various genetic techniques to examine the requirement and contribution of *Meis1*, and additional TALE family members—*Pbx1*, *Pbx2*, and *Pbx3*—in *MLL*-induced AML. The initial observation that the transforming potential of a broad range of *MLL* fusion genes strongly correlates with their capacity to induce endogenous *Meis1* transcription is intriguing and provided the impetus to assess the role of *Meis1* in *MLL* oncogenesis. Using the *Meis1* knockout model, knock-down of *Meis1* by short hairpin RNA (shRNA) and interference of wild-type *MEIS1* activity by dominant-negative genetic techniques, Wong et al. (2007) present convincing evidence that the ability of a panel of *MLL* fusion proteins to induce and maintain the transformation of primary murine progenitors, as measured by colony formation in vitro and leukemia in mice, is dependent and rate-limited by *Meis1*, and is codependent on the redundant contributions of *Pbx2* and *Pbx3*, but not *Pbx1*.

Meis1 is a potent collaborative gene in leukemia

Meis1 was first identified as a common viral integration site in myeloid leukemic cells of BXH-2 mice (Moskow

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et al. 1995). The importance of *MEIS1* in human leukemogenesis was underscored by the finding that it was frequently up-regulated in primary AML and ALL samples (Kawagoe et al. 1999; Rozovskaia et al. 2001; Imamura et al. 2002). We and others have subsequently demonstrated that overexpression of *Meis1* synergizes with multiple native and *NUP98-HOX* fusion genes to accelerate the onset of AML in murine BM transplantation models (Kroon et al. 1998, 2001; Calvo et al. 2002; Pineault et al. 2003, 2004; Fischbach et al. 2005). Curiously, wild-type *Meis1* has no transforming activity alone, but can be engineered to do so when fused to the transactivating domain of VP16 (Mamo et al. 2006; Wang et al. 2006), thus linking its oncogenicity to transcriptional activation of its downstream target genes.

The molecular mechanisms underlying the oncogenicity of *Meis1* are not fully understood. Homeodomain-containing HOX cofactors, like MEIS1 and PBX1, alter HOX–DNA-binding specificity, increase HOX–DNA-binding affinity and augment the transcriptional activity of their constituent protein complexes. Indeed, MEIS1 and HOXA9 form dimeric DNA-binding complexes in myeloid cells (Shen et al. 1997), as well as trimeric complexes containing the HOX cofactor, PBX1 (Shen et al. 1999). Thus, as suggested for *HoxA9*-mediated transformation of myeloid progenitors, *Meis1* collaborates with *Hox* genes through the cooperative role of MEIS1–PBX1–HOX complexes. Consistent with this hypothesis, Wong et al. (2007) and previous studies have demonstrated that MEIS1 requires the PBX interaction domain, presumably for interaction with PBX2 and PBX3, the homeodomain as well as the transactivating C-terminal domain to collaborate with *HoxA9* (Wang et al. 2005; Mamo et al. 2006). This hypothesis, however, does not account for the fact that NUP98-HOXD13 (ND13), lacking both PBX1 and MEIS1 interaction domains, strongly collaborates with *Meis1* (Pineault et al. 2003). Moreover, ND13 strongly collaborates with MEIS1^{N51S}, a DNA-binding-impaired form of MEIS1 (Pineault et al. 2005), while *HoxA9* does not (Wang et al. 2005), indicating homeodomain-dependent and -independent MEIS1 activities. Interestingly, the existence of homeodomain-less MEIS1 isoforms have been identified in vertebrates of which the significance is unknown (Noro et al. 2006). These mechanistic differences illustrate the complex modular nature of MEIS1, the multiple pathways in which it can be recruited to its target genes, and underscore the potential dissimilarities in how it may mediate leukemia depending on the nature of the collaborating events.

On the road to uncovering the molecular mechanisms underlying *Meis1* function

To further explore potential molecular mechanisms underlying the function of *Meis1* in LSC progression, Wong et al. (2007) examined the cell cycle profiles of explanted *MLL/Meis1* leukemic cells and measured the transcript levels of known cell cycle regulators. While revealing a modest and indirect connection with the RB pathway, including the HSC and LSC stem cell renewal factor

Bmi-1, this study is limited to known factors previously demonstrated to be involved in HSC and LSC biology. Studies to identify and characterize *Meis1* target genes in *MLL*-associated leukemia will likely prove crucial to obtaining additional molecular insight into the regulatory networks controlled by *Meis1*.

In this regard, it is of interest that the collaborative effect of *Meis1* in *HoxA9* and *NUP98-HOX* models of AML has been linked to the up-regulation of *FMS-like tyrosine kinase 3* (*Flt3*) (Wang et al. 2005; Palmqvist et al. 2006), a receptor tyrosine kinase oncoprotein that is frequently mutated, and often up-regulated with *HOXA9* and *MEIS1*, in human AML (Quentmeier et al. 2004). In addition to the finding that *Flt3* is a major downstream effector of the leukemic collaboration of *Hox* with *Meis1*, we showed that wild-type *Flt3* is sufficient to collaborate with *NUP98-HOX* fusion genes to induce AML. Interestingly, the development of leukemia observed with *Flt3* as a collaborating gene was significantly longer compared with *Meis1*, suggesting that *Meis1* triggers additional pathways to accelerate leukemia development. This result is corroborated by independent lines of evidence demonstrating the dispensability of *Flt3* to the oncogenic cooperation of *Meis1* with *Hoxa9* (Morgado et al. 2007) or *NUP98-HOX* fusions (our unpublished data).

