[BIOINFO 2025]

Multi-Omics Analysis Highlights The Role of TREM2+ Macrophages in Tumor Progression in Hepatocellular Carcinoma

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Hepatocellular carcinoma (HCC) remains a significant global health challenge. Recent studies have reported TREM2+ macrophages as highly enriched in various cancer types and associated with immunosuppression. In this study, we analyzed scRNA-seq, secretome, bulk RNA-seq and spatial transcriptomics data to investigate the role of TREM2+ macrophages in the progression of HCC. For bulk RNA-seq analysis, data were obtained from two xenograft mouse models transplanted with the human hepatoma Huh7 cell line. The control group was treated with secretome from macrophages, while the test group was treated with secretome from TREM2+ macrophages. Differential gene expression analysis revealed significant upregulation of Mmp12 in the test group. Consistently, secretome profiling showed increased secretion of MMP12 in IL-4/IL-13-treated macrophage supernatants. Spatial transcriptomics-based cell-cell interaction analysis further revealed active MMP12-PLAUR signaling between TREM2+ macrophage and HCC hepatocytes. In scRNA-seq data, PLAUR+ hepatocytes exhibited elevated expression of pro-inflammatory cytokines, including CXCL8, CXCL3, CCL4 and CCL3. Notably, CXCL8 has been implicated in promoting angiogenesis, inflammation, and metastatic progression. Functional assays confirmed that MMP12-induced CXCL8 expression in Huh7 cells was significantly attenuated by the MMP12 inhibitor MMP408, supporting a direct regulatory role of MMP12. Overall, our findings suggest that TREM2+ macrophages may contribute to the activation of genes promoting tumor progression in HCC.

Keywords: TREM2, macrophage, hepatocellular carcinoma