Knocking the *Wnt* out of the Sails of Leukemia Stem Cell Development

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Tumor propagation by cancer stem cells (CSCs) requires their ability to self-renew, and yet the signal pathways involved in this process remain poorly defined. In the December issue of *Cancer Cell*, Zhao et al. (2007) provide compelling evidence that Wnt/β-catenin signaling is crucial for the maintenance of chronic myelogenous leukemia (CML) stem cells.

In recent years, one of the most important advances in our understanding of cancer biology is the realization that the limitless growth of tumor cells seen in this disease seems to be maintained by a reservoir of cells with stem cell characteristics. These cells, termed cancer stem cells (CSCs), spawn a continuous supply of leukemic clones and are believed to be responsible for the recurrence of the disease following anticancer therapy. One of the main goals in cancer research therefore is the identification of CSCs. Leukemia has served as a model disease for studying cancer biology, and a number of studies have focused on the identification and characterization of leukemic stem cells (LSCs) in different leukemia subtypes. There is now convincing evidence showing that even though LSCs share many properties of stem cells, they can sometimes be distinguished by the expression of certain surface markers (Krause and Van Etten, 2007). Moreover, another important aspect is the elucidation of molecular mechanisms and signaling pathways that enable an LSC to self-renew, thereby maintaining itself and feeding the tumor bulk. Even though the capability of self-renewal is believed to be crucial for LSC maintenance, the underlying mechanisms remain poorly defined. Insights into pathways that govern leukemic self-renewal would facilitate the development of therapies targeting these LSC-associated pathways. In the December issue of *Cancer Cell*, Zhao and colleagues (Zhao et al., 2007) report on a conditional *β-catenin* knockout model and identify the Wnt/β-catenin pathway as being essential for the self-renewal of normal and chronic myelogenous leukemia (CML) stem cells.

The Wnt/β-catenin pathway is involved in a number of key developmental processes, and its deregulation is observed in many types of cancer (Reya and Clevers, 2005). Because the deletion of *β-catenin*, an integral component of this pathway, is embryonic lethal, Reya and colleagues specifically deleted this gene in hematopoietic cells by crossing flox-β-catenin mice with vav-Cre mice. They showed that *β-catenin*-depleted HSCs are unchanged compared to normal HSCs with regard to distribution in the cell cycle, multilineage differentiation, and homing ability, but that these HSCs are clearly impaired in their self-renewal capacity. The authors then employed this model for the assessment of leukemia induction by the *BCR-ABL* fusion gene, which has been shown to induce CML and acute lymphocytic leukemia (ALL) in mice (Li et al., 1999). Importantly, loss of β-catenin impeded the development of CML and the self-renewal capability of CML stem cells after retrovirally enforced expression of *BCR-ABL* in bone marrow cells of β-catenin null mice. These data indicate that the impairment of HSC self-renewal in *β-catenin*$^{-/-}$ mice pre-empted the subversion of this property for the generation of CML LSCs (Figure 1). This finding is in line with previous data showing that BCR-ABL cannot transform non-self-renewing progenitors (Huntly et al., 2004). Furthermore, it was previously demonstrated that the acquisition of self-renewal by β-catenin activation in myeloid progenitors seems to be a crucial event in the evolution of chronic phase CML to blast crisis CML (Jamieson et al., 2004). The notion that the leukemogenic potential of oncogenes is dependent on signaling pathways that are essential for stem cell self-renewal is supported by data in an acute myeloid leukemia (AML) model that showed the requirement of the polycomb group gene *Bmi-1*, a critical regulator of stem cell self-renewal, for the maintenance of AML LSCs (Lessard and Sauvageau, 2003). These data confirm the observations that normal and tumor stem cells share overlapping programs (Krivtsov et al., 2006) driven by common genetic determinants.

Strikingly, Zhao et al. (2007) showed that the development of *BCR-ABL*-positive B-ALL as well as the in vivo self-renewal of B-ALL LSCs was unhindered in the absence of *β-catenin*, suggesting the involvement of a distinct self-renewal pathway in *BCR-ABL*-positive B-ALL LSCs. Self-renewal is known to be a complex process involving multiple molecular networks such as the Polycomb/Trithorax group, the *CDX*/*HOX* genes, and the Hedgehog, Notch, and Wnt signaling pathways. Therefore it is conceivable that the self-renewal of LSCs presumably originating from different cell stages (such as BCR-ABL-mediated

