The CD96-CD155 immune checkpoint axis in ACLF is upregulated and correlates with disease severity

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Background: Acute-on-chronic liver failure (ACLF) is a syndrome characterised by multiple organ failure and high short-term mortality. The condition represents an immunological paradox in that rampant systemic inflammation, which drives organ dysfunction, exists alongside immune cell dysfunction and increased susceptibility to bacterial infections. Understanding the mechanisms that control this balance is therefore critical.

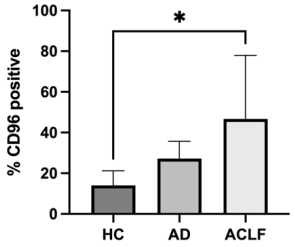
CD96 is an immune checkpoint expressed on T cells and NK cells that transmits an inhibitory signal when bound to its ligand CD155 (PVR). Both CD96 and CD155 have soluble forms, with elevated concentrations found in other immunosuppressive states such as cancer and chronic viral infections. In this study we explored the CD96-CD155 immune checkpoint axis in patients with ACLF.

Method: The expression of membrane bound CD96 on peripheral lymphoid cells was assessed by flow cytometry in patients with acute decompensated cirrhosis (AD) and ACLF, compared to healthy controls (HC) (n = 8 per group). In a separate cohort, concentrations of plasma soluble CD96 and CD155 in patients with AD (n = 8) or ACLF (n = 23), compared to HC (n = 8), was determined with a Luminex multiplex assay.

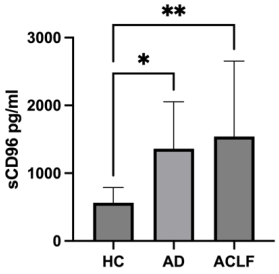
Results: CD4+ T cells from patients with ACLF had increased expression of CD96 than those from HC (46.69 versus 14.04%, p = 0.02, figure A) and sCD96 concentrations were higher in ACLF than HC (1541 versus 563.6pg/ml, p = 0.01, figure B). sCD96 concentration correlated positively with Child Pugh Score (r = 0.43, p = 0.02) and was higher in ACLF non-survivors at 1 month than survivors (2245 versus 1100 pg/ml, p = 0.01, figure C). sCD155 concentrations were also increased in ACLF compared to HC (8875 versus 2686pg/ml, p = 0.01).

Conclusion: Expression of the inhibitory immune checkpoint CD96 is increased on CD4+ T cells in ACLF patients and this is mirrored by higher plasma sCD96 concentrations. The latter correlates with cirrhosis disease severity and is higher in ACLF non-survivors. CD96 could therefore be an immunomodulatory target in ACLF, and sCD96 a useful prognostic marker.

[A] Membrane bound CD96 on CD4+ T cells



[B] Soluble CD96



[C] ACLF survivors vs non-survivors at 1 month