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Natural born survivors: the inglorious TP53

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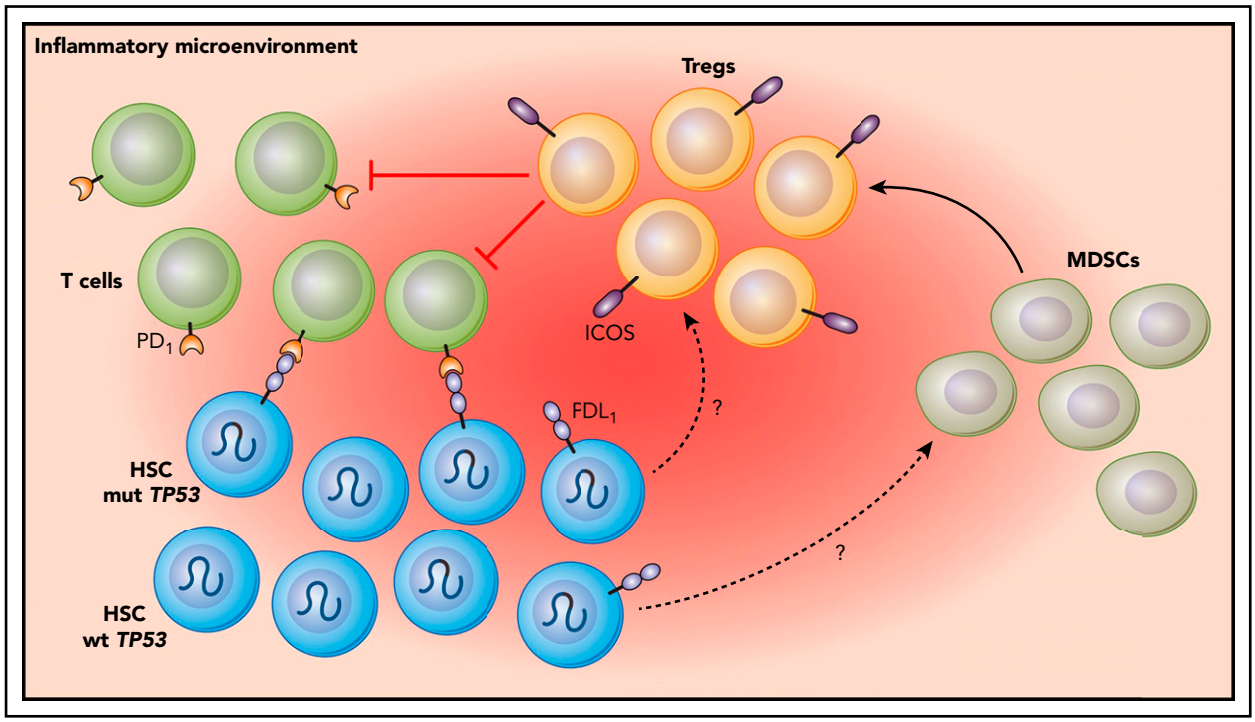
In this issue of *Blood*, Sallman et al[1] show that myelodysplastic syndrome (MDS) and secondary acute myeloid leukemia (sAML) harboring a *TP53* mutation ($TP53_{mut}$) are characterized by immune checkpoint overexpression (programmed death ligand 1 [PD-L1]) at the stem cell level (see figure), which is mediated by dysregulation of the mir-34a/MYC circuit, reduced numbers of cytotoxic T cells, and expansion of myeloid-derived suppressor cells (MDSCs) and $ICOS^{high}/PD\text{-}1^{neg}$ regulatory T cells (Tregs). The latter independently correlated with adverse overall survival. The paucity of additional somatic mutations in $TP53_{mut}$ cases was also confirmed in this study, which indicates that this is a distinct molecular entity. MDS/sAML with $TP53_{mut}$ may be enriched with an immunosuppressive profile that could be the primary driver of the rather dismal prognosis found in this molecularly defined subset.

Although our understanding of somatic mutations and their role in the pathogenesis and clinical outcomes of MDS/sAML has improved significantly in recent years, the dynamic and complex landscape of these mutations and their interaction with the immune system are still emerging.[2] Some of the most common mutations in MDS, such as *DNMT3A* and *TET2*, appear to be early initiation mutations and can be detected in cases with age-related clonal hematopoiesis, known as clonal hematopoiesis of indeterminate potential (CHIP), with an increased risk for developing acute myeloid leukemia (AML). Activation of p53, a tumor suppressor and transcriptional factor, by cellular stresses leads to activation of protective pathways like the induction of apoptosis, cell cycle arrest, and DNA damage repair. Loss of wild-type p53, due to $TP53_{mut}$ or deletions of 17p locus, a common abnormality in cancer, almost always portends a poor prognosis, treatment resistance, and genomic instability. Therefore, the presence of $TP53_{mut}$ in CHIP substantially increases the risk of progression to AML, particularly in the presence of genotoxic stress and inflammation. In MDS, mut*TP53* is commonly seen in patients with complex karyotypes and has a significant negative impact on prognosis.[3] *TP53* mutations are strongly associated with thrombocytopenia, increased blasts, and chromosome 5 abnormalities, in isolated del(5q) and complex karyotypes. Presence of mut*TP53* in patients with a complex karyotype identifies an entity with extremely poor prognosis and median overall survival <6 months. This abysmal survival highlights the unmet need for novel therapeutic approaches in these cases.

