Comment on King et al, page 1525

Interferon and PV stem cells

Josef T. Prchal  UNIVERSITY OF UTAH

IFN-α resuscitates normal dormant hematopoietic cells suppressed by the polycythemia vera clone and induces polyclonal hematopoiesis.1,2 Is the mechanism of this salutary effect mediated by augmentation of immune attack against the mutant clone, by direct suppression of the mutant clone via altering its cytokine signaling, or by a direct effect on clonal and normal stem cells?

In this issue of Blood, King et al demonstrate a novel mechanism of protection of hematopoietic stem cells by a gene that is negatively regulated by interferon signaling.3 This follows previous papers demonstrating that IFN-α stimulates normal hematopoietic stem cells from dormancy,4,6 which may eventually lead to depletion of the hematopoietic stem cell pool. Whether this differential effect is more pronounced on normal stem cells or on stem cells dysregulated by somatic mutations (such as those in polycythemia vera), where a yet-to-be-defined single or several somatic mutations generate a clone7,8 which is followed by a clonal evolution marked by JAK2V617F mutation (see figure panel A), remains to be shown.

King and coworkers now demonstrate some of the molecular mechanisms of interferon action on the stem cells and report that stem cell expression of Irgm1 gene is essential in preserving the dormancy of stem cells and thus, their number and function. Irgm1 (Lyg-47) is a member of GTPases (IRG) family of genes that are induced by interferon signaling. These genes are known to play a role in innate immunity such as macrophage autophagy–mediated destruction of wide-range infectious agents and Irgm1 also regulates the survival of mature effector CD4+ T lymphocytes by protecting them from IFN-γ–induced autophagic cell death. King et al followed up on an observation that Irgm1 knockout mouse is not only prone to succumb to nonviral infection but is also anemic9 and together with Sher’s NIH laboratory demonstrated that Irgm1 also signals in, and inhibits proliferation of, hematopoietic stem cells and this facilitates their self-renewal.10 In the current article, King et al now demonstrate, using careful studies of hematopoietic stem cell proliferation, self-renewal and regulation of autophagy using the various combination of knockout genotypes of Irgm1, Infng1 (IFN-γ receptor 1; Irgm1−/−Ifng1−/−), and STAT1 (Irgm1−/−Stat1−/−) that the effect of Irgm1 requires intact IFN-γ and that Irgm1 is a potent inhibitor of IFN-γ of stem cell proliferation that may ultimately lead to their depletion via altered self-renewal. Their paper also examined another member of IRG family, Irgm3. It is intriguing that Irgm3 was found to have opposite to or competing functions to Irgm1 in stem cell and they may negatively regulate each other. In summary, this work may provide the missing link to the well-known effect of hematopoiesis suppression in...
infection and inflammatory conditions including immune-mediated bone marrow failure and the often-profound pancytopenia seen in those patients treated with interferons. Apparently, IFN-α and IFN-γ have similar effects in this IgM1 pathway (Margaret Goodell, personal communication, June 2011).

These observations have immediate clinical consequences as an easier-to-tolerate pegylated form of IFN-α has been shown to induce complete clinical remission in a majority of patients with polycythemia vera1 and essential thrombocythemia13 and to decrease JAK2 allelic burden and, in some cases, decrease the proportion of cytogenetic abnormality. Previously, Liu and coworkers3 have also shown that IFN-α is the only shown agent that can convert clonal polycythemia vera myeloid hematopoiesis to polyclonal hematopoiesis. As presented at the 2010 American Society of Hematology Meeting, pegylated IFN-α in some patients selectively decreased the JAK2V617F allelic burden without rescuing nonclonal hematopoiesis in some patients, yet in other patients, it resuscitates normal hematopoietic cells with a conversion of polyclonal hematopoiesis without much change of JAK2V617F allelic burden.

Whether these observations could be explained solely by the effect on stem cells is not clear, as alternate mechanisms, or a combination of other mechanisms (such as stimulation of so-called testicular cancer antigens and the immune response against them) as has been shown in chronic myelocytic leukemia and more recently in polycythemia vera,14 or direct suppression of JAK2V617F–bearing hematopoietic progenitors13 remains to be determined. It also remains to be shown if the interferon effect on the stem cells selectively stimulates clonal JAK2V617F–, stem cell of JAK2V617F+ subclone, or normal dormant hematopoietic cells (figure panel B).

Finally, the salutary effect of interferon therapy, which has been used in clinical practice without a full understanding of its mechanisms, is becoming clearer. One can hope that the direct targeting of the control mechanisms that protect stem cells from their depletion without other systemic detrimental effects of interferon, such as depression or promotion of autoimmune complications, could be transferred to a more targeted clinical benefit.

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References


Epigenetic priming: the target?

Alice Mims and Guido Marcucci THE OHIO STATE UNIVERSITY

Despite major advances made over the past 2 decades in our understanding of underlying disease mechanisms, prognostication, risk-adapted treatment stratification, and patient care, clinical outcomes in AML (acute myeloid leukemia) remain overall poor.1 This lack of improvement stresses the need for novel therapeutic strategies, including targeted treatment approaches tailored toward specific biologic and genetic subsets. In this issue of Blood, Scandura and colleagues report the findings of their innovative approach of epigenetic priming in younger, de novo AML patients with the hypomethylating agent, decitabine, followed by intensive induction chemotherapy.2

This work stems from the notion that in addition to recurrent structural chromosome and gene aberrations, epigenetic changes (those that alter gene transcription without changing DNA sequences) also occur in AML blasts.3 DNA hypermethylation is one form of reversible epigenetic alteration that occurs through DNA methyltransferases (DNMTs) enzymatically adding a methyl (CH3) group to cytosine in the context of cytosine-guanine (CpG) dinucleotide sequences. In AML, hypermethylation of CpG islands, CpG-rich regions often associated with gene promoters, results in the silencing of tumor suppressor genes and other genes important for hematopoietic differentiation. Different DNMT isoforms have distinct roles in genomic methylation in normal and malignant cells. DNMT1 is the most abundant, and preferentially methylates newly synthesized hemimethylated DNA strands during DNA replication in proliferating cells. In contrast, DNMT3a and DNMT3B are responsible for establishing de novo methylation.4 In AML, all 3 DNMT isoenzymes are overexpressed in malignant blasts compared with normal bone marrow cells.3 DNA hypermethylation has been found to be a suitable therapeutic target for nucleoside analogs called azanucleosides (ie, azacitidine and decitabine), approved for treatment of myelodysplastic syndrome.6 In AML, we and others have demonstrated that decitabine incorporates into newly synthesized DNA, covalently binds DNMTs and blocks their activity thereby inducing DNA hypomethylation, gene re-expression, and clinical response.
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