Chapter 12

Responses of Leukemia Cells to Hematopoietic Growth Factors

Involvement of Autocrine Growth Mechanisms, Cytogenetic Abnormalities, and Defective Maturation Signaling

Ivo P. Touw and Fan Dong

1. INTRODUCTION

All blood cells produced throughout life descend from a small number of pluripotent hematopoietic stem cells, which, in adult man, reside predominantly in the bone marrow. The pluripotent stem cells generate progenitor cells committed to proliferate and mature toward the different functional end cells. The mature blood cells have a limited life span and need to be produced continuously. The hematopoietic system adapts in a highly dynamic fashion to changes in the requirements for different blood cells, for instance, during stages of infection or following sudden loss of blood. The rapid and variable needs for the various blood cell types demand a tight and complex control mechanism that finely regulates renewal, commitment, proliferation, maturation, and survival of hematopoietic cells. The hematopoietic growth factors (HGFs) play a central role in these processes (Clark and Kamen, 1987; Metcalf, 1989).

Leukemias are neoplastic conditions characterized by the accumulation of malignant myeloid or lymphoid cells, arrested at distinct stages of development, in the bone marrow.
and peripheral blood. Leukemic cells escape from the balanced control of proliferation, maturation, and cell survival characteristic of the normal hematopoietic system. Leukemias present either as acute or chronic diseases. The most common types of acute leukemia are B-cell precursor acute lymphoblastic leukemia (BCP-ALL) and acute myeloblastic leukemia (AML). T-cell ALL and undifferentiated or “null” ALL represent rarer forms of acute leukemia. Chronic myeloid leukemia, characterized by the chromosomal translocation (9;22)(q34;q11), known as the Philadelphia translocation, originates in primitive multilineage hematopoietic precursors (Fainkow et al., 1977). The chronic lymphoid leukemias arise from the B lymphocyte stages (B-cell chronic lymphocytic leukemia and hairy-cell leukemia) or the immunoblast/plasma cell stages (multiple myeloma) (Table I).

In this chapter, we first briefly summarize some general aspects of HGF and cytokine responses of human leukemia cells. Subsequently, we discuss in more depth studies concerning the proliferation and maturation properties of progenitor cells in two pathologic conditions characterized by defective myeloid maturation: AML and severe congenital neutropenia (SCN), a disease that may progress toward AML. These investigations specifically dealt with autocrine mechanisms of growth, HGF responses in relation to cytogenetic abnormalities, and the involvement of HGF receptor defects in leukemogenesis. They illustrate how the analysis of HGF responses and HGF receptor function provide new insights into the heterogeneous pathobiology and clinical behavior of leukemia and related diseases.

2. LEUKEMOGENESIS

It is generally accepted that leukemogenesis is a multistep process (Hunter, 1991; Sawyers et al., 1991). The leukemic mass arises from the clonal evolution and expansion of a single-cell clone, which may initially have limited genetic damage, resulting in only marginal changes in growth properties (Sawyers et al., 1991). With the acquisition of additional genetic defects, the normal growth and differentiation program becomes increasingly perturbed, which may ultimately result in full leukemic transformation. Genes affected in leukemia encode proteins that are normally involved in the regulation of cell proliferation, survival, and differentiation. With few exceptions, these proteins fall into four major categories: growth factors, growth factor receptors, cytoplasmic signal transducers, and transcription factors (Cantley et al., 1991). Proteins from these different categories usually act in collaboration to accomplish full leukemic transformation (Hunter, 1991).

3. GROWTH FACTORS FOR HUMAN LEUKEMIA CELLS

The availability of recombinant growth factors and cytokines has allowed detailed characterization of the proliferative responses of human leukemia to these stimuli. Primary human leukemia cells from most patients respond to growth factors in vitro. Thus, leukemic cell expansion is usually not associated with growth factor independence but with more subtle deviations of growth control. The proliferative responses of leukemia cells to growth factors grossly reflect those of normal cells at comparable stages of differentiation. A