T CELL EXHAUSTION IN HEMATOLOGICAL MALIGNANCIES

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Acute myeloid leukemia (AML) and myeloproliferative neoplasms (MPN), including myelofibrosis (MF), are associated with profound immune dysregulation that is increasingly recognized as a contributor to disease evolution and therapeutic response [1-3]. Among immune alterations, T cell exhaustion has emerged as a dominant functional state, marked by sustained antigen exposure, chronic inflammatory signaling, and progressive loss of effector capacity [4]. Exhausted T cells display impaired cytotoxicity, altered differentiation trajectories, metabolic dysfunction, and upregulation of inhibitory receptors, ultimately limiting antitumor immunity [5].

In AML, high-dimensional transcriptomic and single-cell analyses have defined distinct dysfunctional T cell states, including progenitor exhausted, terminally exhausted, and senescent-like populations, which coexist within the bone marrow microenvironment [1]. These states correlate with interferon gamma–dominant immune signatures, adverse molecular lesions, and resistance to conventional chemotherapy [1]. Importantly, emerging immune dysfunction signatures may complement established risk stratification models by helping to delineate patient subsets with potentially distinct therapeutic vulnerabilities, including differential sensitivity to conventional therapy and immune checkpoint inhibition [1,2,5]. While checkpoint blockade can transiently reinvigorate specific exhausted T cell subsets, sustained clinical benefit in AML has been limited, highlighting the complexity of leukemia-driven immune suppression.

In MPN and MF, chronic inflammation driven by constitutive oncogenic signaling promotes continuous T cell activation and progressive exhaustion [3,6,7]. Expanded populations of dysfunctional CD8 T cells, impaired antigen-specific responses, and defective immune synapse formation have been described [3,6]. Oncogenic calreticulin mutations further contribute to immune escape by altering antigen presentation and dampening T cell–mediated surveillance [8]. These mechanisms help explain the modest activity of checkpoint inhibitors in MPN and underscore the interaction between malignant hematopoiesis, inflammation, and immune failure.

Collectively, evidence from AML and MPN indicates that T cell exhaustion is not merely a consequence of disease burden but a dynamic process influencing response to both conventional and immune-based therapies. A deeper understanding of immune dysfunction, its molecular drivers, and its temporal evolution across disease stages is essential to design rational combination strategies. Optimizing the timing of immunomodulatory interventions may be critical to restore immune competence and improve durable clinical responses.

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