The Genomic Landscape of Myeloid Malignancies: Options for Pan-myeloid Therapies?

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During aging of the hematopoietic system, the acquisition of somatic mutations can lead to a decline in hematopoietic stem and progenitor cell function and increased myeloid differentiation. Recently, exome sequencing studies of peripheral blood cells demonstrated the presence of clonal aberrations in healthy elderly individuals, referred to as clonal hematopoiesis of indeterminate potential (CHIP) that are associated with an increased risk of hematologic cancers.[1-3] The group of genes with the highest incidence of such mutations within the aging human hematopoietic system includes epigenetic modifiers (*DNMT3A*, *TET2*, *ASXL1*), signaling related molecules (*JAK2*, *CBL*, *GNB1*, *GNAS*), components of the spliceosome machinery (*SF3B1*, *SRSF2*), and *TP53*. Mutations in several of these candidate genes have previously been described in patients with myeloid malignancies such as myeloproliferative neoplasms (MPNs), myelodysplastic syndromes (MDSs), or acute myeloid leukemia (AML), suggesting that these clones may represent a premalignant state.[4,5] These findings supported the concept that an underlying clonal architecture of the hematopoietic system may be "fertile soil" for the development of hematopoietic cancers. Although the transformation rate from clonal hematopoiesis into myeloid neoplasms is below 1% per year, the occurrence of these mutations as early events in MDS clearly underlines their role in the erosion of the epigenetic landscape of hematopoietic stem cells and predisposition to malignant transformation.[6] On the other hand, the occurrence of these mutations may itself be a consequence of (accelerated) aging and a higher tendency of cells to develop malignancies. The presence of common mutations throughout the spectrum of myeloid malignancies identifies them as potentially targetable pan-myeloid vulnerabilities.

An excellent example of how mutations that exist in the premalignant clone may be targeted by epigenetic compounds has very recently been demonstrated for *NPM1c* mutations.[7] While *DNMT3A* mutations have been frequently described in individuals with CHIP, the acquisition of *NPM1c* mutation has rather

been associated with rapid disease progression and development of AML. In this study, *NPM1c* mutations were detected in 12% of MDS samples that had subsequently progressed rapidly to secondary AML (sAML).[7] Using *Dnmt3a* and *NPM1c* double mutant mouse models that recapitulate the clonal development as indicated above, the dependency of self-renewing leukemic cells on NPM1c and the progression to AML were both confirmed by serial transplantations in vivo. Importantly, epigenetic therapies targeting the mixed-lineage-leukemia-complex component Menin reduced expression of essential NPM1c targets such as Pbx3 and Meis1a and could eradicate the premalignant clone. While clinical data are eagerly awaited, these preclinical models provide the first evidence that patients harboring high-risk mutations predictive of transformation into acute leukemia might benefit from preventative therapy with epigenetic drugs.

Precision oncology, defined as molecular profiling of tumors to identify targetable alterations, is appealing as it combines the hope for a more effective treatment with lower levels of toxicity compared with conventional therapies. Hotspot mutations in isocitrate dehydrogenase 1 and 2 (*IDH1*, *IDH2*) occur in a variety of myeloid malignancies. AML patient cells harboring IDH mutations show a hypermethylated DNA phenotype and expression of IDH mutants in preclinical mouse models results in impaired differentiation. As IDH mutations are oncogenic drivers of myeloid cancers, targeting their activity may provide additional therapeutic benefit. In MDS and AML, therapies targeting IDH have recently emerged.[8] In early clinical trials, enasidenib (AG221), a selective inhibitor of mutant IDH2, was used as a monotherapy in refractory/relapsed AML patients leading to an overall response rate of 38%. In MDS, around 4%-5% of patients are found to carry an *IDH2* and 2%-3% an *IDH1* mutation. While IDH1 and IDH2 inhibitors are currently not approved for AML or MDS patients in Europe, enasidenib has received approval from the Food-and-Drug-Administration for elderly patients with relapsed/refractory AML. Responses seen here may also be achievable in patients with MDS (or MPN), especially in those undergoing transformation to sAML, highlighting their potential as a pan-myeloid personalized medicine. This is further emphasized by recent data indicating frequent overlap of *IDH2* and spliceosome (*SRSF2*) mutations that may promote leukemia development through coordinated effects on the epigenome and RNA splicing.[9] The presence of *IDH2* mutations showed impact on splicing effects induced by mutant SRSF2, resulted in more profound splicing changes than either mutation alone and induced an aggressive disease phenotype.

Mutations in spliceosome genes such as *SF3B1* have shown a strong impact on disease biology and are independent prognostic factors in MDS.[10] Of note, mutations affecting other members of the spliceosome machinery (*SRSF2* or *U2AF1*) are prognostically

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relevant in MPN and are incorporated in advanced scoring systems.[11] Recently, groundbreaking work has been published on how modulation of splicing catalysis could be used for therapeutic targeting of hematopoietic cancers harboring mutations in spliceosome genes.[12] In elegant mouse models, the authors provide the first evidence that *Srsf2* mutations, which are always heterozygous in human MDS or AML, rely on the wildtype allele for survival. Using pharmacologic modulation of the spliceosome machinery, they demonstrate that the magnitude of splicing modulation by the spliceosome inhibitor E7107 is greater in *Srsf2* mutated than in nonmutated cells. These findings indicate a therapeutic index as cells harboring spliceosomal gene mutations appear preferentially susceptible to additional pharmacologic perturbation of the splicing machinery. Besides being mutated, splicing factors may also exert altered function by undergoing posttranslational modifications. Most recently, a global view on the phosphoproteomic landscape downstream of mutated Jak2 kinase has identified messenger RNA splicing and processing related molecules as relevant targets of Jak2-dependent posttranslational modification.[13] Inactivation of nonmutated splicing factors sensitized Jak-inhibitor persistent cells to apoptosis and resulted in RNA mis-splicing, intron retention, and thereby disruption of relevant oncogenic signaling pathways. Genetic and pharmacologic targeting of these molecules and pathways led to regression of the malignant clone in vivo and induced molecular remission. This finding is of clinical interest as persistence of the malignant clone is a unifying challenge in myeloid neoplasms. While inhibitors of mutant JAK kinases can target the inflammatory activity in MPN, they fail to efficiently reduce or eliminate the malignant clone.[14] Here, pharmacologic targeting of the spliceosome machinery or of splicing regulatory proteins may therefore induce molecular remissions and eventually facilitate disease eradication.

Taken together, in addition to specific driver mutations such as oncogenic fusions, myeloid neoplasms show commonalities and unifying mechanisms at the level of the genomic landscape that clearly have functional consequences. These overlaps in pathophysiology across the myeloid spectrum provide targets for the development of pan-myeloid therapies that may complement additional personalized treatment approaches.

Disclosures

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