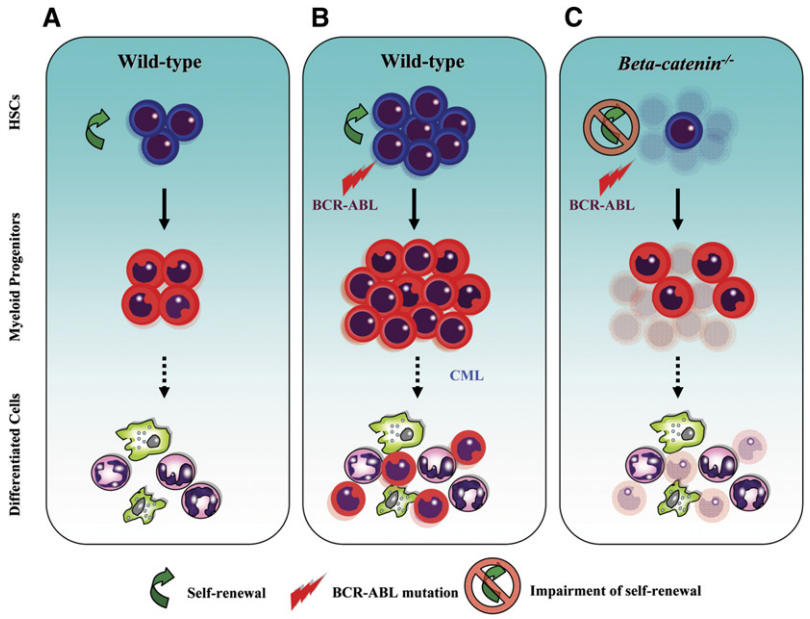

Figure 1. Activated Wnt Signaling in CML Development

(A) A depiction of the normal process of HSC self-renewal and myeloid differentiation.

(B) Expression of *BCR-ABL* in normal HSCs gives rise to CML generating abnormally proliferating myeloid cells.

(C) The depletion of *β-catenin*, a key mediator of Wnt signaling, impairs self-renewal and the ability of BCR-ABL to induce CML, thus characterizing this pathway as a potential target of CML therapies.

CML originating from a stem cell and B-ALL from a B cell precursor) is governed by different mechanisms. These results also highlight the need to identify LSC-specific pathways separately for different leukemia subtypes, as suggested by Zhao et al. (2007), and even for different developmental stages of the same molecular subtype of leukemia.

These findings have important clinical implications, as they turn the spotlight on the Wnt signaling pathway as a major player in the self-renewal of CML LSCs and as a potentially important target for the eradication of this disease. It will be interesting to see whether these results can be applied to other cancers as well, especially because activated Wnt signaling has been observed in tumors of various tissues (reviewed in Willert and Nusse, 1998; Reya and Clevers, 2005). Even though the potential use of Wnt inhibitors holds the promise of inducing clinical remission in patients with aberrantly activated Wnt signaling, the shared dependence of normal and tumor stem cells on this pathway might be detrimental to the selective targeting of CSCs, underlining the need for identifying CSC-specific pathways. Recently Van Etten and colleagues (Krause et al., 2006) have shown that the homing and engraftment of *BCR-ABL*-positive stem cells, unlike their normal counterparts, is dependent on the adhesion molecule CD44 and that the deletion of this gene leads to the abrogation of BCR-ABL-mediated CML induction in mice. These results underscore the point that multiple avenues could be pursued for LSC eradication in CML.

CML, probably more than any other cancer, has continued to provide us with valuable insights into the biology of malignant tumors. In several ways, this disease might serve as a paradigmatic model for other human cancers: the involvement of a renegade tissue stem cell that is responsible for a hyperproliferative state and the subsequent, stepwise acquisition of additional mutations in these stem cells or their progeny, resulting in progression to a more aggressive form of the disease. Some years ago, the development of oncogene-specific molecular therapy in CML paved the way for the exploration of similar "rational drug design" strategies in other neoplastic disorders. Continuing in this tradition, valuable insights into CSC biology emerging from these studies in CML could expedite the development of CSC-specific drugs in multiple human malignancies.

REFERENCES

Huntly, B.J., Shigematsu, H., Deguchi, K., Lee, B.H., Mizuno, S., Duclos, N., Rowan, R., Amaral, S., Curley, D., Williams, I.R., et al. (2004). Cancer Cell *6*, 587–596.

Jamieson, C.H., Ailles, L.E., Dylla, S.J., Muijtjens, M., Jones, C., Zehnder, J.L., Gotlib, J., Li, K., Manz, M.G., Keating, A., et al. (2004). N. Engl. J. Med. *351*, 657–667.

Krause, D.S., and Van Etten, R.A. (2007). Trends Mol. Med. *13*, 470–481.

Krause, D.S., Lazarides, K., von Andrian, U.H., and Van Etten, R.A. (2006). Nat. Med. *12*, 1175–1180.

Krivtsov, A.V., Twomey, D., Feng, Z., Stubbs, M.C., Wang, Y., Faber, J., Levine, J.E., Wang, J., Hahn, W.C., Gilliland, D.G., et al. (2006). Nature *442*, 818–822.

Lessard, J., and Sauvageau, G. (2003). Nature *423*, 255–260.

Li, S., Ilaria, R.L., Jr., Million, R.P., Daley, G.Q., and Van Etten, R.A. (1999). J. Exp. Med. *189*, 1399–1412.

Reya, T., and Clevers, H. (2005). Nature *434*, 843–850.

Willert, K., and Nusse, R. (1998). Curr. Opin. Genet. Dev. *8*, 95–102.

Zhao, C., Blum, J., Chen, A., Kwon, H.Y., Jung, S.H., Cook, J.M., Lagoo, A., and Reya, T. (2007). Cancer Cell *12*, 528–541.