

Control of Leukemic Cells by Hematopoietic Regulators

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The discovery of the regulators controlling normal blood cell formation has allowed the situation in the myeloid leukemias to be investigated. Hematopoietic myeloid regulators like the colony stimulating factors (CSFs) or the IL-6-leukemia inhibitory factor (LIF) group have multiple actions on responding cells, including a mandatory action in stimulating cell proliferation but also opposing actions of differentiation commitment and maturation induction that can lead to cessation of cell division. The action of these regulators in myeloid leukemia are therefore quite complex.

The leukemic cells in the vast majority of patients with acute or chronic myeloid leukemia are not autonomous. They depend for all proliferation on the same hematopoietic regulators as corresponding normal cells and at the same concentrations. The emergence of a myeloid leukemic population from the initiating leukemogenic cell is therefore completely dependent on hematopoietic regulator stimulation. However, from studies in mice, excessive proliferative stimulation by these regulators alone merely leads to hyperplasia, not leukemic transformation.

Analysis has shown that two changes are essential for leukemic transformation. The first, for reasons not understood, is an acquired capacity of the cells for *autocrine* growth stimulation, either by regulator production, the development of constitutively activated receptors, or abnormal signaling molecules in the pathway from the receptors to the relevant nuclear genes. The second abnormality needed is an intrinsic fault in differentiation commitment in the responding cells, so that they generate an abnormally high proportion of progeny that are parental-like, rather than committed to terminal differentiation.

This information has not provided much clinical assistance to the management of myeloid leukemia patients because suppression of hematopoietic regulators would merely lead also to suppression of normal hematopoiesis. The CSFs have been used clinically to force myeloid leukemic cells to enter cell division and become susceptible to the action of cell cycle-specific cytotoxic agents and they can, of course, be used to stimulate the regeneration of normal hematopoietic populations if the leukemic population has been eliminated by therapy. The second action of hematopoietic regulators in suppressing self-renewal and initiating maturation is potentially more interesting because it would offer a non-toxic method for suppressing leukemic populations.

This can be achieved with certain murine or human leukemic cell lines and, provided appropriate receptors are present on the leukemic cells, many regulators such as the CSFs, IL-6, LIF or thrombopoietin can achieve this suppression. The major problem with this approach is that few primary myeloid leukemias exhibit these types of suppression responses following regulator stimulation.

Studies to identify why so many myeloid leukemias are unable to exhibit suppression responses have identified some leukemias that are unresponsive because they fail to produce or display receptors for the regulator used. This is probably not a common situation because most myeloid leukemias in fact respond to proliferative stimulation by these regulators and therefore must express membrane receptors.

A more intriguing series of discoveries has led recently to the identification of a family of cytoplasmic proteins—the SOCS family—whose production is induced by regulator receptor signaling but which function to terminate receptor-initiated responses by blocking activation of the receptor or associated signaling molecules. For example, if SOCS-1 is overexpressed in M1 leukemic cells, the cells become refractory to suppression by IL-6, LIF, oncostatin-M or interferon- γ . At least certain members of this family of 20 suppressors of cytokine signaling (SOCS) function in a similar manner to SOCS-1, and it is possible that some leukemias are refractory to regulator suppression due to overexpression of one or more of these molecules. SOCS proteins are expressed in many tissues not simply in hematopoietic cells. Therefore, attempts to control myeloid leukemias by interfering with SOCS proteins need to be approached with care. For example, SOCS-1 is essential for life in neonatal mice (otherwise they die from the toxic effects of IFN- γ), but SOCS-1 depletion in adult animals in the absence of IFN- γ may have less serious consequences. The situation with other members of the SOCS family is under study using mice with inactivation of the various SOCS genes.

The opposing powerful actions of hematopoietic regulators on myeloid leukemic cells offer the future possibility of more sophisticated therapeutic intervention. However, the biology involved is exceedingly complex, and much more basic information is needed before the most appropriate cytoplasmic protein targets can be identified for possible biological intervention.