CD99L2. While many aspects of CD99L2 biology remain to be explored, the present paper takes the all-important first step in linking this molecule to transmigration.

Conflict-of-interest disclosure: The author declares no competing financial interests. ■

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NEOPLASIA

Comment on Guo et al, page 5463

Uncontrolled Wnt signaling causes leukemia

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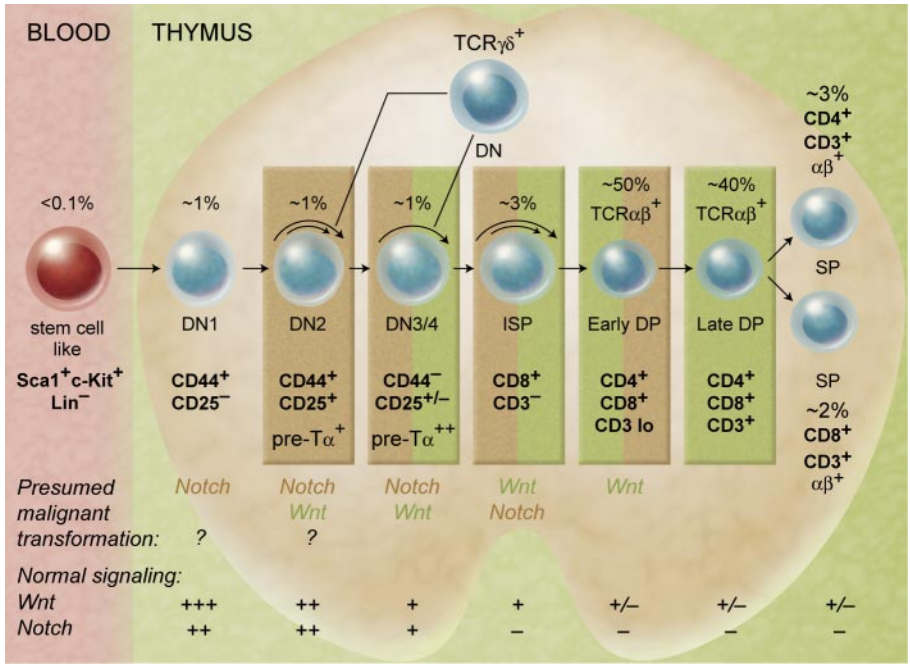
In this issue of *Blood*, Guo and colleagues provide the first solid evidence that thymic overexpression of stabilized β-catenin, the central player in the Wnt signal transduction route, leads to the development of T-cell lymphomas. The development of T-cell lymphomas in the mouse is an excellent model for human T-cell acute lymphoblastic leukemia (T-ALL). Similar to human T-ALL, the murine lymphomas often arise due to overexpression of oncogenic forms of factors that regulate normal T-cell development in the thymus.

Normal T-cell development in the thymus is an ordered and tightly controlled process (see figure). Two exogenously activated signaling pathways, the Notch and the Wnt signaling cascades, are crucial at the earliest stages of normal T-cell development.[1] Both act as molecular switches: the executing transcription factor that is normally bound to the DNA as a transcriptional repressor is converted into an activator. For the Notch pathway, set in motion by ligands of the Delta and Jagged family, this transcription factor is CSL. For the Wnt pathway, which is activated by secreted Wnt proteins, these are factors of the Tcf/Lef family, in thymocytes mainly Tcf-1. There now is compelling evidence that uncontrolled Notch signaling is a causative factor in the development of many T-ALLs.[2] For Wnt signaling, strong evidence that deregulated Wnt signals lead to T-ALL was lacking until now. There were good reasons to believe that uncontrolled Wnt signals could cause leukemias, as many solid tumors have somatic mutations in key regulatory genes of the Wnt pathway. Given the importance of Wnt signals in normal T-cell development, we have previously proposed that by analogy with Notch signaling, constitutively active Wnt signals should lead to ALL.[4] Such evidence has now been provided, making use of powerful mouse genetics.

The elegant study by Guo and colleagues makes use of various transgenic and tissue-specific conditional-knockout mouse models. Key is the conditional deletion of exon 3 in β-catenin, leading to a constitutively active form of β-catenin that can no longer be phosphorylated and broken down. When expressed using the Lck or CD4 promoters driving the cre recombinase, the activated form of β-catenin is specifically expressed in the thymus from early in the double negative (DN) 2 and DN4 stages and onwards. As canonical Wnt signals are absent to low from the double-positive (DP) stage and onwards,[3] there is massive uncontrolled Wnt signaling during late thymocyte differentiation in both of these types of mice. This leads to the development of aggressive T-cell lymphomas that can invade the bone marrow and are transplantable into irradiated recipient mice. Although the Lck-cre and CD4-cre mice develop tumors with somewhat different latency and incidence, the phenotype of these lymphomas is very similar: TCRαβ + CD4 + CD8 + DP. Interestingly, when



Wnt and Notch signaling during murine T-cell development in the thymus. The roles of Wnt and Notch signaling in both normal and malignant development are indicated. The stages in which constitutively activated forms of molecules in the Wnt or Notch pathways lead to malignant transformation are still somewhat speculative. Data from various sources combining human and mouse models are summarized.[1-3] Illustration by A. Y. Chen.

crossed with RAG2-deficient mice, no malignant transformation was observed, indicating that TCR signals or expression are required for the development of the T-cell lymphomas. Similarly, in *cMYC*–deficient mice that overexpress the stabilized form of β-catenin, no lymphomas developed, demonstrating that c-Myc activity is required for β-catenin–mediated lymphomagenesis.

