Abstract

Acute Myeloid Leukemias (AML) are clonal hematopoietic malignancies that in the majority of patients remain incurable. The therapy of AML has not changed over the past four decades and aside from bone marrow transplantation the disease remains unacceptably fatal in the majority of cases. Frequency of AML increases with age, therefore, the proportion of patients eligible for bone marrow transplantation is small and development of novel, effective and safe anti-AML therapies remains a major unmet need. Acute promyelocytic leukemia (APL) still stands alone as the only curable subtype of AML, accounting only for 5% of all cases. In a remarkable way it has been shown in 1980s that APL cells are highly sensitive to the physiologically active metabolite of vitamin A all-trans-retinoic acid (ATRA), which as a single agent effectively differentiates the leukemic clone leading to disease remission in over 80% of APL patients. Currently, using ATRA together with other therapeutic agents APL has become a curable disease. Success in APL has brought new hope for the development of differentiation therapies in other AML subtypes, using ATRA and/or other agents. Although some promising results has been obtained, unfortunately for patients with non-APL AML, ATRA has little effect. Consequently, 85% of these patients will succumb to their disease despite conventional approaches. Little has been known about mechanisms of resistance to ATRA in non-APL AML. This knowledge gap limits the use of ATRA in a disease that desperately needs novel and successful therapies. Our long term goal has been the development of novel and improved approaches to cancer treatment through elucidation of the molecular mechanisms underlying the transcriptional deregulation and pathogenesis of leukemia. We propose 1) to identify small molecules and cellular targets that potentiate or inhibit ATRA signaling and 2) to validate, by both in vitro and in vivo the screened epigenetic drugs in differentiation therapy of AML with or without ATRA. These studies will identify new targets for anti-cancer therapies, in particular development of new epi-drugs (those targeting epigenetic mechanisms) and differentiation-based treatments in AML.