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Epigenetic regulation of leukemia

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Abstract

Acute myeloid leukemia (AML) has a poor prognosis in both adults and children, with a long-term survival of only 25% and 60% respectively. No major development has occurred of the treatment since, the last decades and the majority of treatments for AML consist of cytotoxic drugs with low specificity. AML is associated with perturbed epigenetic regulation, with early mutations in and chromosomal translocations of different epigenetic regulators. This indicates that epigenetic mechanisms may play an essential role in the development of AML and are potentially very potent drug targets. A network of epigenetic factors regulates DNA methylation, post-translational histone modifications and chromatin structure and relays information to the transcriptional program that dictates hematopoietic cell fate and differentiation. We have previously demonstrated the importance of epigenetic mechanisms in hematopoietic differentiation and AML development. Especially we have showed that epigenetic regulation of enhancer activity is crucial for normal myelopoiesis and AML. We have recently demonstrated that the generation of leukemic - specific gene expression involves interplay of combinational epigenetic mechanisms at specific enhancer elements with their cognate promoters. Our results suggest that the normal epigenetic remodeling of enhancers is perturbed during the evolution of leukemia and contribute to the leukemic phenotype.

Over the past decade, it has become clear that both genetics and epigenetics play pivotal roles in cancer onset and progression. The importance of epigenetic regulation in proper maintenance of cellular state is highlighted by the frequent mutation of chromatin modulating factors across cancer subtypes. Identification of these mutations has created an interest in designing drugs that target enzymes involved in DNA methylation and posttranslational modification of histones. In this review, we discuss recurrent genetic alterations to epigenetic modulators in both myeloid and lymphoid leukemias. Furthermore, we review how these perturbations contribute to leukemogenesis and impact disease outcome and treatment efficacy. Finally, we discuss how the recent advances in our understanding of chromatin biology may impact treatment of leukemia.

Over the past decades, our molecular understanding of acute myeloid leukemia (AML) pathogenesis dramatically increased, thanks also to the advent of next-generation sequencing (NGS) technologies. Many of these findings, however, have not yet translated into new prognostic markers or rationales for treatments. We now know that AML is a highly heterogeneous disease characterized by a very low mutational burden. Interestingly, the few mutations identified mainly reside in epigenetic regulators, which shape and define leukemic cell identity. In the light of these discoveries and given the increasing number of drugs targeting epigenetic regulators in clinical development and testing, great interest is emerging for the use of small molecules targeting leukemia epigenome. Together with their effects on leukemia cell-intrinsic properties, such as proliferation and survival, epigenetic drugs may affect the way leukemic cells communicate with the surrounding components of the tumor and immune microenvironment. Here, we review current knowledge on alterations in the AML epigenetic landscape and discuss the promises of epigenetic therapies for AML treatment. Finally, we summarize emerging molecular studies elucidating how epigenetic rewiring in cancer cells may as well exert immune-modulatory functions, boost the immune system, and potentially contribute to better patient outcomes.

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