JCI The Journal of Clinical Investigation

In This Issue

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J Clin Invest. 2001;108(5):639-639. https://doi.org/10.1172/JCI119933.

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By John Ashkenas, Science Editor

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The presence of healthy cells holds leukemia in check

(See article on pages 709–715.)

The *NF1* gene encodes the tumor suppressor Neurofibromin 1, so named because of its effects on cells in the CNS, but myeloid cells with *NF1* mutations are also prone to uncontrolled growth. In one useful model of juvenile myelomonocytic leukemia (JMML), lethally irradiated mice receive hematopoietic cells from the liver of a fetal mouse lacking this growth-inhibiting protein. Although this protocol reliably yields overgrowth by mutant monocytes, Zhang and colleagues note that it is highly artificial, since leukemic cells would more typically arise as a minor population within a large number of normal cells. Testing the population dynamics in a more realistic setting, the authors show that the *NF1* mutation provides the cells only a limited growth advantage that depends on the cell's genetic background. In addition, although $NF1^{-/-}$ liver cells can also yield fast-growing lymphoid cells, lymphocytic leukemias are not seen, either in recipient animals or in JMML families carrying an *NF1* mutation. In the case of the myeloid lineage, when NF1 deficient cells are present below a threshold number, they outgrow normal cells for only a limited period, after which they represent a stable population for a period of months. Some additional event must therefore be required if the cells are to grow out of control after achieving this pattern of stable chimerism. The finding raises troubling questions about experiments modeling tumor growth using a homogeneous source of tumor-prone cells.

T cell responses in aplastic anemia

(See article on pages 765–773.)

Immunosuppressive drugs generally lead to substantially improved blood cell counts in individuals with aplastic anemia (AA), a severe decline of all blood cell lineages in which the marrow is deficient in hematopoietic cells. For this reason, although AA's pathogenesis is obscure, it seems likely that autoimmune responses block hematopoiesis at an early stage but do not entirely eliminate early pluripotent stem cells. Here, Zeng and coworkers provide a first glimpse at some quirks of the immune system in AA patients. These authors have prepared T cells from within the marrow of 5 people with serious but treatable aplastic anemia. Cloning and DNA analysis of the T cell receptors from one of these patients shows that one sequence form of the complementarity determining region CDR3 is highly represented in patients' marrow. This form, dubbed JZ1.1, carries a specific heptapeptide sequence that is also found in the other patients studied but is absent in controls. Isolated T cells of this TCR type can suppress hematopoietic stem cell proliferation in co-culture experiments, diminishing the growth of myeloid and erythroid cell precursors alike. Interestingly, these JZ1.1 T cells appear to be specific for autologous stem cells derived from the patient at a time of severe disease—marrow cells derived from a healthy, MHC-matched control donor, or even from the patient after successful treatment, are not killed by exposure to JZ1.1 cells. Hence, it appears that T cells of this type are activated to respond to some still-unknown determinant that is present on early hematopoietic stem cells during periods of acute disease.