An important topic is the dependency of these β-catenin–induced lymphomas on Notch signals. Guo and colleagues suggest that Notch mutations are not required for these lymphomas to develop, because Notch signaling is low, expression of Notch genes is decreased, and no activating mutations in Notch1 are found in these tumors. Although not formal proof, these data suggest that β-catenin and intracellular (IC)–Notch–mediated leukemogenesis can act independently. During normal T-cell development, both Wnt and Notch are required at the early stages of development, but the requirement for Notch signaling stops earlier, at the late DN3 stage, while Wnt signals are required until at least the ISP stage. Similarly, malignant transformation by IC Notch may act earlier in thymocyte development (see figure), and β-catenin may induce malignant transformation up until the DP stage. Thus, mutations in both the Wnt and Notch pathways may act as initiating events during T-cell leukemogenesis, causing arrest in differentiation and abnormal expression of oncogenes such as the shared target gene *cMYC*. Additional genetic alterations may result in changes in cell-cycle control and cellular metabolism, as well as abnormal expression of stem-cell self-renewal genes, collectively leading to uncontrolled cell growth and clonal expansion.

It will be fascinating to see if deregulated Wnt signals can be found in a series of human T-ALL cases, and whether or not these will be Notch independent. If found, such ALL cases can be targeted therapeutically by specific inhibitors of β-catenin signaling, as Guo and colleagues propose. However, given that both Wnt and Notch signals also are intimately involved in development of the normal intestine, gastrointestinal side effects, as occur with γ-secretase inhibitors that block Notch signals, may limit the therapeutic use of such inhibitors.

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HEMATOPOIESIS

Comment on Fabriek et al, page 5223

Scavenger receptor helps erythroblasts stay on island

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In this issue of *Blood*, Fabriek and colleagues identify CD163, a scavenger receptor expressed on macrophages, as a mediator of erythroblast-macrophage adhesion in erythroblastic islands. Given that CD163 is also the macrophage receptor for circulating hemoglobin-haptoglobin complexes and its expression varies in response to inflammation, it may play a role in feedback regulation of erythropoiesis related to iron recycling and inflammation.

As part of interactions between stromal and hematopoietic cells, late-stage erythropoiesis has a morphologically recognized, functional unit termed the erythroblastic island, which is composed of a central, stromal macrophage surrounded by adherent erythroblasts.[1] Erythroblastic islands are found in extramedullary sites such as the spleen during erythropoietic stress, as well as normal erythropoietic sites such as fetal liver and adult bone marrow. These islands support erythroid progenitors and precursor cells from the stages of erythropoietin dependence (erythroid colony-forming units [CFU-Es], and proerythroblasts) through enucleation and the formation of immature reticulocytes. Interaction with the central macrophages enhances erythroblast survival, proliferation, and differentiation during these terminal stages of erythropoiesis. Central macrophages also phagocytose nuclei extruded from erythroblasts during the formation of reticulocytes. Four specific proteins on the surface of macrophages have been previously shown to mediate the adherence of erythroblasts.[1] These previously identified macrophage proteins and their binding partners on erythroblasts include: vascular cell adhesion molecule-1 (VCAM-1), which binds to $\alpha_4\beta_1$ integrin (VLA-4); α_V integrin (eg, $\alpha_V\beta_1$), which binds interstitial cell adhesion molecule-4 (ICAM-4); erythroblast-macrophage protein (EMP), which is thought to interact with itself; and sialoadhesin (CD169; Siglec-1), which binds sialated glycoproteins. Now, CD163 can be added to this group of macrophage proteins that mediate erythroblast adhesion. Antibodies and/or blocking peptides to each macrophage adhesion protein or its respective erythroblast binding partner have disrupted, to varying amounts, the macrophage–erythroblast adherence. These disruptions of adherence raise the possibilities that the adhesion proteins may associate in complexes, cooperate in their expressions or activities, or function at different times during the course of late erythroid differentiation.

CD163 is a member of the scavenger receptor cysteine–rich (SRCR) family of transmembrane glycoproteins that are commonly found on cells of the immune system.[2] Although its binding partner on the erythroblast has not yet been identified, Fabriek and colleagues have demonstrated that the site in the extracellular portion of macrophage CD163 that binds the erythroblast is different than the binding site for the hemoglobin-haptoglobin complex. Macrophage binding and endocytosis of hemoglobin-haptoglobin complexes remove and degrade plasma hemoglobin, a potentially toxic product of intravascular hemolysis. The subsequent degradation of the heme and recycling of its iron by macrophages is important for the production of new erythrocytes in these hemolytic anemias. CD163 expression, which is restricted to the monocyte/