Significance of Clonal Mutations in Bone Marrow Failure and Inherited Myelodysplastic Syndrome/Acute Myeloid Leukemia Predisposition Syndromes

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KEYWORDS

• Myelodysplastic syndrome • Bone marrow failure syndromes
• Genetic predisposition • Clonal hematopoiesis

KEY POINTS

- Clonal evolution in myelodysplastic syndromes can be driven by specific extrinsic and intrinsic selective pressures.
- Acquired somatic mutations in inherited bone marrow failure syndromes can partially complement underlying cellular defects leading to a selective clonal advantage that might be distinct from myeloid transformation.
- Long-term mutational studies with systematic analysis of serial samples in a larger number of patients are required to define prognostic and therapeutic implications of clonal hematopoiesis in patients with bone marrow failure syndromes.

INTRODUCTION

Myelodysplastic Syndrome Pathogenesis

Myelodysplastic syndrome (MDS) is a heterogeneous group of clonal hematopoietic disorders characterized by dysfunctional hematopoiesis, bone marrow dysplasia, and an increased risk of development of acute myeloid leukemia (AML).[1] Although MDS is most common in older patients (>70 years), it can occur in all age

Disclosure Statement: The authors have no relationship with a commercial company that has a direct financial interest in subject matter or materials discussed.
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Hematol Oncol Clin N Am ■ (2018) ■–■
https://doi.org/10.1016/j.hoc.2018.03.005 hemonc.theclinics.com

groups, including children and young adults. Primary MDS emerges without known predisposing cause and is associated with advanced age, whereas secondary and therapy-related MDS (t-MDS) are proportionally more common in younger MDS patients and develop in the context of inherited or acquired bone marrow failure or after exposure to chemotherapy, respectively.

Genetic studies have demonstrated that MDS molecular alterations are closely associated with clinical outcomes and disease characteristics.[2,3] Indeed, the spectrum of genetic alterations in young MDS patients is different than that of older MDS patients, consistent with the distinct age-associated mechanisms of MDS pathogenesis.[2] Whereas older patients more frequently harbor somatic mutations in genes encoding epigenetic modifiers (*TET2* and *DNMT3A*) or RNA splicing (*SRSF2* and *SF3B1*), younger patients have much higher frequency of genes associated with germline conditions (*GATA2* and *SBDS*) and acquired predispositions (*PIGA*). Mutations in other genes, such as *TP53*, *RUNX1*, or *RAS*, are common across all age groups.[2]

Clonal Hematopoiesis and Aging

Advancing age is the most established risk factor for developing clonally restricted hematopoiesis. During normal aging, individual hematopoietic stem cells (HSCs) steadily accumulate somatic mutations. By age 60, it is estimated that each HSC harbors 8 mutations affecting its coding genome.[4] Although most of these mutations do not measurably alter stem cell function, some confer a competitive advantage over normal HSCs and cause preferential contribution to mature hematopoietic cells. This phenomenon, when occurring in otherwise healthy individuals, is termed Clonal Hematopoiesis of Indeterminate Potential (CHIP), which has several key properties:

1. A strong association with advancing age,
2. An increased risk of developing frank hematologic malignancy (overall risk = 1% per year),
3. An increase in all-cause mortality related to an elevated risk of cardiovascular events.[5]

The age-dependent accumulation of somatic mutations may underlie the increasing prevalence of MDS among older individuals; the median age at MDS diagnosis is 71 to 76 years.[6] The close genetic and epidemiologic concordance between CHIP and primary MDS has engendered a model whereby clinically unapparent clonal HSC expansion is caused by an initiating mutation affecting particular genes, such as *DNMT3A*, *TET2*, and *ASXL1*, whereas transformation to frank myeloid malignancy is mediated by subsequent stepwise acquisition of additional myeloid driver mutations.[3,5] The factors that influence the frequency, genetic spectrum, and clinical implications of CHIP remain incompletely understood.

Extrinsic Selection and Clonal Hematopoiesis: Clonal Hematopoiesis of Indeterminate Potential and Therapy-Related Myelodysplastic Syndrome

Changes in cell extrinsic selection pressures due to specific therapeutic exposures or disease characteristics may influence the development and clinical implications of clonal hematopoiesis. For example, CHIP is present in about 30% of patients with non-Hodgkin lymphoma who undergo autologous stem cell transplantation, reflecting a rate more than 5 times higher than healthy adults of similar age spectrum.[7] Similarly, clonal hematopoiesis is common among patients with nonhematologic cancers.[8] The genetic spectrum of CHIP that arises in the context of therapeutic exposure is distinct, showing an enrichment of mutations affecting *TP53* and *PPM1D*, genes that are important for the cellular stress response. Mutations in *TP53* and *PPM1D* are also