Leo Sachs

Joseph Lotem
Veronica Reiss

Control of Development of Normal and Malignant Stem Cells: From Basic Studies on Blood Cells to New Therapies

Department of Molecular Genetics

Tel. 972 8 934 **4068** **Fax.** 972 8 934 **4108**
E-mail: leo.sachs@weizmann.ac.il
Web page: www.weizmann.ac.il/molgen/members/sachs.html

Normal bone marrow stem cells can give rise to different types of blood cells and to other cell types such as neuronal, muscle and epithelial cells. This is an excellent system to study regulation of the developmental potentials of stem cells and the use of stem cells from adults for therapy. Our establishment of a cell culture system for the clonal development of hematopoietic stem cells made it possible to discover the 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 are cytokines now called colony stimulating factors (CSFs) and they also now include interleukins and various other cytokines for blood cells and other cell types. There is a network of cytokine interactions which includes a cytokine cascade that ensures effective coupling of cell multiplication and differentiation.

Malignancy can be suppressed in certain types of leukemic stem cells by inducing differentiation with cytokines that regulate normal hematopoiesis, or with other compounds that use alternative differentiation pathways. This created the basis for the clinical use of differentiation therapy. The suppression of malignancy by inducing differentiation can bypass genetic abnormalities that give rise to malignancy and shows that cancer stem cells, which are genetically abnormal, can be epigenetically reprogrammed (Fig. 1). Epigenetics can thus win over genetics.

In addition to inducing cell multiplication and differentiation, different cytokines including CSFs suppress apoptosis. The same cytokines suppress apoptosis in normal and leukemic cells and an excess of cytokines can increase cancer cell resistance to cytotoxic therapy. The tumor suppressor gene wild-type p53 induces apoptosis and oncogenic p53 mutants suppress apoptosis. There is a network of apoptosis-inducing and apoptosis-suppressing genes. Apoptosis induced by wild-type p53 can be suppressed by cytokines and various other agents such as calcium mobilizing compounds, antioxidants, coumarin and flavone inhibitors of NAD(P)H:quinone oxidoreductase 1 (NQO1) and some other inhibitors. Dissection of the pathways of apoptosis has shown that there are different pathways of apoptosis that are suppressed by cytokines and by different inhibitors. The use of DNA microarrays and cluster analysis of expressed genes (Fig. 2) has shown, that a cytokine can suppress wild-type p53-induced apoptosis without affecting expression of p53-regulated genes.

A hematopoietic cytokine such as granulocyte CSF is now used clinically to correct defects in hematopoiesis, including repair of irradiation and chemotherapy associated suppression of normal hematopoiesis in cancer patients, repair of normal granulocyte development in patients with infantile agranulocytosis, and to induce migration of stem cells from the bone marrow to peripheral blood

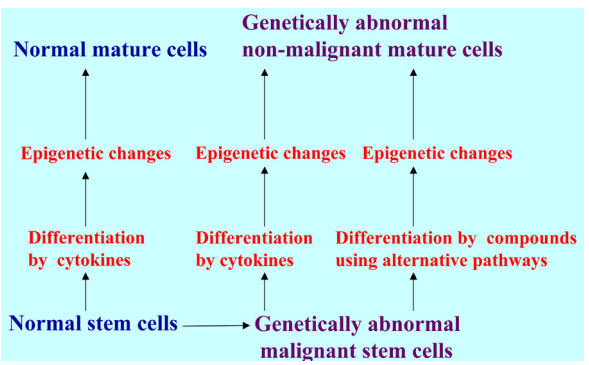

Fig. 1 *Epigenetic suppression of malignancy by inducing differentiation. Malignant cells are genetically abnormal. The malignant phenotype can be epigenetically reprogrammed to a non-malignant phenotype by inducing differentiation (Lotem and Sachs, 2002a).*

for stem cell transplantation. Anti-cytokine therapy to decrease the level of apoptosis suppressing cytokines could improve cytotoxic cancer therapy. The basic studies on normal bone marrow and leukemic stem cells have provided new approaches to therapy, including the therapeutic use of stem cells from adults.

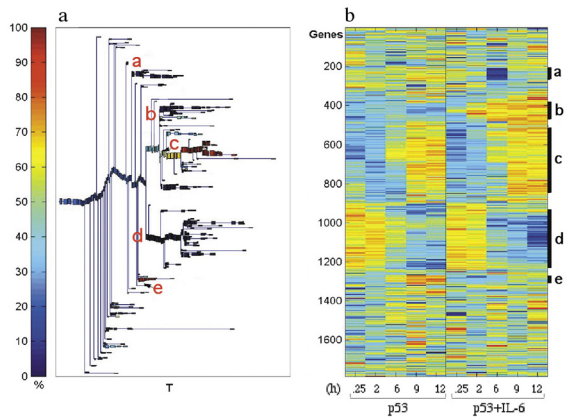

Fig. 2 *Cluster analysis of up-regulated and down-regulated genes by wild-type p53 in the absence or presence of the cytokine IL-6. a, dendrogram and b, expression matrix in which colors represent induction (red) or suppression (blue) (Lotem et al., 2003).*

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