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A unique role for Stat5 in recovery from acute anemia

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The precise role of erythropoietin receptor–activated (EpoR-activated) Stat5 in the regulation of erythropoiesis remains unclear. In this issue of the JCI, Menon and colleagues present new experimental data that indicate a distinct role for Stat5 in the regulation of stress-induced erythropoiesis, such as during acute anemic states (see the related article beginning on page 683). A critical function for Stat5 is to promote cell survival, possibly through transcriptional induction of the antiapoptotic protein Bcl-X. In the present experimental system, erythropoietinin-Stat5 signals did not induce Bcl-X expression but did induce oncostatin-M. Moreover, oncostatin-M was found to enhance survival of erythroid progenitors. This work differentiates between steady-state (or homeostatic) erythropoiesis and stress-induced erythropoiesis at the level of EpoR signaling.

In adults, red blood cell production by bone marrow progenitors maintains the steady-state level of circulating cells. But during times of “stress,” such as acute anemia, the erythropoietic response is predominantly generated by hematopoietic progenitors residing in the spleen, at least in mice. In both circumstances, erythropoietin (Epo) and SCF are the central regulators, albeit that compensatory circulating Epo levels are higher during recovery from acute anemia. The study of development of stress signals and play redundant roles in heart development. Mol. Cell. Biol. 24:8467–8476.

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production and oncostatin-M positively modulates erythroid expansion (Figure 1). How Epo, SCF, and new oncostatin-M signals converge to effect erythroid expansion and whether this is unique to stress-induced erythropoiesis, in vivo, remain to be determined.

**Are bone marrow and splenic erythroid progenitors distinct?**

Are EpoR-H signals unique to adult splenic progenitors? In other words, are adult splenic erythroid progenitors distinct from adult bone marrow erythroid progenitors? Apparently not, since ex vivo cultures of EpoR-HM adult bone marrow–derived erythroid progenitors also exhibited defects in Epo-induced proliferation and evidence of increased apoptosis — defects rescued by restoration of the Stat5 PY site (3). But these analyses are, by their nature, performed out of biological context and thus do not account for potential differences in microenvironmental regulation. The recent reexamination of *flexed-tail* (f) mutant mice is particularly informative in this regard (12). Like Stat5a,b<sup>−/−</sup> and EpoR-HM mice, adult f/f mice exhibit normal steady-state erythropoiesis but do not respond to acute erythropoietic stress. Mutant f/f mice have a mutation in the *Madh5* gene, a functional Smad molecule downstream of bone morphogenic protein (BMP) receptor signaling (Figure 1). BMP4 is rapidly, and transiently, induced in the splenic red pulp (site of erythropoiesis) in response to acute anemia and was found to stimulate immature progenitors to give rise to Epo-responsive progenitors. Importantly, only spleen, not bone marrow, progenitors responded to BMP4 in ex vivo cultures. This result suggests that the spleen does indeed contain a unique erythropoietic microenvironment that may distinctly influence erythroid progenitors present therein. Likely, BMP4 expression will be induced in the spleen of both EpoR-HM and EpoR-H mice, since BMP4 transcription appears to be regulated by hypoxia-responsive elements (11). Whether immature, Epo-nonresponsive splenic progenitors from EpoR-HM and EpoR-H mice differ in their response to BMP4 warrants testing, since BMP4 can affect CNS stem cell fate in a pathway activating Stat3 (13).

Finally, studies such as that of Menon et al. (3) highlight the importance of studying and disseminating genetically modi-

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**Figure 1**

Cytokine regulation of stress-induced erythropoiesis. In this issue of the *JCI*, Menon et al. report that Stat5, activated by EpoR signals, uniquely regulates stress-induced erythropoiesis (3). Other contributors to stress-induced erythropoiesis include synergy between SCF and Epo, oncostatin-M, BMP4, and possibly Gas6. EpoR-Stat5 signals were found to induce the expression of oncostatin-M, and oncostatin-M cooperates with SCF/Epo signals to enhance erythroid survival. Thus EpoR-Stat5 signals set up a positive feedback loop whereby the signal induces secretion of oncostatin-M, which then contributes to regulation of erythropoiesis during times of acute anemic stress. 

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**Stress-induced erythropoiesis**

The authors looked at the induction of a group of known Epo- and Stat5-responsive genes (3). WT EpoR– and EpoR-H–containing primary erythroid progenitors induced expression of Pim-1 kinase, oncostatin-M, and SOCS-3 (Figure 1), but, surprisingly, not Bcl-x, an antiapoptotic factor important for red blood cell survival (10), whose expression has been reported to be either decreased (5, 7) or unaffected in Stat5a,b<sup>−/−</sup> mice (6). This result raises the possibility that factors other than, or in addition to, Bcl-x are important for the survival of developing red blood cells. Since oncostatin-M has been suggested to contribute to erythroblast survival (11), Menon et al. (3) asked whether oncostatin-M signals cooperate with Epo/SCF signals to regulate erythropoiesis. Oncostatin-M treatment significantly enhanced the survival of EpoR-H bone marrow erythroid progenitors in ex vivo cultures, suggesting the presence of a positive feedback loop whereby Epo induces oncostatin-M

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**Stress-induced erythropoiesis**

If Stat5 signals are uniquely critical for stress-induced erythropoiesis, then what is the nature of this signal? The authors are, by the finding that some adult Stat5a,b<sup>−/−</sup> mice are also compromised in their response to phenylhydrazine-induced acute anemia (7). A potential limitation of the present study is whether removal of the distal cytoplasmic tail of the EpoR, which has been shown to function as a negative regulatory domain (9), might, in addition to Stat5, also contribute to the stress-induced erythropoietic response.