Gene expression analyses have been performed with microarrays to identify the *Meis1* transcriptome in the *Hoxa9* model of AML (Wang et al. 2005, 2006; Hess et al. 2006). These studies have identified a “*Meis1* genetic signature” that includes genes previously implicated in stem cell function. Among the most interesting genes are *Cd34*, a proniche homing cell surface receptor, and *Erg*, a transcriptional activator of the *Ets* proto-oncogene family. The *c-Myb* proto-oncogene was also activated upon overexpression of *HoxA9* and *Meis1*, and was shown to be required, but not sufficient, for *HoxA9/Meis1*-mediated leukemogenesis (Hess et al. 2006). Further functional characterization and identification of additional *Meis1* target genes will undoubtedly shed light on the molecular mechanisms of *Meis1* leukemogenesis.

The role of *Meis1* in normal hematopoiesis

While this current study illustrates the critical influence of *Meis1* on *MLL* LSCs, the role of *Meis1* in normal hematopoiesis remains unclear. In recent years, investigations into the origin of LSCs have revealed that these cells are strikingly similar to normal HSCs, with respect to their ability to self-renew, cell surface markers, and differentiation capacities (Blair et al. 1998; Miyamoto et al. 2000; Hope et al. 2004; Taussig et al. 2005). Thus, in light of the current study, it is conceivable and likely most probable that *Meis1* plays a pivotal role in normal HSC biology as well. Several additional lines of evidence indicate that this may be the case. First, *Meis1*, along with *Hox* genes, are coexpressed in the most primitive hematopoietic subpopulations and are down-regulated following differentiation (Imamura et al. 2002; Pineault et al. 2002). Second, *Meis1*-deficient mice die by embry-

onic day 14.5, presenting with extensive hemorrhaging due to the lack of megakaryocytes (Hisa et al. 2004). While definitive myeloerythroid lineages are present in these embryos, the total numbers of colony-forming cells are significantly reduced. *Meis1*^{-/-} fetal liver cells fail to radioprotect lethally irradiated recipient mice and they compete poorly in repopulation assays even though they support the formation of all hematopoietic lineages. It is possible that gene redundancy among the closely related *Meis* family members may compensate for the loss of *Meis1*, and thus may prevent the complete abrogation of HSC activity in these mice. Taken together, these studies provide strong support for the hypothesis that *Meis1* plays an important role in the HSC self-renewal/proliferation. Future studies to delineate the function of *Meis1* in normal hematopoiesis will provide additional molecular insights into the biology of stem cell self-renewal and will identify critical pathways for LSC formation.

Meis1: a force to be reckoned with

While the synergy between *Meis1* and *Hox* or *NUP98-HOX* fusion genes has been extensively documented, the dependency of *Meis1* in leukemic transformation, as shown in the present study for MLL-associated leukemias, was not previously appreciated. Several important questions emerge from this study. Is the initiation or maintenance of other leukemias dependent on *Meis1* function? *Meis1* is oncogenic by virtue of overexpression rather than mutation (*MEIS1* mutations have yet to be identified in human leukemias). Thus, what cells within the hematopoietic hierarchy are susceptible to *Meis1* overexpression and what cells are dependent on *Meis1* activity? From the current study, it is evident that myeloid progenitors are the target cells for MLL-induced transformation but, more importantly, the transforming potential of the MLL oncoproteins tested was *Meis1* dependent at this stage. Furthermore, in the case of *MLL-AF9*, the highest inducer of *Meis1* expression in the current study, leukemia was initiated in myeloid cells distal to the committed progenitors (Somervaille and Cleary 2006).

Meis1: a knockout punch for leukemia

In the recent past, many regulators of HSC and LSC self-renewal have been identified (e.g., *Bmi1*, *Zfx*, *Pten*, *Mcl1*, *Tel/Etv6*, *Gfi1*, and *Stat5*). These genes, which now include *Meis1*, may represent the "Achilles' heel" of LSCs. Indeed, the study on *Meis1* reported in the previous issue (Wong et al. 2007) and previous studies showing the critical requirement for *Bmi1* (Lessard and Sauvageau 2003; Iwama et al. 2004) in LSC function suggest that the development of tools to inhibit these regulators, or their downstream targets, may have enormous therapeutic implications. With respect to *Meis1*, elucidation of the molecular mechanisms involved in its activity, the potential to target MEIS1 to suppress its oncogenic activ-

ity, and identification of MEIS1 target genes seems likely to shed light into the basic processes involved in the progression of MLL-associated leukemia as well as in normal hematopoiesis. Indeed, it is interesting to speculate that the dependency of MLL-associated leukemias on *Meis1* may actually extend to a broader range of leukemias. While obvious candidates include those linked to *Hox* deregulation or *HOX* translocations, it is possible that, because of the apparent essential role of *Meis1* in normal HSC function, any leukemia arising directly from HSC may continue to be dependent on *Meis1* function. The demonstration of the strict dependence and rate-limiting nature of *Meis1* on MLL-induced AML provides the impetus to explore *Meis1* and/or *Pbx2* and *Pbx3* as potential targets for therapeutic intervention in AML. Selective inhibition and/or depletion of these factors could compromise LSC self-renewal and, thus, merit further development for the possible treatment of AML and other *Meis1*-expressing malignancies.

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