Secondary leukemia - Section 1

Biology of secondary leukemia

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Take Home Messages

- Secondary acute myeloid leukemia (sAML) is defined by the presence of an identifiable antecedent condition, which may include prior hematologic malignancy (MDS, MPN), bone marrow failure, or chemotherapy/radiation (tAML).
- In contrast, de novo AML (dnAML) is diagnosed in the absence of an identified antecedent condition, although some such cases may also be preceded by an occult phase of clonal hematopoiesis.

Introduction

Acute myeloid leukemia (AML) is a cancer of hematopoietic progenitors characterized by the accumulation of recurrent somatic mutations, resulting in maturational arrest and clonal expansion. AML may develop either de novo (dnAML), or following an antecedent hematologic condition, a subgroup categorized as secondary AML (sAML).1 Secondary leukemias can be further divided into leukemia arising out of a prior myelodysplastic syndrome (MDS) or myeloproliferative neoplasm (MPN), leukemia arising from a bone marrow failure state (BMF), and leukemia secondary to antecedent chemotherapy or radiation exposure (tAML), most commonly topoisomerase inhibitors or alkylating agents (Figure 1). For reasons we do not yet understand, the vast majority of secondary leukemias are myeloid. sAML is distinguished from dnAML by having a confirmed prior clinical diagnosis, although increasing understanding of the genomic underpinnings of sAML suggests that some de novo cases with “sAML-like” mutations such as SRSF2, SF3B1, U2AF1, ZRSR2, TP53, ASXL1, EZH2, BCOR, or STAG2, may have had an antecedent, previously undiagnosed, hematologic process. Patients with sAML have dismal clinical outcomes; understanding its pathogenesis may help to improve sAML treatment paradigms.

Current state-of-the-art

Inherited conditions leading to sAML

Recent sequencing studies suggest that inherited predisposition to leukemia may be more common than previously appreciated. These cases may present initially as a congenital bone marrow failure syndrome (e.g., Fanconi Anemia, Shwachman-Diamond Syndrome, telomeropathies, Severe Congenital Neutropenia), or as autosomal dominant syndromes, which may present as MDS/AML with variable penetrance and latency, with or without preceding stigmata (caused by germline mutations in GATA2, CEBPA, RUNX1, ANKRD26, SRP72, or ETV6). The most recently described predisposition genes are DDX41 and SAMD9/SAMD9L, which localize to chromosomal regions frequently deleted in myeloid malignancies (5q and 7q, respectively).2-4 Additional somatic mutations are required for transformation to MDS/AML in familial cases, including genes that are recurrently mutated in dnAML; however, the frequencies of these mutations appear to differ (e.g., more frequent mutations in ASXL1, BCOR, and TP511 in familial cases). In addition, patients with congenital bone marrow failure syndromes may develop clonal hematopoiesis long before the diagnosis of overt malignancy, which may contribute to the risk of MDS or AML.5 For instance, patients with congenital neutropenia syndromes exhibit clonal hematopoiesis which varies by clinical presentation; patients with severe congenital neutropenia often have clonal hematopoiesis with truncating CSE3R mutations, while roughly half of patients with Shwachman-Diamond Syndrome have clonal hematopoiesis with TP53 mutations.6

From clonal hematopoiesis to AML

The finding of clonal hematopoiesis in individuals without a cancer diagnosis, also termed Clonal Hematopoiesis of Indeterminate Potential (CHIP), extends beyond those with a familial leukemia predisposition. Initial reports found detectable CHIP populations in approximately 10% of septuagenarians, but with ultra-sensitive sequencing approaches, CHIP appears to be ubiquitous across the population, suggesting it may be an inevitable consequence of aging.7,8 Expanded clonal populations often harbor somatic mutations characteristic of MDS, AML, and other advanced myeloid neoplasms. While the rate of subsequent malignancy is increased among patients with CHIP, most will live long periods without progression. Additional mutations, beyond those identified in clonally restricted hematopoiesis, must accumulate to produce a pre-leukemic progenitor clone with the potential to progress to leukemia. Moreover, clonal evolution is subject to selective pressures, such as chemotherapy or radiation exposures, that influence the fate of pre-leukemic clones. For instance, patients with tAML frequently have TP53-mutated clonal hematopoiesis that predates the treatment exposure and which is a component of their subsequent leukemia.9,10
**MDS-derived sAML**

In MDS, the majority of the bone marrow hematopoiesis is clonal, even in low-risk cases without elevated myeloblast counts. Interestingly, the subsequent progression to sAML is invariably characterized by emergence of additional subclones. This clonal evolution may proceed either by the sequential acquisition of mutations within a dominant clone until progression to sAML (linear), or may occur via the emergence of a subclone that expands to clonal dominance with extinction of other subclones (branching). Certain acquired mutations may be associated with leukemic transformation, such as NRAS, FLT3, WT1, PTEN11, IDH1/2, and NPM1 mutations, but are nonetheless imperfect predictors of progression and may be present long before clinical changes are apparent. Epigenetic changes may drive progression, independent of mutational status; recent data suggest that an immature progenitor gene expression profile, in contrast to increased erythroid/megakaryocytic lineage gene expression, may identify MDS cases at greater risk for evolution to sAML.

**Distinguishing sAML from dnAML**

Recent work has suggested that the underlying genomic “footprint” may distinguish sAML cases from dnAML. Historically it has been known that cytogenetic abnormalities in tAML are distinct from dnAML, enriched for MLL-rearrangements or monosomal karyotypes, depending on the exposure. Sequencing efforts have further identified characteristic somatic mutation patterns that predominate in sAML. Although sAML typically has been defined on the basis of a known predisposing condition or exposure, the finding that some clinical diagnoses of dnAML harbor mutation profiles and outcomes more characteristic of sAML, such as the presence of a mutation in SRSF2, SF3B1, U2AF1, ZRSR2, ASXL1, EZH2, BCOR, or STAG2, raises the possibility that tumor genetics may provide a more objective classification system. However, while suggestive, existing tools do not provide perfect discrimination between sAML and dnAML cases.

**Future perspectives**

In spite of ongoing understanding of the clonal underpinnings of sAML transformation, translation into clinically actionable pathways remains incomplete. While clonal evolution is a clear component of sAML, changes over time within individual preleukemic cells remain unknown. Single cell RNA-seq may provide insight into the events preceding leukemic transformation, including potential targets to prevent or alter this transformation.

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**Figure 1.** Secondary AML (sAML) arises out of an antecedent hematologic condition, generally through the acquisition of additional mutations over time. Common conditions preceding sAML include myelodysplastic syndromes (MDS), myeloproliferative neoplasms (MPN), bone marrow failure syndromes (BMF), and prior exposure to chemotherapy or radiation (tAML). Subsequent mutations drive clonal evolution through linear or branching hierarchies. At presentation, sAML is distinct from de novo AML both as relates to clinical history, as well as the genetic composition of disease. Some patients without a clearly defined antecedent condition may nonetheless develop AML with genetic features more commonly seen in sAML, potentially evolving from a clonally restricted pre-leukemic population such as CHIP, or unrecognized preceding MDS.
Clonal selection also depends upon interactions with stromal and immune cells; understanding the role of bone marrow microenvironment survival signals and immune surveillance may further provide insight into how sAML develops and direct future therapeutic targets. Ongoing efforts to better distinguish the exact mutations within pre-leukemic cells that result in sAML, along with their interactions with the marrow environment, may provide prognostic information and, potentially, future therapeutic targets for this challenging disease.

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