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Regulation of breast tumor metastasis by the dynamic interaction between the TMEM macrophage, tumor cell and endothelial cell

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Tumor cell intravasation is an essential step in the metastatic cascade, but its exact mechanism is not completely understood. We have previously shown that the direct physical association of a tumor cell over-expressing Mena, a perivascular Tie2hi/Vegfhi macrophage and an endothelial cell, forming a cell triad termed tumor microenvironment of metastasis (TMEM), increases vascular permeability, facilitating intravasation of tumor cells. It is only at the TMEM site that intravasation takes place leading to breast tumor metastasis. TMEM density is a clinically validated prognostic marker of distant metastasis in breast cancer patients. The precise molecular mechanisms relating TMEM function had not been elucidated. Here we describe the molecular mechanism. We show here that TMEM function involves the three cells in TMEM: firstly endothelial cell-secreted Ang2 stimulates VEGF build up in the TMEM macrophage, secondly a tumor cell secretes CSF1 which, third, stimulates the TMEM macrophage VEGF secretion, leading to vascular opening and metastasis. In addition, we show that acute blockage of CSF1R and Tie2-Ang2 signaling by inhibitors and blocking antibodies both *in vitro* and in mammary tumors leads to decreased macrophage VEGF production and secretion, decreased trans-endothelial migration of tumor cells, and decreased TMEM-dependent vascular permeability, circulating tumor cells and lung metastases. We conclude that dynamic interaction between the cells associated with TMEM leads to Ang2 and CSF1-mediated stimulation of macrophage VEGF expression and secretion leading to vascular opening, resulting in tumor cell intravasation. This is the first description of the molecular mechanism behind the predictive power of the clinically used prognostic marker TMEM and represents a major step in defining new biomarkers and targets for the treatment of metastatic tumors.

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