JCI The Journal of Clinical Investigation

In This Issue

J Clin Invest. 2011;121(3):823-823. https://doi.org/10.1172/JCI57370.

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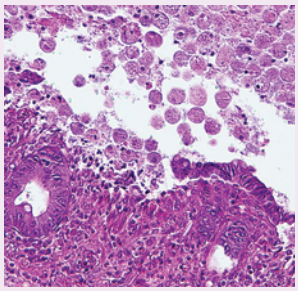
To self-renew or differentiate: an HSC decision for Notch2 When HSCs divide, they have the choice to either self-renew or differentiate to give rise to multipotent cells whose progeny are committed to specific blood cell lineages. Surprisingly, little is known about the molecular control of this choice to self-renew or differentiate and whether the same factors regulate it under homeostatic conditions and following bone marrow injury induced by chemotherapy or irradiation. Insight into these issues has now been provided by the work of Varnum-Finney and colleagues (1207–1216), which indicates that, in vitro, signaling via Notch2 inhibits the differentiation of HSC-enriched mouse bone marrow cells into myeloid lineage cells and enhances the generation of precursor cells. In vivo, a similar role for Notch2 in impeding myeloid differentiation and promoting the generation of both short-term and long-term repopulating HSCs was observed in mice recovering from bone marrow injury induced by chemotherapy or following irradiation and HSC transplantation. Importantly, a role for Notch2 in regulating HSC self-renewal once homeostasis was achieved was not observed. These data indicate that Notch2 has a key role in ensuring orderly bone marrow regeneration during stress hematopoiesis and have implications for patients undergoing HSC transplantation following chemo- or radiotherapy. Overcoming tumorigenic missense p53 mutations Genetic mutation of the P53 gene leading to loss of p53 transcriptional activity […]

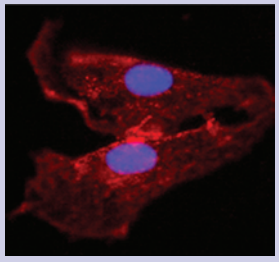
Genetic link to parasite infection



Amebiasis is a potentially fatal enteric infection that is caused by infection with the parasite *Entamoeba histolytica*. In children, malnutrition increases susceptibility to infection and disease severity. As levels of the hormone leptin are low in malnourished children, Duggal, Guo, and colleagues hypothesized that polymorphisms diminishing leptin function would increase susceptibility to infection with *E. histolytica* (1191–1198). Prospective observation of a cohort of children living in an urban slum in Dhaka, Bangladesh, through home visits every other day for 9 years generated data supportive of the hypothesis. Specifically, the data revealed that a common polymorphism in the leptin receptor (*LEPR*) — Q223R — was associated with increased susceptibility to amebiasis. The same polymorphism also associated with amebic liver abscess, a common manifestation of invasive amebiasis, in an independent cohort of adult patients. Consistent with these observations in humans, mice carrying a 223R *Lepr* allele were more susceptible to infection with *E. histolytica* and developed more severe damage to the intestinal epithelium. These data therefore indicate that leptin signaling is important in immunity to the enteric pathogen *E. histolytica*.

A STAR(S)ring role for SRF in insulin resistance

Insulin resistance in skeletal muscle, adipose tissue, and hepatocytes increases an individual's risk of developing type 2 diabetes (T2D). Despite the clinical significance of this condition, little is known about the molecular mechanisms underlying it. Jin, Goldfine, and colleagues therefore set out to identify transcriptional phenotypes associated with skeletal muscle insulin resistance (918–929). Genes regulated by the transcription factor serum response factor (SRF) and its coactivator megakaryoblastic leukemia 1 (MKL1) were found to be expressed at higher levels in individuals with a parental family history of diabetes and those with T2D than in controls with no family history of diabetes. Further analysis indicated that striated muscle activator of Rho signaling (STARS), an activator of SRF, was also upregulated in individuals with a parental family history of diabetes and those with T2D. Moreover, STARS upregulation was inversely correlated with insulin sensitivity. Equivalent data were obtained when skeletal muscle from insulin-resistant mice was analyzed. Of potential clinical interest, pharmacological inhibition of SRF enhanced glucose uptake by human and mouse myotubes in vitro and improved glucose tolerance in insulin-resistant mice. The authors therefore suggest that the SRF pathway is a therapeutic target for the treatment of insulin resistance and possibly T2D.



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Overcoming tumorigenic missense *p53* mutations

Genetic mutation of the *P53* gene leading to loss of p53 transcriptional activity is seen in approximately half of all human cancers. This has led to the suggestion that restoring p53 expression might be a promising anticancer therapy. However, in the majority of cases, the mutations are not null mutations but missense mutations that give rise to mutant p53 proteins that lack p53 transcriptional activity and exhibit new functions; it is not known whether restoring p53 expression will be of benefit in this context. Wang and colleagues have addressed this issue in mice inheriting the $p53^{R172H}$ missense mutation, which is equivalent to a *P53* mutation found in approximately 6% of human cancers (893–904). Restoring wild-type p53 expression in these mice halted tumor growth. However, it did not result in tumor regression, as occurred in mice lacking p53. This is likely because the mutant p53 encoded by the $p53^{R172H}$ missense mutation had a dominant-negative effect, dampening the activity of the restored wild-type p53. Thus, while not optimal, the authors believe that p53 restoration should still be pursued as a potential strategy to treat human cancers with missense *P53* mutations.