Myelodysplasia in younger adults: outlier or unique molecular entity?

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Myelodysplastic syndrome (MDS) is a disease of the elderly with a median age at diagnosis of 71 years and a sharp increase in incidence reported after the sixth decade of life.[1] This age-associated increase in incidence also applies to pre-MDS and pre-leukemic states such as clonal hematopoiesis of indeterminate potential, clonal cytopenias of uncertain significance, and idiopathic cytopenias of uncertain significance, with 10% of individuals over 65 years of age harboring these conditions while they are extremely rare in individuals less than 40 years of age.[2-4] Despite this, MDS can sporadically affect younger adults and occurs rarely in the pediatric population. Although evidence suggests that pediatric MDS, compared to its adult counterpart, is associated with a distinct pathophysiology hallmarked by an increased incidence of hereditary syndromes and disparate mutational landscape,[5,6] whether MDS in younger adults is a unique molecular entity or simply a continuum of "classic adult disease" is unknown.

Comprehensive molecular annotation of MDS and secondary acute myeloid leukemia has identified somatic variants in the vast majority of patients, with these having a significant impact on diagnosis, prognosis and treatment selection.[7-9] Using this evidence as a benchmark, Hirsch and colleagues present data on 634 patients with MDS, MDS/myeloproliferative neoplasms (including chronic myelomonocytic leukemia) or secondary acute myeloid leukemia and investigate the landscape of mutations based on age at presentation.[10] The authors utilized whole exome sequencing or a targeted next-generation sequencing panel of 60 genes representing the most common myeloid neoplasm-associated mutations. As expected, the age distribution of the cohort was unimodal with early onset MDS defined as that occurring in patients less than 50 years of age (10% of cohort). Classified according to World Health Organization criteria, patients with early onset MDS more frequently had refractory anemia with excess blasts. Targeted next-generation sequencing and/or whole exome sequencing both demonstrated an increasing number of mutations, independently of World Health Organization classification, associated with age by both linear correlation and average median number of mutations. Interestingly, the increased mutational complexity was also independent of cytogenetic complexity, which was not significantly different based on age.

The evaluation of differences in gene mutation frequencies between younger and older adults with MDS showed that the older patients had a higher incidence of mutations in genes associated with the spliceosome and epigenetic regulator families, data which correlate strongly with those in the literature on aging clonal hematopoiesis.[7-9] Specifically, *TET2* and *SRSF2* mutations were significantly more common in older patients, a finding corroborating recent investigations using ultra-deep sequencing in a cohort of 4,000 patients in which *SRSF2* mutations were observed exclusively in patients greater than 70 years of age.[11] Together, these data and those presented by Hirsch *et al.* suggest that spliceosome mutations appear to be particularly associated with an aging hematopoietic environment. In a similar analysis of acute myeloid leukemia in the elderly (>65 years of age, n=100), Silva and colleagues also showed spliceosome (*SRSF2* in 23% of patients) and epigenetic modifiers (*TET2* and *ASXL1* in 24% and 21% of patients, respectively) to be the most commonly mutated genes in their cohort which was significantly increased compared to younger patients from the TCGA database.[12,13]

However, molecular profiling did not demonstrate any specific mutations or family of mutations as being present uniquely in patients with early onset MDS. Rather, gene mutation rates of the known drivers described above appear to increase linearly with age, suggesting a continuum rather than a unique molecular disease. These data differ from those of patients with juvenile myelomonocytic leukemia, for example, in whom RAS family mutations are found in the vast majority while being present in only 30% of patients with chronic myelomonocytic leukemia.[14-16] In fact in this study, there was a trend for an increase in RAS family mutations in patients greater than 50 years of age. As expected, familial mutations were more common in the early onset cohort, which correlates with the known earlier age at diagnosis of familial MDS/acute myeloid leukemia.[17] This was particularly exemplified by the fact that the majority of asymptomatic carriers had clonal hematopoiesis by the age of 50 (>80% with *RUNX1* germline mutations).[17]

In addition to performing comprehensive assessment of mutational frequency based on age, Hirsch and colleagues additionally described the clonal architecture in selected patients. Although there were differences regarding dominant clonal mutations based on age (i.e. *RUNX1*, *SF3B1*, *TP53* in early onset patients and *TET2*, *SF3B1*, and *STAG2* in older patients), these differences were not universally associated with age but rather a gradual representation of a biological continuum.

Unlike other hematologic neoplasms that occur with bimodal distributions such as aplastic anemia, cases of early onset MDS do not constitute a distinct, molecularly defined subgroup.[18] Instead, they represent a continuum of MDS in older patients with molecular distinction largely attributable to mutations associated with clonal hematopoiesis of aging. As age-related clonal hematopoiesis leads to hematologic malignancy in only a minority of cases, these data support a growing body of literature describing serial acquisition of genomic events over time with consequent progression to overt disease. Although it is plausible that early onset MDS may simply be a consequence of age-related outliers with characteristic pre-leukemic states described above, future studies are required to understand the inciting molecular events in this population. For example, do patients with early onset MDS have co-morbidities that contribute to accelerated aging or inflammatory states conducive to the pathological events that lead to MDS? Or do they harbor occult germline variants with low penetrance that have yet to be described

thereby provoking somatic variants characteristic of classic MDS?

Although these important questions require further investigation, the work by Hirsch *et al.* suggests a clear distinction between MDS and other hematologic diseases with bimodal distributions. For example in aplastic anemia, it has become increasingly clear that younger patients have distinct pathophysiologies and therapeutic vulnerabilities with important clinical implications.[19] However, the analysis by Hirsch *et al.* indicates that the molecular underpinnings of adult MDS, regardless of age, are likely more similar than they are different and that our clinical management, including enrollment in interventional studies, should reflect this.

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Immunoglobulin genes in chronic lymphocytic leukemia: key to understanding the disease and improving risk stratification

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While triggering through the B-cell receptor (BcR) facilitates B-cell development and maintenance, it also carries intertwined risks for the emergence of lymphoid malignancies, since malignant B cells can exploit BcR signaling pathways in order to initiate and fuel clonal expansion. Indeed, substantial research into chronic lymphocytic leukemia (CLL), largely based on immunogenetic data, supports the notion that the clonotypic BcR immunoglobulin (IG) engages in the recognition of and selection by putative (auto)antigen.[1] This highlights the critical role of the BcR IG in the pathophysiology of CLL and implies that disease development is functionally driven and dynamic, rather than being a simple stochastic process. From a clinical perspective, the remarkable therapeutic efficacy of novel drugs such as ibrutinib and idelalisib which target effectors of the BcR signaling pathway (BTK and PI3Kδ, respectively), further vouch for this idea, and herald a major paradigm shift which may ultimately