The role of the immune checkpoint TIGIT in CD4+ T cell dysfunction in patients with decompensated cirrhosis

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Background and Aims: Patients with decompensated cirrhosis are highly susceptible to bacterial infections. CD4+ T cells, which play a key role in anti-bacterial immune responses, are functionally impaired in cirrhosis, but the mechanisms underlying this are not well understood. TIGIT, an immune checkpoint on T cells, transmits inhibitory signals when bound to its ligand, CD155, on antigen-presenting cells. CD226, an activating receptor on T cells, also binds CD155. This study aimed to investigate the TIGIT-CD226-CD155 immune checkpoint axis in decompensated cirrhosis and assess if TIGIT blockade could improve CD4+ T cell function.

Methods: The study included patients with stable decompensated cirrhosis (SD, n=11), acute decompensated cirrhosis (AD, n=21), and acute-on-chronic liver failure (ACLF, n=19), recruited within 48 hours of hospital admission, along with healthy controls (HC, n=18). Flow cytometry was used to assess the expression of TIGIT, CD226, and CD155 on immune cell subsets in peripheral blood. TIGIT+/- CD4+ T cells from AD and ACLF patients were isolated by flow sorting and bulk RNA sequencing was performed. An anti-TIGIT monoclonal antibody (MBSA43 clone, 10 μg/ml) was used for *ex vivo* TIGIT blockade. CD4+ T cell function was evaluated by measuring exhaustion markers (PD-1, LAG-3, TIM-3), proliferation, and cytokine production (IFN-gamma, IL-2, TNF-alpha) after CD3 stimulation.

Results: CD4+ T cells from AD and ACLF patients expressed more TIGIT compared to those from HC (1915 vs. 1340 mean TIGIT MFI, $p = 0.04$). The expression of CD226 on CD4+ T cells, and CD155 on CD14+ monocytes, was unchanged between groups. Patients who developed bacterial infections or died within 90 days had a higher ratio of TIGIT to CD226 expression on their CD4+ T cells at baseline compared to those who remained infection-free or survived.

TIGIT+ CD4+ T cells had a distinct transcriptomic profile, with downregulation of genes involved in leukocyte chemotaxis and trans-synaptic signalling compared to TIGIT- CD4+ T cells. *Ex vivo* TIGIT blockade reduced exhaustion markers LAG-3 and PD-1 and increased IFN-gamma production by CD4+ T cells from AD and ACLF patients. However, this blockade did not affect CD4+ T cell proliferation.

Conclusion: This study identifies a potential mechanism for CD4+ T cell dysfunction in cirrhosis. Expression of the inhibitory checkpoint TIGIT on CD4+ T cells is increased in AD and ACLF and is associated with subsequent bacterial infections. *Ex vivo* TIGIT blockade partially reversed CD4+ T cell exhaustion and enhanced proinflammatory cytokine production, suggesting TIGIT could serve as a novel immunomodulatory target in decompensated cirrhosis.