Ham-Wasserman Lecture

The Molecular Control of Hematopoiesis and Leukemia: From Basic Biology to the Clinic

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The establishment of a cell culture system for the clonal development of hematopoietic cells made it possible to discover proteins that regulate cell viability, multiplication and differentiation of different hematopoietic cell lineages, and the molecular basis of normal and abnormal blood cell development. The first proteins discovered in this way were cytokines, now called colony stimulating factors (CSFs). They also now include various other cytokines. There is a network of cytokine interactions, which has positive regulators such as CSFs and interleukins (ILs) and negative regulators such as transforming growth factor β and tumor necrosis factor. This multigene cytokine network provides flexibility depending on which part of the network is activated and allows amplification of response to a particular stimulus. Abnormalities in the developmental program can lead to hematopoietic diseases including leukemia. Malignancy can be suppressed in certain types of leukemic cells by inducing differentiation with cytokines that regulate normal hematopoiesis or with other compounds that use alternative differentiation pathways. This created the basis or the clinical use of differentiation therapy. The suppression of malignancy by inducing differentiation can bypass genetic abnormalities that give rise to malignancy. Different CSFs and ILs suppress programmed cell death (apoptosis) and induce cell multiplication and differentiation, and these processes of development are separately regulated. The same cytokines suppress apoptosis in normal and leukemic cells, including apoptosis induced by radiation and cytotoxic cancer chemotherapeutic compounds. An excess of cytokines can increase leukemic cell resistance to cytotoxic therapy. The tumor suppressor gene wild-type p53 induces apoptosis that can also be suppressed by cytokines. The oncogene mutant p53 suppresses apoptosis. A hematopoietic cytokine such as granulocyte-CSF is now used clinically 1) to correct defects in hematopoiesis, including repair of radiation- and chemotherapy-associated suppression of normal hematopoiesis in cancer patients, stimulation of normal granulocyte development in patients with infantile congenital agranulocytosis, and 2) to increase of hematopoietic precursors for blood cell transplantation. Treatments that decrease the level of apoptosis-suppressing cytokines and downregulate expression of apoptosis-suppressing genes in cancer cells could improve cytotoxic cancer therapy. The basic studies on hematopoiesis and leukemia have thus provided new approaches to therapy (reviewed in 1-3).

REFERENCES