The Prognostic Significance of the Spatial Distribution of Tumor Associated Macrophages in Colorectal Cancer

S. Holten[1], M. Bleul[1], N. Paeger[1], S. Quitter[1], T. Schaschinger[1], C. Tuffs[1,2], M. Schneider[2], and M.J. Strowitzki[1,2]

1 Department for General, Visceral & Transplantation Surgery, Heidelberg University Hospital, Heidelberg, Germany.
2 Department for General, Visceral, Thoracic &Transplantation Surgery, Giessen University Hospital, Giessen, Germany.

Background:

Macrophages, known as tumor-associated macrophages (TAMs), constitute the predominant cellular component in the tumor microenvironment (TME) of solid tumors. Depending on their polarization state, TAMs confer tumor growth and metastasis. Macrophage polarization is broadly categorized into classically activated (inflammatory) M1 phenotype or alternatively activated (immunomodulatory) M2 phenotype. Macrophage activity and polarization are dynamically regulated by various local cues within the TME, including hypoxia. HIF-1α is an important transcription factor promoting polarization and angiogenetic properties of TAMs. Here we assess the prognostic relevance of macrophage infiltration in patients with colorectal cancer (CRC) while considering the spatial distribution of TAMs.

Methods:

Immunohistochemical staining of three different TAM markers (CD68, CD163, and CD206) combined with whole slide imaging and automated image analysis was performed on tumor tissue from patients with CRC who underwent primary tumor resection (N = 49). Abundance and spatial distribution of TAMs within the TME were correlated with metastasis timepoint and overall survival.

Results:

The association of TAM infiltration with overall survival varied depending on their location within the TME. When evaluating the total number of positive cells throughout the entire tumor tissue, only CD206+ TAMs positively correlated with overall survival, while other markers showed no significant correlation. TAM infiltration significantly increased towards the tumor border (TB); higher spatial resolution analysis of this area revealed a positive correlation with overall survival for CD68+ and CD163+ TAMs in distinct regions of tumor tissue near the TB, while analysis of CD163+ TAMs on the opposite side of the TB showed contrasting results. CD163+ TAMs in normal tissue near the TB could be identified as an independent prognostic factor of overall survival.

Conclusion:

Our findings contribute to a nuanced understanding beyond the traditional M1/M2 categorization of TAMs. CD163 and CD206, both considered M2-like markers, displayed divergent spatial distribution and prognostic effects. The TAM localization within the TME, particularly around the TB, seems crucial for their role in CRC prognosis. The pronounced accumulation of TAMs at the TB underlines the significance of this region, aligning with their ability to directly interact with other immune cells and modulate the TME towards immunosuppression and mutagenesis. Further investigation of TAM metabolic reprogramming through spatial transcriptomics could identify potential prognostic markers as well as therapeutic targets, facilitating patient risk stratification and personalized treatment approaches in CRC.