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Mutational complexity in myelodysplasia

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A B S T R A C T

Myelodysplastic syndromes are characterized by genetic and clinical heterogeneity. Some mutations are able to drive clonal hematopoiesis without causing clinical consequences, while other mutations may have significant impact, including the transformation to leukemia. This review aims to describe the pathogenesis of myelodysplastic syndromes (MDS) by focusing on 3 aspects: combinatorial genetic events, environmental factors, and inherited genetic conditions.

1. Introduction

The seed of normal hematopoiesis is the hematopoietic stem cell, which is defined by its capacity for self-renewal and its multilineage potential. Rarely, a single stem cell acquires a mutation in a small subset of genes, which endows that cell with enhanced self-renewal and competitive advantage. In some cases, this does not cause severe clinical consequence and hematopoiesis remains largely intact. In other cases, however, there are subtle, but clinically apparent alterations, such as mild cytopenias or monocytosis. Acquisition of additional mutations may confer further selective clonal advantage, often associated with progressive dysfunction of hematopoiesis that causes more severe peripheral cytopenias. Further clonal degeneration can results in frank transformation to leukemia.

Three aspects of pathogenesis of myelodysplastic syndromes (MDS) are covered in this review: first, how genetic events cooperate to drive MDS pathogenesis; second, the influence of environmental selection—in particular leukemogenic exposures—on MDS pathogenesis; and third, the influence of inherited genetic conditions.

2. Genetic events driving MDS pathogenesis

Over the past 5 years, a number of large, MDS-focused sequencing studies have been published [1–6]. These studies all demonstrate concordant core findings: MDS is as genetically complex as it is clinically heterogeneous and unpredictable. There are dozens of recurrently mutated genes that involve a wide range of biological processes. The typical MDS patient has multiple mutations in different genes affecting different pathways and these studies clearly demonstrate that there is a large number of different genetic pathways to clonal dominance and disease.

The unifying biological property of MDS driver mutations is their potential to drive clonal dominance. In other words, in the right context, every MDS driver mutation causes enhanced self-renewal over neighboring cells, whether they be normal stem cells, parental clones, or sister subclones. This is true of mutations affecting regulators of DNA methylation, mutations affecting RNA splicing factors, and mutations affecting other pathways like cellular stress or DNA damage response, chromatin organization, lineage-specific transcription, or growth factor signaling. Although they all have the

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potential to drive clonal dominance, observations in patients and model systems demonstrate that a given mutation is not necessarily deterministic of biology. Mutations are stitched together over time to drive forward parallel processes of genetic and clinical evolution.

Fig. 1 shows the overlapping processes of clonal and clinical evolution [2,7,8]. The complement of mutations at any point in time and their relative abundance represent "clonal architecture", and the changes in clonal architecture over time is "clonal evolution". Importantly, in MDS and acute myeloid leukemia (AML), the clonal architecture at a single moment reflects a long history of oncogenesis and is the substrate for diversification and selection as therapeutic or other bottlenecks are applied. Clinically, it is imperative to understand how clonal genetic architecture may predict clonal evolution.

3. Fundamental challenges

There are two fundamental challenges to achieve the imperatives of understanding clonal and clinical evolution. One is how to engage the tremendous combinatorial genetic diversity of MDS in a coherent way, and the other is how to understand this diversity in the context of temporal or evolutionary dynamics. Our growing understanding of MDS suggests that there might be more order than chaos in MDS genetics. Evidence of this are the strong patterns of co-mutation association and exclusivity and the stereotyped positions of individual mutations in the clonal hierarchy of disease.

As an example, RNA splicing mutations are the most common class of genetic alterations in MDS patients. And these four genes—*SF3B1*, *U2AF1*, *SRSF2*, and *ZRSR2*—exhibit the most striking and consistently identified mutual exclusivity in MDS genetics. These mutations almost never co-occur in the same patient [8]. This mutual exclusivity in human genetics has been shown to reflect a cellular intolerance for severe spliceosome dysfunction [9]. This mutual exclusivity may potentially be leveraged therapeutically through pharmacologic inhibition of the spliceosome.

The second concept is that mutations have stereotyped positions in the clonal hierarchy. Spliceosome mutations occur early in the evolution of disease [5]. They are more often initiating or early progression mutations, whereas RAS pathway mutations that drive activated growth factor signaling occur later and in the context of more clinically advanced disease. In our study of paired MDS and secondary AML samples from individual patients, only a subset of mutation classes were acquired during that transformation. Mutations gained at transformation were largely limited to those affecting myeloid transcription factors or RAS/TK signaling, while never involving splicing factors or chromatin modifiers [8]. Even though MDS driver mutations all can cause clonal dominance, they are not randomly selected and accumulated through time to cause disease. Instead they are very stereotyped and manifest their biological functions in restricted genetic and temporal contexts.

As clinical sequencing platforms become more widely deployed in routine care, the question arises whether we possess enough understanding of the basic regulatory logic of MDS genetics to use sequencing to inform clinical decision-making in a dynamic and facile way. MDS patients are sequenced at multiple time points, and knowledge of context dependence and position in the clonal hierarchy may help make clinical predictions about what treatments to use and potentially when to initiate them. One example (Fig. 2) is a patient who had three sequencing assessments over 2 ½ years that showed dynamic acquisition of mutations associated with transformation. The FLT3 and KRAS mutations were detected at a low level approximately 7 months before frank transformation to leukemia. Whether this is a point of access for clinically actionable maneuvers remains to be determined. But the growing body of evidence indicates that using serial assessments of clonal architecture and patient-specific definitions of evolution may lead to more individually tailored therapeutic approaches.

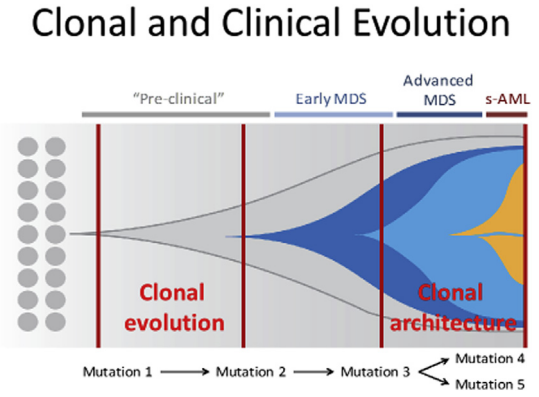

Fig. 1. MDS clonal and clinical evolution. In this figure depicting clonal and clinical evolution, clonal time is on the x-axis and proportional involvement of the bone marrow is on the y-axis. The gray circles represent normal stem cells in the bone marrow. Acquisition of an initial pathogenic mutation, also shown in gray, drives selective stem cell expansion. Additional mutations, shown by different colors moving through "clonal time," define individual daughter subclones, each with successive competitive advantage over its parent. The specific complement of mutations at any single point in time and their relative abundance form the clonal architecture; the dynamic changes in clonal architecture over time define clonal evolution.

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