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TREM2⁺ Macrophages Promote Hepatocellular Carcinoma Progression via the MMP12-PLAUR Axis

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Hepatocellular carcinoma (HCC) is the most common form of liver cancer, characterized by high recurrence rates and poor survival. Tumor-associated macrophages (TAMs) within the tumor microenvironment (TME) have been implicated in tumor progression and immune evasion; however, their underlying mechanisms remain incompletely defined. This study aimed to characterize the features of TAMs and elucidate their tumor-regulatory mechanisms, thereby uncovering the interactions between macrophages and cancer cells within the TME. Analysis of single-cell RNA sequencing (scRNA-seq) data from the liver expression atlas and spatial transcriptomics revealed an enrichment of TREM2⁺ macrophages in HCC tissues. Immunohistochemical staining of tumor microarray samples further demonstrated an increase in TREM2⁺CD68⁺ macrophages in malignant regions, which correlated with tumor stage. To establish cellular models, macrophages were differentiated from U937 monocytes, and TREM2 expression was induced by co-treatment with IL-4 and IL-13. Proteomic profiling of the secretome from IL-4/IL-13-treated macrophages revealed a marked increase in MMP12 compared with controls, which was further validated by qPCR, Western blot, and ELISA. Spatial transcriptomics revealed a significantly higher MMP12-PLAUR interaction in HCC patients with high malignancy scores than in those with low scores. Treatment of Huh7 cells with the IL-4/IL-13-treated macrophage secretome resulted in increased cell surface expression of PLAUR in vitro. Analysis of clinical datasets showed that high expression of TREM2, MMP12, and PLAUR was associated with poor prognosis in HCC patients. Furthermore, cytokine candidates enriched in PLAUR⁺ HCC were identified, and their expression was increased in Huh7 cells treated with recombinant MMP12 or the IL-4/IL-13-treated macrophage secretome, but suppressed by the

MMP12 inhibitor MMP408. Collectively, these findings indicate that TREM2$^+$ macrophages promote HCC invasion and growth through the MMP12–PLAUR axis, highlighting this pathway as a potential prognostic marker and therapeutic target.