New Challenges to Developing Animal Models for Human Immune-Mediated Marrow Failure

Antonio M. Risitano, MD

[See related article pp. 102-108]

Bone marrow failure syndromes are a heterogeneous group of diseases characterized by impaired hematopoietic function resulting, clinically, in pancytopenia. Several different pathogenic mechanisms may be involved depending upon the particular disease.¹⁻³ Besides the constitutional syndromes, where intrinsic defects of hematopoietic stem cells are identified, the more common acquired marrow failure syndromes are thought to result from extrinsic action over hematopoiesis. Radiation and chemicals have a well-known toxic action over the bone marrow, but likely play a marginal role in human disease. On the other hand, infectious agents (mostly viral) and drugs may have a higher impact, but their injury is, at least in part, indirect. In this scenario, a pivotal role is played by the immune system, both as an effector mechanism of some etiologic agents described above and as the primary cause of marrow failure. Clinically, most marrow failures remain idiopathic, and are considered immune-mediated.

In this issue of *Clinical Medicine & Research*, Chen⁴ reviews animal models for acquired bone marrow failure syndromes giving an overview of almost a century of efforts that have not always been productive. In fact, for many years marrow failure, and aplastic anemia in particular, was the field in which clinical models overcame experimental ones because most animal models were designed to investigate the role of toxins, such as benzene or busulfan, that certainly are not involved in the great majority of patients with aplastic anemia. Thus even interesting information about the specific mechanisms of toxicity of such agents did not contribute to the understanding of the human disease. In contrast, clinical and laboratory observations claimed that the immune system damages hematopoiesis in most marrow failure patients leading to the broad application of immunosuppressive therapy. Thus, even basic research investigating the pathophysiological mechanisms of aplastic anemia took directions different than animal models and did not address the putative immune-mediated pathogenesis. Recently a new interest for such approaches came from the development of new mouse models that more closely mimic the human immune-mediated disease, aplastic anemia.^{5,6} In the infusion-induced marrow failure model described by Chen and colleagues,⁵ the infusion of parental lymph node cells into sublethally irradiated hybrid recipients induces a marrow failure that shares many pathophysiological signs with the human disease. In

Keywords:

Bone marrow diseases;
Aplastic anemia;
Animal models

Reprint Requests:

Antonio M. Risitano, MD
Division of Hematology
Federico II University of Naples
Via Pansini 5, 80131 Naples, Italy
Tel: +39 081 746 2037
Fax: +39 081 746 2165
E-mail: amrisita@unina.it

fact, the hematopoietic damage appears to be mediated by lymphocytes, mainly CD8+, infiltrating the bone marrow; this parallels findings in humans, where pathogenic T cells were dissected at the clonal level.⁷ Moreover, effector mechanisms involve inhibitory type 1 cytokine production (e.g., IFN- γ , TNF- α) that is known to be increased *in vivo* in patients with aplastic anemia.⁸⁻¹⁰ In this model, the immune attack leads to extreme contraction of the hematopoietic stem cell pool, and possibly of marrow stromal cells. Residual cells retain the stigmata of the damage and may destroy normal marrow cells as innocent bystanders.

These recent findings fill the gap between experimental models and human marrow failure syndromes opening new and intriguing directions of investigation. Even if the immune-mediated pathophysiology of marrow failure is well supported, information on the causes triggering the immune system and the specific target of the immune attack are still lacking, namely, putative antigen(s) are still to be identified. The possibility of a fine “surgical” antigen-specific destruction versus a more indiscriminate cell damage needs to be investigated. The combination of such new animal models with more recent molecular techniques may be very suitable for this purpose. For instance, one could hypothesize to move from the complex allogeneic immune response to highly pure antigen-specific immune responses utilizing T cell receptor transgenic mice. This could also be performed in an autologous setting with the aim of identifying antigen(s) putatively involved in the disease. A more imaginative challenge would be to develop chimeric animals harbouring human hematopoiesis to be targeted by clonal T cells harvested from patients with aplastic anemia. However imaginative, this model of allogeneic immune-mediated marrow failure is, in itself, of great interest. In fact, it involves many pathogenic mechanisms responsible for the human disease. Thus it represents a perfect model for testing new treatments and specifically those targeting immune-effector mechanisms, such as cytokine inhibitors or new biological agents interfering with lymphocyte function.

References

1. Young NS. Acquired aplastic anemia. In: Young NS, ed. Bone Marrow Failure Syndromes. Philadelphia, PA: W.B. Saunders;2000: 1-46.
2. Young NS, Maciejewski J. The pathophysiology of acquired aplastic anemia. *N Engl J Med* 1997;336:1365-1372.
3. Young NS. Hematopoietic cell destruction by immune mechanisms in acquired aplastic anemia. *Semin Hematol* 2000;37:3-14.
4. Chen J. Animal models for acquired bone marrow failure syndromes. *Clinical Medicine & Research* 2005;3:102-108.
5. Chen J, Lipovsky K, Ellison FM, Calado RT, Young NS. Bystander destruction of hematopoietic progenitor and stem cells in a mouse model of infusion-induced bone marrow failure. *Blood* 2004;104:1671-1678.
6. Bloom ML, Wolk AG, Simon-Soos KL, Bard JS, Chen J, Young NS. A mouse model of infusion-induced bone marrow failure. *Exp Hematol* 2004;32:1163-1172.

7. Risitano AM, Maciejewski JP, Green S, Plasilova M, Zeng W, Young NS. In-vivo dominant immune responses in aplastic anemia: molecular tracking of putatively pathogenetic T-cell clones by TCR γ -CDR3 sequencing. *Lancet* 2004;364:355-364.
8. Maciejewski J, Selleri C, Anderson S, Young NS. Fas antigen expression on CD34+ human marrow cells is induced by interferon gamma and tumor necrosis factor alpha and potentiates cytokine-mediated hematopoietic suppression in vitro. *Blood* 1995;85:3183-3190.
9. Selleri C, Maciejewski JP, Sato T, Young NS. Interferon-gamma constitutively expressed in the stromal microenvironment of human marrow cultures mediates potent hematopoietic inhibition. *Blood* 1996;87:4149-4157.
10. Sloan E, Kim S, Maciejewski JP, Tisdale J, Follman D, Young NS. Intracellular interferon-gamma in circulating and marrow T cells detected by flow cytometry and the response to immunosuppressive therapy in patients with aplastic anemia. *Blood* 2002;100:1185-1191.

Author Affiliation

Antonio M. Risitano, MD, Division of Hematology, Federico II University of Naples, Via Pansini 5, 80131 Naples, Italy