Monocyte-like cells promotes liver metastasis via THBS1-mediated CD8+ T cell inactivation in aggressive colorectal cancer

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Abstract

Colorectal cancer (CRC) with mesenchymal features exhibits a high metastatic potential and poor prognosis. Recent studies have revealed multiple inflammatory signatures enriched in this high malignant CRC. In this study, we focus on thrombospondin-1 (THBS1), which is a matricellular protein, typically expressed in inflammatory processes. We found a positive correlation between high THBS1 expression, mesenchymal phenotype, and poor prognosis in bioinformatics and histological analyses of human CRCs. Results from immunocompetent orthotopic implantation of aggressive mouse tumor organoids demonstrated that THBS1 contributed to liver metastasis via suppressing CD8+ T cell-mediated anti-tumor immunity. Single-cell transcriptomic analyses of CRCs revealed tumor-infiltrating monocyte-like cells as a primary source of THBS1 . Additionally, we identified stroma-derived CXCL12 as a key chemoattractant of THBS1-producing monocyte-like cells by analyzing orthotopic MTO tumors treated with CXCL12 inhibitor. Our study contributes to a better understanding of the processes underlying THBS1 production by monocyte-like cells that mediates immune evasion that confer aggressive features to CRCs. These findings provide insights for the treatment of this poor-prognosis malignancy.