THE MOLECULAR CONTROL OF DEVELOPMENT IN NORMAL AND LEUKEMIC BLOOD CELLS

Leo SACHS

Department of Molecular Genetics, Weizmann Institute of Science, Rehovot 76100, Israel

Hematopoiesis gives rise to blood cells of different lineages throughout normal life. Abnormalities in this developmental program lead to blood cell diseases including leukemia. 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. These regulators include cytokines now called colony stimulating factors (CSFs) and interleukins (ILs). The production of different types of hematopoietic cells with a limited lifespan, both under normal conditions and in different emergency situations such as infections, wound healing and various diseases, requires a system with considerable flexibility. A multigene family of interacting cytokines is more useful for the functions required today and for adaptation to functions that may be required in the future, than the existence of only single cytokines with high specificity where a lack of function and lack of flexibility would be lethal. A family of cytokines some of which have overlapping functions is also a useful safeguard, so that if one cytokine does not function effectively under certain conditions another can take over. A good way to obtain flexibility would be for different factors to function within a network of interactions and there is such a network of hematopoietic cytokines. This network of cytokine interactions has positive regulators such as CSFs and ILs and negative regulators such as transforming growth factor β (TGF-β) and tumor necrosis factor (TNF) (Fig. 1). This multigene cytokine network provides flexibility depending on which part of the network is activated and also allows amplification of response to a particular stimulus.

Parts of this cytokine network were found to function not only within the hematopoietic cell system but also in some non-hematopoietic cell types. For example, endothelial cells that make blood vessels produce interleukin-6 (IL-6) at the time of new blood vessel formation, angiogenesis, and the production of IL-6 is switched off when angiogenesis has been completed. The transient expression of IL-6 in the endothelial cells indicates a role for IL-6 in angiogenesis in addition to its role in regulating the development of myeloid and lymphoid hematopoietic cells. IL-6 can also induce the production of acute phase proteins in liver cells. The pleiotropic effects of a cytokine such as IL-6 raises the question

Figure 1 The network of interactions between hematopoietic cytokines

whether these effects on different cell types are direct, or are indirectly mediated by IL-6 switching on production of other regulators that vary in the different cell types. Interpretation of experimental data on the effect of each cytokine therefore has to take into account that the cytokine functions in a network of interactions, so as to avoid an incorrect assignment of a specific effect to a direct action of a particular cytokine. This network has also to be taken into account in the clinical use of these cytokines. What can be therapeutically useful may be due to the direct action of an injected cytokine, or to an indirect effect due to other cytokines that are switched on *in vivo*.

Identification of the cytokines that control normal hematopoiesis raised the question whether cytokines that induce differentiation of normal hematopoietic cells can also induce leukemic cells to differentiate to mature non-dividing cells. It was shown that there are some myeloid leukemic cells that can be induced to terminally differentiate to mature macrophages or granulocytes by some normal differentiation inducing cytokines, or by some other compounds that use alternative differentiation pathways. This created the basis for the clinical use of differentiation therapy. Studies with a variety of compounds, other than normal hematopoietic cytokines, have shown that other compounds that can induce differentiation in myeloid leukemic cells include glucocorticoid hormones, compounds that are used today in cancer chemotherapy, such as cytosine arabinoside, methotrexate and others, and irradiation. At high doses, irradiation and compounds used in cancer chemotherapy kill cells by inducing apoptosis, whereas at low doses they can induce differentiation. Not all these compounds are equally active on the same leukemic clone. A variety of compounds can also induce differentiation in clones that are not induced to differentiate by a normal hematopoietic cytokine, and in some of these clones induction of differentiation requires combined treatment with different compounds. In addition to certain steroids, chemotherapeutic compounds and radiation, other compounds that can induce differentiation in myeloid leukemic cells include insulin, bacterial lipopolysaccharide, certain plant lectins, tumor promoting phorbol esters and retinoic acid. Induction of differentiation by retinoic acid in human promyelocytic leukemia cells is now used clinically in the therapy of these leukemias, showing the successful application of the concept of differentiation
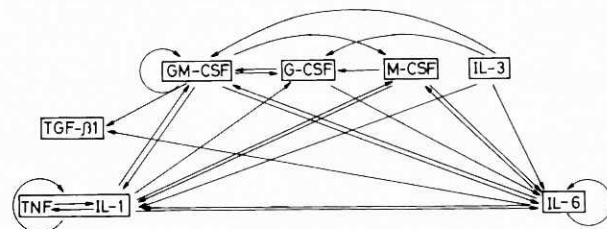
therapy in the clinic. It is possible that all myeloid leukemic cells which are no longer susceptible to the normal hematopoietic cytokines by themselves can be induced to differentiate by the appropriate combination of compounds. The experiments with myeloid leukemic cells have shown that there are different pathways of gene expression for inducing differentiation, and that genetic changes which suppress induction of differentiation by one compound need not affect differentiation by another compound that uses alternative pathways. 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 irradiation and cytotoxic cancer chemotherapeutic compounds. An excess of cytokines can increase leukemic cell resistance to cytotoxic therapy. The regulation of apoptosis by cytokines involves interactions with other cellular genes that control apoptosis. A variety of such apoptosis inducing and apoptosis suppressing genes have been identified and apoptosis is regulated by the balance between these genes. The apoptosis inducing genes include the tumor suppressor gene wild-type p53 and induction of apoptosis by wild-type p53 can also be suppressed by cytokines. The apoptosis suppressing genes include the oncogene mutant p53 and this can explain the high frequency of mutant 53 in many types of tumors.

Hematopoietic cytokines such as granulocyte CSF (G-CSF) are now used clinically to correct defects in hematopoiesis, including repair of chemotherapy associated suppression of normal hematopoiesis in cancer patients, stimulation of normal granulocyte development in patients with infantile congenital agranulocytosis, and 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 the molecular control of development in normal and leukemic blood cells have thus provided new approaches to therapy (reviewed in Sachs, 1995, 1996).

References

Sachs, L. (1995). The adventures of a biologist: Prenatal diagnosis, hematopoiesis, leukemia, carcinogenesis and tumor suppression. Adv. Cancer Res. 66: 1-40.

Sachs, L. (1996). The control of hematopoiesis and leukemia: From basic biology to the clinic. Proc. Natl. Acad. Sci. USA 93: 4742-4749.