

APL. Instead, an optimal low level of PML-RAR α expression appears to be favorable for APL development. Furthermore, the knock-in model may target PML-RAR α expression to a more proper population of myeloid cells for APL development. It has been reported previously that PML-RAR α triggers cell death in most cell lines. On one hand, PML-RAR α expression may favor leukemia development; on the other hand, it may mitigate against leukemia. The disruption of such a balance with additional mutations may lead to leukemogenesis. Most importantly, this report urges the search for additional mechanisms besides the dominant-negative effect of PML-RAR α via HDAC to fully explain how t(15;17) is involved in the development of APL.

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The iron gatekeeper: keys to the front and back doors

The duodenal mucosa serves as a gatekeeper for iron entry into the body, permitting absorption of dietary iron in quantities sufficient to match body requirements. Because there are no significant physiologically regulated means for iron excretion in humans, homeostasis depends on tight regulation of iron entry. Enterocyte iron absorption can be divided into 2 functionally distinct events: (1) uptake across the apical membrane (front door), mediated by divalent metal transporter 1 (DMT1); and (2) transfer across the basolateral membrane (back door), mediated by IREG1 (also called ferroportin1). This latter event is dependent upon activity of the ferroxidase hephaestin. The duodenal expression of each

of these 3 gene products is up-regulated in response to systemic iron deficiency. Two major systemic “regulators” of intestinal iron absorption have been proposed (see Finch, *Blood*. 1994;84:1697-1702). The “store-regulator” decreases intestinal iron absorption when tissue iron stores (hepatic and splenic) are high. The “erythroid-regulator” increases intestinal iron absorption in response to increased erythropoietic activity. Recent evidence suggests that the liver peptide hepcidin may be the circulating component of the store regulator and/or erythroid regulator. Whether these systemic regulators act by influencing local changes in enterocyte iron content is unclear. Understanding the influences of systemic and enterocyte iron status on intestinal iron absorption is central to dissecting the pathogenesis of common disorders of iron homeostasis, including iron-deficiency anemia, anemia of inflammation, and hemochromatosis.

In this issue of *Blood*, Chen and colleagues (page 1893) make clever use of the *sla* mouse, a model of iron-deficiency anemia consequent to a naturally occurring mutation in the hephaestin gene. The *sla* mice are defective in transferring iron from duodenal enterocytes into the circulation. Thus, while the mouse is systemically iron deficient, iron concentrations in the duodenal enterocytes are excessive. The investigators compared expression of Dmt1, Ireg1, and hephaestin in *sla* mice with expression of these genes in 3 other groups: (1) control wild-type mice, (2) mice with combined systemic and enterocyte iron deficiency, and (3) mice with combined systemic and enterocyte iron overload. They observed that expression of the apical transporter Dmt1 was influenced by enterocyte rather than

systemic iron status. On the other hand, expression of the genes involved in basolateral transport (IREG1 and hephaestin) was influenced by systemic rather than enterocyte iron status.

Interpreting these observations requires the recognition that enterocyte and systemic iron status are not completely separable. As the authors point out, changes in systemic iron status may affect enterocyte iron status and influence Dmt1 expression. It should also be noted that expression of each of the 3 examined genes changed only in response to iron deficiency, not excess. Both iron-deficiency models had a systemic component (ie, there was no model of enterocyte iron deficiency with systemic iron sufficiency). As such, enterocyte iron deficiency, while not requisite, may contribute to increased expression of hephaestin and/or IREG1. Indeed, iron chelation was reported to increase expression of IREG1 in the intestinal CaCo2 cell line (see Zoller H et al, *Blood Cells Mol Dis*. 2002;29:488-497). Perhaps the safest conclusion, then, is that enterocyte iron status predominates over systemic iron status in regulating Dmt1, whereas systemic iron status predominates in regulating IREG1 and hephaestin. This conclusion is supported by studies on the mucosal block phenomenon by the same team of investigators (see Frazer et al, *Gut*. 2003;52:340-346). The systemic regulators of intestinal iron absorption thus appear to act primarily at the “back door” of the duodenal enterocyte to modulate basolateral iron transfer. This step appears key in the regulation of iron homeostasis by the duodenal iron gatekeeper.

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