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**Stress-induced erythropoiesis**

**Stat5-induced oncostatin-M, but not Bcl-x, cooperates with Epo/SCF**

If Stat5 signals are uniquely critical for stress-induced erythropoiesis, then what is the nature of this signal? The authors looked at the induction of a group of known Epo- and Stat5-responsive genes (3). WT EpoR– and EpoR-H–containing primary erythroid progenitors induced expression of Pim-1 kinase, oncostatin-M, and SOCS-3 (Figure 1), but, surprisingly, not Bcl-x, an antiapoptotic factor important for red blood cell survival (10), whose expression has been reported to be either decreased (5, 7) or unaffected in Stat5a,b<sup>−/−</sup> mice (6). This result raises the possibility that factors other than, or in addition to, Bcl-x are important for the survival of developing red blood cells. Since oncostatin-M has been suggested to contribute to erythroblast survival (11), Menon et al. (3) asked whether oncostatin-M signals cooperate with Epo/SCF signals to regulate erythropoiesis. Oncostatin-M treatment significantly enhanced the survival of EpoR-H bone marrow erythroid progenitors in ex vivo cultures, suggesting the presence of a positive feedback loop whereby Epo induces oncostatin-M
fied mice with minimal or no steady-state phenotype. In many ways these mice could be viewed as models for otherwise normal adult humans who exhibit exaggerated or unexpected responses to inflammation, infectious agents, or cancer progression. As such, they have the potential to identify and dissect regulatory pathways that influence but do not cause disease.

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Conflict of interest

No conflict of interest exists.

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An unexpected role for the anaphylatoxin C5a receptor in allergic sensitization

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The anaphylatoxins complement component 3a and 5a (C3a and C5a, respectively) are classically seen as proinflammatory mediators of allergic asthma that recruit inflammatory cells, induce edema, and cause bronchoconstriction. A few years ago, controversy arose when it was shown that C5-deficient mice were more susceptible to experimental asthma compared with C5-sufficient mice. In a study by Köhl et al. in this issue of the JCI, it is shown in a series of truly “complementary” experiments that C5a receptor (C5aR) blockade promotes Th2 sensitization upon first exposure to inhaled allergen, whereas C5aR blockade during established inflammation suppresses the cardinal features of asthma (see the related article beginning on page 783). Blockade of C5aR alters the function of airway DCs, crucial for inducing and maintaining Th2 responses in the lung. Targeting C5aR as a treatment for established asthma could be beneficial, but might be accompanied by sensitization to novel antigens.

Allergy is mediated by Th2 cells

The incidence of allergic diseases is currently on the rise. In western societies, up to 25% of children are sensitized to allergens such as the house dust mite (HDM), pollen, animal dander, or food components. This sensitization is indicated clinically by the presence in the serum of allergen-specific IgE and by an immediate wheal and flare reaction after skin prick testing with these allergens. In most, but not all, sensitized individuals, natural allergen exposure via food or inhalation can lead to allergic diseases such as allergic asthma, allergic rhinitis, or atopic dermatitis. These diseases have an inflammatory component characterized by edema, plasma extravasation, accumulation of eosinophils and mast cells, and overproduction of mucus (1, 2). In the case of allergic asthma, an additional symptom is airway hyperresponsiveness (AHR) to all kinds of specific and nonspecific stimuli, which is caused by excessive smooth muscle contraction, resulting in airway narrowing. Allergic sensitization is the result of an aberrant Th2 response to allergens. Th2 lymphocytes produce cytokines that control Ig-class switching toward IgE production (e.g., IL-4), allergic eosinophilic inflammation (e.g., IL-5), and AHR (e.g., IL-9, IL-13). In support of a critical role for Th2 cells, experimental asthma does not develop in mice deficient in CD4 cells or most of the above cytokines (3).

The complemen system in asthma

The complement system is crucial for innate host defense because of its formation of a lytic effector system that protects against pathogens. Serine proteases generated in response to classical and alternative activation of complement can cleave the anaphylatoxotic peptides complement 3a (C3a) and C5a from C3 and C5, respectively (4). Various components of the complement pathway have been implicated in mediating allergic inflammation (5, 6). First, the anaphylatoxins C3a and C5a are found in increasing concentrations in the bronchoalveolar lavage fluid of asthm-