Somatic Mutations in Aplastic Anemia

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KEYWORDS

• Aplastic anemia • Somatic mutations • Myeloid neoplasms • Treatment

KEY POINTS

- The occurrence and significance of somatic mutations in aplastic anemia (AA) are closely linked to the immune response that occurs in AA.
- Somatic mutations in *PIGA* and HLA genes (and possibly *BCOR/BCORL1*) represent immune escape clones that are associated with response to immunosuppressive therapy and very low risk of progression to myelodysplastic syndrome in adults.
- Myeloid-specific somatic mutations, such as *DNMT3A* and *ASXL1*, are found in a proportion of AA patients. When detected at diagnosis, their significance is unclear and difficult to distinguish from age-related clonal hematopoiesis.

IMMUNE FEATURES OF THE DISEASE THAT IMPACT ON THE SIGNIFICANCE OF SOMATIC MUTATIONS IN APLASTIC ANEMIA

Acquired idiopathic aplastic anemia (AA) is in most cases an immune-mediated bone marrow failure disorder.[1–3] AA is characterized by a proinflammatory environment that occurs after an initial insult (likely viral) to the bone marrow, which is driven initially by the $CD4^+$ T-cell compartment. This immune response is characterized by increased helper T cells—T_H1 (clonal) and T_H17 cells—and reduced or absent regulatory T cells (Tregs). Tregs in AA are also dysfunctional because they show reduced ability to suppress autologous T effectors proliferation. This results in oligoclonal expansion of $CD8^+$ cytotoxic T cells (CTLs) and apoptosis of hematopoietic stem cells (HSCs) and progenitor cells, respectively.[4–7] Response to immunosuppressive therapy (IST) using antithymocyte globulin with cyclosporine occurs in approximately 70% of AA patients.[8–10] Using high-dimensional immunephenotyping by mass cytometry using cytometry by time-of-flight (CyTOF), 2 identified distinct Treg subpopulations (Treg A and Treg B) differing significantly in number and immune phenotype have been

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identified between responders and nonresponders to IST. Treg B population predominates in responders to IST and has a memory/activated phenotype (as shown by high expression of CD95, CCR4, and CD45RO).[11]

Considerable overlap exists between AA and other clonal HSCs disorders. AA may be difficult to distinguish from the hypocellular subtype of myelodysplastic syndrome (MDS), hypocellular MDS,[12] and AA may later transform to MDS/acute myeloid leukemia (AML) in approximately 15% of patients at 10 years after IST.[8–10,13] Immune mechanisms to keep mutations in general under check involve innate and adaptive immune responses, including the expression of mutation-related neoantigens, their binding to HLA, and hence their ability to elicit an immune response.[14] Some disease clones may be kept under control by an effective immune system leading to their elimination, whereas other clones may escape such a response. The significance of somatic mutations in AA, therefore, will depend on the underlying immune pathogenetic mechanisms for clonal transformation. The immune response in AA is mainly due to Treg dysfunction and a T_H17 inflammatory response, leading to a subsequent $CD8^+$ T-cell response. With the development of MDS, however, there is a change from a proinflammatory to an immune-suppressive environment, with an increase in Tregs and decrease in T_H17 cells. The number of Tregs is higher in high-risk MDS compared with low-rick/intermediate-risk MDS. In contrast, T_H17 cells are significantly higher in low-risk MDS compared with high-risk MDS, and the high level of T_H17 correlates with increased bone marrow apoptosis. Thus, the balance between T_H1, T_H7, and Tregs reflects the characteristic immune signature of the bone marrow failure; if the balance is toward T_H1 and T_H17 with low/normal Tregs, as in AA and low-risk MDS, there is a proinflammatory immunosuppressive environment, with autoreactivity of the adaptive immune system. In the presence of increased Tregs, as seen in high-risk MDS, immune surveillance switches to immune subversion and subsequent disease progression.[15,16] From preliminary work by the authors' group, the immune response in AA patients with MDS-related somatic mutations is perhaps directed more toward mutation-related neoantigens.[17] Thus, the immune response plays a key role in modulating the fate of abnormal mutated clones, especially low-level clones during the disease course in AA (discussed later).

The immune-mediated nature of AA has other implications for the interpretation of somatic mutations. Abnormal clones may emerge in AA, escape this immune attack, and proliferate with a survival advantage over normal HSCs. This is a feature not only of specific cytogenetic clones, such as trisomy 8, due to increased expression of WT1 and del(13q) but also paroxysmal nocturnal hemoglobinuria (PNH) clones due to acquired somatic mutations of PIG-A or acquired copy number neutral loss of heterozygosity for 6p (6pLOH) or other structural HLA gene mutations. Such clones are in general associated with a good prognosis and low risk of clonal evolution to MDS/AML in adults.[18–22] In addition to the immune response seen in AA and during disease progression, aging is associated with many changes in the immune system, including a chronic low-grade proinflammatory state (termed, *inflammaging*), driven by intracellular inflammasomes that are important mediators for age-related diseases.[23] This may contribute to clonal transformation particularly in older patients with AA. Of relevance here is the biphasic age distribution for AA with peaks at 15 years to 20 years and greater than 60 years.[24,25] It is this older group of AA patients where the possible impact of age-related clonal hematopoiesis (ARCH) is at its greatest and in whom the likelihood that their bone marrow failure might be due to hypocellular MDS instead of AA is increased compared with younger patients.