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Perspective

Genetic Determinants of Acute Myeloid Leukemia and Their Clinical Significance

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DESCRIPTION

Leukemia is a heterogeneous group of hematological malignancies that originate in the bone marrow and result in the uncontrolled proliferation of abnormal white blood cells. Its development has long been recognized as a multifactorial process involving both genetic predispositions and environmental triggers, but in recent decades, advances in molecular biology have made it clear that genetic abnormalities represent the core driving force of leukemogenesis. The ability of genetic mutations to alter normal hematopoiesis and disrupt the delicate balance of proliferation, differentiation, and apoptosis in blood cells provides the foundation for understanding leukemia as a disease of the genome. The genetic basis of leukemia is an evolving field that continues to unravel how inherited mutations, somatic genetic changes, chromosomal rearrangements and epigenetic dysregulation combine to initiate and sustain malignant transformation of hematopoietic stem and progenitor cells.

Leukemia is broadly categorized into acute and chronic forms, and the genetic alterations vary accordingly. Acute leukemias, including Acute Lymphoblastic Leukemia (ALL) and Acute Myeloid Leukemia (AML), are characterized by the rapid accumulation of immature precursor cells known as blasts. In these cases, mutations often affect genes that regulate transcription, differentiation, and apoptosis. Chronic leukemias, such as Chronic Lymphocytic Leukemia (CLL) and Chronic Myeloid Leukemia (CML), tend to involve genetic abnormalities that enhance cell survival and proliferation without completely abolishing differentiation. The genetic landscape of CLL also reveals clonal evolution, in which leukemic cells accumulate new mutations over time, leading to disease progression or resistance to therapy.

Beyond translocations and fusion genes, point mutations and small insertions or deletions in genes involved in cell signaling, epigenetic regulation, and tumor suppression play a critical role in leukemogenesis. These mutations alter the methylation and hydroxymethylation patterns of DNA, leading to abnormal gene expression programs that contribute to leukemic transformation. The recognition of epigenetic regulators as key players in leukemia has expanded the view of genetics beyond simple coding mutations to include modifications that alter gene expression without changing DNA sequences.

The genetic basis of leukemia also involves inherited predispositions. While most cases arise from somatic mutations, certain germline mutations increase the risk of developing leukemia. Another important aspect of leukemia genetics is the concept of clonal hematopoiesis, in which hematopoietic stem cells acquire somatic mutations that confer a selective growth advantage, leading to the expansion of clones that may eventually progress to leukemia. While clonal hematopoiesis does not inevitably progress to leukemia, it represents a fertile ground in which additional hits can trigger malignant transformation. This multistep model of leukemogenesis mirrors the classic paradigm of cancer development, where sequential genetic and epigenetic alterations drive progression from normal to malignant states.

The identification of genetic lesions in leukemia has profound implications for diagnosis, prognosis, and therapy. Cytogenetic and molecular profiling are now integral to the classification of leukemia, enabling clinicians to distinguish subtypes that differ in their biological behavior and therapeutic response. Similarly, the advent of tyrosine kinase inhibitors for CML transformed the disease from a fatal malignancy into a manageable chronic condition for most patients. These therapies illustrate how genetics not only explains disease mechanisms but also guides therapeutic innovation.

Despite these advances, the genetic heterogeneity of leukemia poses ongoing challenges. Within a single patient, leukemic cells often harbor multiple mutations that interact in complex ways, influencing disease course and response to treatment. The phenomenon of clonal evolution, where subclones with distinct genetic profiles emerge over time, can lead to therapy resistance and relapse.

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