

Omental macrophages of embryonic origin promote metastatic spread of ovarian cancer

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Macrophages are found in all tissues after birth and are endowed with trophic functions that contribute to organ development, remodeling and tissue homeostasis. Experimental evidence has shown that tumor-associated macrophages (TAMs) have important pro-tumoral properties that reflect the trophic functions of tissue-resident macrophages in development. Consistent with this the transcriptome of TAMs from mammary gland tumors has been shown to be enriched for genes that also define embryonic macrophages. In this study, we have characterized the ontogeny and function of TAM subsets in a mouse model of metastatic ovarian cancer that is representative for visceral peritoneal metastasis. We show that the omentum is a critical pre-metastatic niche for development of invasive disease in this model and defined a unique subset of CD163⁺Tim4⁺ tissue-resident macrophages in omentum of embryonic origin and maintained independently of bone marrow-derived monocytes. Transcriptomic analysis showed that resident CD163⁺Tim4⁺ omental macrophages were phenotypically distinct and maintained their resident identity during tumor growth. Selective depletion of CD163⁺Tim4⁺ macrophages in omentum using genetic and therapeutic tools prevented tumor progression and metastatic spread of disease. These studies describe a specific role for tissue-resident macrophages in the invasive progression of metastatic ovarian cancer. The molecular pathways of cross-talk between tissue-resident macrophages and disseminated cancer cells may represent new targets to prevent metastasis and disease recurrence.