Other than its general role in cancer biology, little is known about how $TP53_{mut}$ may shape the "immunome" in MDS and sAML. PD-L1 is expressed on several



MDS and sAML harboring mut*TP53* are characterized by immune checkpoint overexpression at the stem cell level, as well as a reduced number of cytotoxic T cells and expansion of MDSCs and $ICOS^{high}/PD\text{-}1^{neg}$ Tregs. HSC, hematopoietic stem cell.

cancer cell and immune cell types and binds to programmed death-1 (PD-1) and CD80, 2 negative regulators of T-lymphocyte activation. The binding of PD-L1 to these receptors suppresses T-cell migration, proliferation, and cytotoxic function against tumor cells. PD-L1 protein expression in tumor cells is the best predictive biomarker for response to PD-1/PD-L1–targeted therapy in solid tumors. PD-L1 protein expression has been shown to be upregulated in MDS, representing a potential mechanism for the resistance to HMAs. The exhausted T-cell phenotype, characterized by PD-1 overexpression, is also reported in MDS, which contributes to an inefficient immune response[4] and suggests that immune checkpoint inhibitors (CPIs) should be useful. Nevertheless, the overall response to CPIs in molecular unselected cohorts of patients has been modest so far.

Immune dysregulation in MDS is complicated, consisting of myeloid-derived inflammation, as well as a range of immune cell aberrations. An NLRP3 inflammasome-driven inflammatory circuit is a feature of MDS, which contributes to the "myeloid bias" and disease phenotype. Although inflammation could promote *TP53* mutated clones, some other mutations, such as *U2AF1*, also trigger inflammasome activation and pyroptosis. Cellular immune response is particularly diverse in MDS, ranging from a relatively "activated" immune response in lower-risk disease to a highly suppressed immune system in high-risk disease,[5,6] which is supported by the findings in the current study.

Similar to some other malignancies, the presence of mutation-related neoantigens may improve immune response and survival in some MDS patients.[7] Nevertheless, immunotherapies targeting p53-related neoantigens have not been very successful. Although these clinical trials of immunotherapy in MDS are disappointing, some patients do respond.[8] Novel combinations of therapies may also improve the response. The issue, however, is the lack of biomarker(s) to predict response to therapies like CPIs or immunomodulators and stratify patients early in the course of treatment. Although the Revised International Prognostic Scoring System is an excellent tool to predict outcome in MDS, it has proved to be less efficient in predicting response to therapy, which may well be due to the omission of somatic mutations and the "immunome" in this scoring system.

This study by Sallman et al, despite investigating a rather small and heterogeneous group of MDS/sAML patients, is one of the few studies in which immune signatures are linked with a specific somatic mutation, thereby identifying a potential immune pathway that may predict response and can be targeted to improve response to therapies such, as CPIs. Another interesting finding of this study is the expansion of $ICOS^{high}PD1^{neg}$ Tregs. Expansion of immunosuppressive cells, such as Tregs,[5] MDSCs, progenitor B cells, and thrombomodulin-expressing monocytes, are reported in MDS and AML, and they are usually correlated with a higher risk for progression.

Human Tregs are a heterogeneous cell population with remarkable plasticity in response to microenvironmental changes. For instance, in an inflammatory environment, Tregs could switch their profile to a less proliferative and apoptosis-resistant phenotype.[9] Whether the expansion of $ICOS^{high}PD1^{neg}$ is a result of exposure to inflammatory environment and expansion of MDSCs or a direct/indirect effect of $TP53_{mut}$ clone expansion is yet to be determined. It is also important to investigate whether these Tregs are playing a protective role against effector T cells or are part of the stem cell niche, as suggested for other Treg subsets in animal models,[10] or a combination of both. Although the Sallman et al study provides novel and very important insights into the pathophysiology of MDS/sAML, as well as the interaction between a common somatic mutation and immunome, it creates additional questions that will be the subject of research in this field for perhaps years to come. The long-standing "chicken or the egg" (immunome or genome) argument is far from over.

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