TGF-β critically determines the activation state of both, the macrophage subpopulation that is particularly recruited in the context of MASH progression, as well as of TAMs

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Abstract

Hepatocellular carcinoma (HCC) is the third leading cause of cancer-related death worldwide. Metabolic dysfunction-associated steatotic liver disease (MASLD) will become the predominant cause for the development of HCC worldwide by 2030, currently accounting for 20% of HCC cases in Western countries. There are two main subtypes of MASLD-related HCC, with and more rarely without cirrhosis. Microenvironmental factors are thought to be the driving force for HCC development in both, with steatohepatitis being the major cause of HCC in non-cirrhotic patients. Using spatial transcriptomics of MASH-HCC patient samples, we identified tumor-associated CD68-positive macrophages (TAM) that exhibit an activation state distinct from non-tumor regions, with for example reduced expression of the TGF-β activator Dermatopontin (DPT). This suggests an altered response of macrophages to TGF-β signaling with disease progression. Interestingly, CITE-seq analysis of liver tissue from a Western-type diet-(WD) fed mouse model suggests a selective increase in a macrophage subpopulation characterized by high CD11b/CD14 expression, whose activation state is particularly determined by TGF-β early during the progression from MASLD to MASH. Blunting TGF-β signaling in these macrophages changes their acitvation state towards increased production of IL-10 and upregulated expression of CD163 and CD206, representing known features of TAM. In conclusion, these results suggest that TAMs are characterized by an altered sensitivity to TGF-β. TGF-β signaling influences the activation state of distinct macrophage subpopulations, which are also important in the progression of MASH and may be a prerequisite for the development of TAM.