Chapter 8 Integrated Diagnosis of Hemopoietic Neoplasms: Principles and General Approach

ABSTRACT

Hematopoietic neoplasms' molecular landscape and pathogenesis impact diagnosis and prognosis and ultimately guide personalized management. Genomic alterations determine the fate of the neoplastic clone and correlate with disease phenotypes. In myeloid neoplasms, mutations may drive neoplastic clones through one of the following tracks: ineffective hematopoiesis, with cytopenia and myelodysplasia; proliferation and arrested maturation in acute leukemia; failing to die, with orderly development in chronic leukemia and myeloproliferative neoplasms; or a combination of tracks with overlapping features of MDS/MPNs syndromes. Lymphoid neoplasms often correspond to specific maturation stages; of the immune system. Genetic abnormalities and hereditary disorders may predispose to hematologic neoplasms, necessitating their investigation in their diagnostic workup. Detecting clonal hematopoiesis is critical in the risk stratification of many hemopoietic neoplasms.

INTRODUCTION

Neoplastic transformation often commences at an early stem cell level. The evolving phenotype hinges on disruptions in proliferation, clonal expansion, differentiation, and apoptosis pathways.

Subsequent mutations successively promote subclone development and expansion, gradually replacing normal hemopoiesis. (Emadi, 2020).

Host factors may modulate the neoplastic behavior. Local and immune control can initially retain indolent neoplastic clones' differentiation and maturation potential. Later, escape mechanisms lead to disease progression and resistance to most endogenous control systems and therapeutics. According to the affected lineage, hematologic neoplasms may present as myeloid or lymphoid, each with diverging subtypes and pathogenic mechanisms. (Kurzer & Weinberg, 2021).

A highly conserved epigenetic transcriptional regulator "Plant homeodomain (PHD) finger proteins (PHF6)," is critical for neurodevelopment and hematopoiesis with a broad expression in almost all tissues, including CD34+ precursors and B-cells, with lower levels in NK cells and monocytes. Acquired deletions/mutations of PHF6 determine the fate of the resulting neoplasia. In T-ALL, these abnormalities arise early and are insufficient for transformation. In myeloid neoplasms, they develop later and pos-

DOI: 10.4018/978-1-6684-5818-1.ch008

sibly lead to disease progression. Inactivating mutations of PHF6 in myeloid or B-cell precursors may promote T-cell gene expression with the development of mixed phenotype acute leukemias. PHF6 also contributes to the lineage plasticity of hematopoietic malignancies. Figure 1 outlines a model of PHF6 in hematopoietic malignancies neoplasms. (Kurzer & Weinberg, 2021).

Figure 1. Role of PHF6 in hematopoietic malignancies



(Kurzer & Weinberg, 2021)

The objective of this chapter is to explore the molecular pathogenesis of hemopoietic malignancy subtypes and the role of genomic alterations in shaping the phenotype, clinical behavior, and potential diagnostic and therapeutic implications.

MOLECULAR LANDSCAPE AND PATHOGENESIS OF HEMATOLOGIC NEOPLASMS

The genomic landscape of hematopoietic neoplasms holds crucial diagnostic and prognostic implications, shaping personalized management strategies. Genomic profiles correlate with disease phenotypes and are the basis for the recently proposed update of the classification of hemo-lymphopoietic neoplasms. (Zhang et al., 2021).

The Molecular Pathogenesis of Myeloid Neoplasms

A somatic driver mutation initiates a transformation producing genetically unstable clones. New mutations and subclones gradually change the primary phenotype into a more aggressive one, e.g., chronic leukemia and myelodysplastic syndromes can evolve into acute leukemia. The initial event and the following mutations will determine the fate of the clone producing one of the following four phenotypes: (Gao et al., 2022).

- A. Abnormal Maturation With Ineffective Hematopoiesis, Cytopenia, And Myelodysplasia In Myelodysplastic Syndromes (MDS).
- B. Excessive Proliferation And Arrested Maturation In Acute Leukemia.
- C. Failing To Die And Accumulation In Blood And Tissues In Chronic Leukemia And Myeloproliferative Neoplasms.
- D. Exhibiting More Than One Track With Overlapping Features In MDS/MPN Syndromes

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