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Genetic and Epigenetic Alterations that Drive Leukemic Stem Cell Self-Renewal

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Abstract

Acute myeloid leukemia has emerged as a paradigm for the concept of the cancer stem cell. This hypothesis presumes that the disease is maintained by a rare population of leukemia-initiating stem cells which have acquired genetic or epigenetic changes. It is most likely that a single (epi)genetic event will not be sufficient to cause leukemia, but that a number of sequential events are required. Similar to normal hematopoietic stem cells, both intrinsic as well as extrinsic factors that arise from the bone marrow niche, provide essential cues that regulate cell fate decisions such as leukemic stem cell self-renewal and differentiation. In this chapter, we will review the current understanding of genetic and epigenetic abnormalities that underlie the process of leukemic transformation, and will discuss which events potentially co-operate to induce leukemia.

Introduction

Acute myeloid leukemia (AML) arises from genetic defects in the hematopoietic stem cell [1]. HSCs can undergo self-renewal divisions to ensure maintenance of the stem cell pool as well as generate large numbers of mature functional blood cells via migration, differentiation, proliferation and (anti-) apoptotic events. Complex processes such as self-renewal and differentiation must be tightly controlled as a shift in the balance towards self-renewal severely impairs the hematopoietic process and might ultimately lead to the development of AML [2]. Thus a thorough understanding of the mechanisms involved in the regulation of self-renewal divisions of normal and leukemic stem cells are pivotal in tackling the highly malignant disorder of AML.

AML is in most cases a stem cell disease [3-5]. The malignant clone is hierarchically organized - strikingly similar to the normal hematopoietic system [6] - and consists of rare leukemic stem cells (LSC)

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