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Perspective

Clonal Evolution in Myeloid Malignancies: Implications for Therapy and Disease Monitoring

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DESCRIPTION

The concept of clonal evolution has fundamentally altered our understanding of myeloid malignancies, transforming our view of these diseases from static entities to dynamic processes characterized by ongoing genetic diversification and selection. This evolutionary perspective has profound implications for therapeutic approaches, disease monitoring, and our conceptualization of remission and cure. As our understanding of the molecular landscape of myeloid neoplasms has deepened, so too has our appreciation for the complexity of clonal architecture and its clinical significance.

The advent of high-throughput sequencing technologies has revealed the remarkable heterogeneity of myeloid malignancies at the genetic level. Acute Myeloid Leukemia (AML), once classified primarily by morphologic and cytogenetic features, is now recognized as a constellation of genetically distinct entities, each characterized by specific patterns of mutations and distinct clinical behaviors. Similarly, Myelodysplastic Syndromes (MDS) and Myeloproliferative Neoplasms (MPNs) have been reclassified based on molecular findings, with specific mutations carrying diagnostic, prognostic, and therapeutic implications. This genetic heterogeneity exists not only between patients but also within individual patients, where multiple subclones bearing different constellations of mutations may coexist and compete.

The recognition of Clonal Hematopoiesis of Indeterminate Potential (CHIP) has further complicated our understanding of the boundary between normal and malignant hematopoiesis. The detection of somatic mutations in genes commonly altered in myeloid malignancies, such as *DNMT3A*, *TET2*, and *ASXL1*, in apparently healthy individuals has challenged traditional concepts of disease initiation and progression. These mutations, which confer a selective advantage to hematopoietic stem cells, can persist for years or decades without progressing to overt malignancy, yet they increase the risk of subsequent hematologic disorders and, intriguingly, cardiovascular events. The relationship between CHIP and frank myeloid neoplasia represents a continuum rather than a sharp divide, with additional genetic and epigenetic alterations driving progression from premalignant to malignant states.

The temporal sequence of mutation acquisition in myeloid malignancies follows discernible patterns that inform our understanding of disease pathogenesis. "Founder" mutations in epigenetic regulators such as *DNMT3A*, *TET2*, and *ASXL1* typically occur early in disease evolution and persist throughout the disease course, including during morphologic remission. These mutations establish a permissive environment for subsequent genetic alterations but are often insufficient to cause overt disease. In contrast, mutations in signaling pathway components like *FLT3*, *RAS*, and *KIT* often arise later and may fluctuate over time, reflecting their role as "accelerators" rather than initiators of disease. This hierarchical organization of mutations has therapeutic implications, as targeting early founder mutations may be necessary for disease eradication, while addressing later subclonal mutations may offer only transient benefits.

The phenomenon of clonal selection under therapeutic pressure represents a formidable challenge in myeloid malignancies. Treatment with targeted agents or conventional chemotherapy can eliminate sensitive clones while allowing resistant subclones to expand, leading to disease progression or relapse with altered genetic features. The remarkable adaptability of myeloid malignancies to selective pressures reflects their underlying genetic instability and the diversity of their clonal reservoirs. This dynamic process necessitates ongoing molecular monitoring and adaptive therapeutic strategies that anticipate and address emerging resistance mechanisms.

The clinical implications of clonal evolution extend beyond disease progression to include therapy-related Myeloid Neoplasms (t-MNs). These secondary malignancies, occurring after exposure to cytotoxic therapy for a primary condition, frequently exhibit distinct genetic profiles characterized by adverse cytogenetic features and mutations in *TP53*. The selective pressure exerted by cytotoxic therapy appears to favor the expansion of pre-existing *TP53*-mutated clones, which may have been present at undetectable levels before treatment. This phenomenon highlights the double-edged nature of cancer therapy, which can both eradicate malignant cells and create conditions for the emergence of therapy-resistant clones.

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