MEPs were also identified, suggesting an early function in myeloerythroid cell fate specification. Myelopoiesis was not affected in these mutants.

Interestingly, *Gata1* transcription was not affected by loss of *Trim28*, but the expression of genes encoding several other erythroid transcription factors and heme biosynthetic enzymes was reduced. Expression of apoptosis pathway genes was increased. In addition, as reported recently in another study, *Trim28* mutant red cells failed to activate mitophagy-associated genes. Together, these observations indicate a crucial early role for *Trim28* in erythroid development.

One of the other monikers of *Trim28* is KAP1, from the ability of the protein to interact with Krüppel domain-containing zinc finger proteins. The founding member of the vertebrate erythroid Krüppel-like zinc finger protein family, EKLF/KFL1, is a master regulator of erythropoiesis and can function as either a transcriptional activator or a repressor. It will be of interest to determine whether *Trim28* partners with EKLF/KFL1 during erythroid differentiation.

In summary, *Trim28* has critical functions in at least 3 hematopoietic lineages. In maturing erythroblasts, *Trim28* regulates the expression of key transcription factors, heme biosynthetic enzymes, mitochondrial genes, and genes involved in cell survival. *Trim28* is generally considered a corepressor, and it is known to recruit repressors such as HP1 and SETDB1. However, coactivator functions have been reported.

Interestingly, RNAseq analysis of 2 large populations of immature erythroblasts identified 1500 to 1600 genes that were downregulated in the *Trim28*-deficient cells. Additional work will be required to determine how many of these genes are direct targets of *Trim28*-containing complexes and whether *Trim28* coactivates their expression or represses a repressor.

*Trim28* has been implicated not only in transcriptional regulation but also in chromatin modifications. Blood. 2011;118(24):6258-6268.


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**LYMPHOID NEOPLASIA**

Comment on Neven et al, page 3713

**No immunosurveillance in human IL-10R deficiency**

Martin Oft1 1ARMG BIOSCIENCES

In this issue of Blood, Neven et al report that a third of the patients with interleukin-10 receptor (IL-10R) deficiency develop B-cell lymphomas in the first decade of their life. The lymphomas uniformly contained amplifications of c-rel, activation of inflammatory nuclear factor κB (NF-κB) target genes, and a defective intratumoral CD8+ T-cell tumor immunosurveillance.

IL-10 is an immune regulatory cytokine with anti-inflammatory properties but stimulatory functions on B cells and CD8+ T cells. However, because of its anti-inflammatory properties, IL-10 is frequently considered an immune-suppressive and tumor-promoting cytokine. To complicate the picture, IL-10 enhances the proliferation and survival of the differentiation, the expression of major histocompatibility complex class II (MHC II) molecules, immunoglobulins, and isotype switching in B cells. Therefore, IL-10 has been considered to promote the development of B-cell lymphomas.

Two seemingly opposing functions in immune regulation were independently ascribed to IL-10 with its discovery in 1990, first B-cell-derived T-cell growth factor (B-TCGF), and secondly the cytokine synthesis inhibitory factor.

As a B-TCGF, IL-10 induces the expression of CD3 and CD8 on adult thymocytes and consequently the proliferation of those cells. Further studies showed that IL-10 induced not only the proliferation but also the cytotoxicity of CD8+ T cells. Treatment of mouse tumor models with recombinant human IL-10 or expression of IL-10 in tumor cells led to tumor inhibition and rejection, with CD8+ T cells being essential for the tumor rejection. Genetic deficiency of IL-10 in mice (IL-10−/− mice) leads to inflammatory bowel disease (IBD) and to the development of colon carcinoma. Mice expressing elevated levels of IL-10 are resistant to tumor induction by carcinogens, with enhanced CD8+ T-cell infiltration and expression of antigen-presenting molecules (MHC molecules) in the premalignant tissues. IL-10 directly induces cytotoxic effector molecules and interferon
IL-10 balances proinflammatory immune regulation against the stimulation of CD8+ T-cell-mediated immunity and immunoglobulin G (IgG) production in B cells. In the absence of IL-10 receptors, patients with very-early-onset IBD suffer from severe childhood colitis. The absence of CD8+ T-cell–mediated immunosurveillance leads to the development of diffuse large B cell lymphomas.

Inhibition of IL-12 expression by IL-10 led to a call for the development of IL-10–inhibiting antibodies for cancer immune therapy by tumor immunologists. However, immune-mediated inflammatory responses are also thought to promote tumor growth and subdue cytotoxic T-cell responses to tumors.

Although adult human IBD is not linked to a known genetic defect in the IL-10 pathway, the treatment of patients with Crohn’s disease with recombinant IL-10 led to clinical improvement. Closing the species gap between mice and humans, genetic mutations in IL-10R were recently found in mice with aberrant cytokine production and CD4+CD25+ TH1-like responses. These findings are the first direct genetic evidence for the convergence of the diverse tumor inhibitory functions of IL-10 and for the dependence of tumor immunosurveillance on IL-10 in humans.

The IL-10 receptor is expressed only on hematopoietic cells and, in particular, on cells of the immune system. Neven et al consequently report that several patients treated with hematopoietic stem cell transplantation are in remission since hematopoietic stem cell transplantation would restore tumor immunosurveillance.

Conflict-of-interest disclosure: M.O. is an employee of ARMO BioSciences, Redwood City, CA.

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Martin Oft