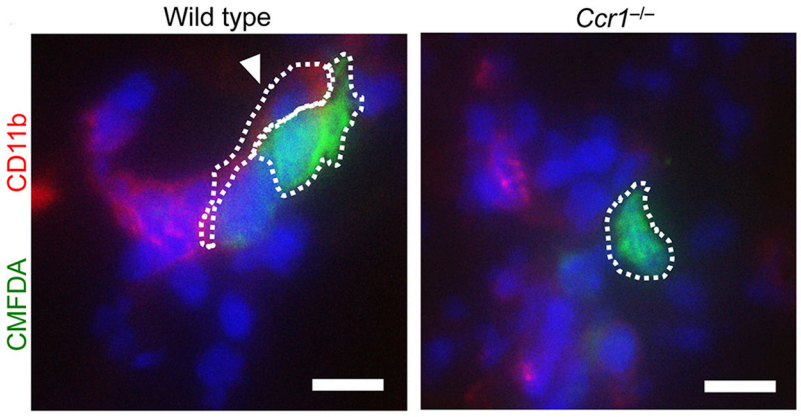
Fatal attraction: How macrophages participate in tumor metastases

Insight from Dmitry Gabrilovich

Macrophages are critically important for the regulation of tumor growth and metastases. They contribute to tumor angiogenesis, tumor cell extravasation, and survival at the sites of metastases. Now, Kitamura et al., using mouse models of breast cancer, have uncovered a major role for a CCL2-induced chemokine cascade that supports macrophage recruitment and retention in metastatic sites in the lung.

Macrophages found in metastatic sites have a distinct phenotype and are referred to as metastasis-associated macrophages (MAMs). Similar to other tumor-associated macrophages, MAMs originate from circulating inflammatory monocytes, which are recruited to the tumor site in response to the chemokine CCL2. This raised the attractive possibility of controlling metastasis by targeting CCL2. However, an anti-CCL2 antibody was found to be ineffective in humans. Furthermore, loss of CCL2 signaling reduced the numbers of circulating monocytes, leading to an increased susceptibility to infection in mouse models. This necessitated the search for more precise mechanisms regulating MAM migration, as addressed by Kitamura et al. in the current study.

Kitamura et al. found that MAMs expressed the CCL2 receptor CCR2, and activation of CCR2 signaling prompted MAMs to secrete another chemokine, CCL3. The increased CCL3 secretion resulted in enhanced MAM–cancer cell interaction, at least in part through integrin α4, and prolonged the retention of MAMs in the metastatic sites, resulting in extravasation of cancer cells. The authors implicated the CCL3 receptor CCR1 on MAMs as the main mechanism responsible for CCL3-mediated retention of MAMs in metastatic sites.



Representative fluorescence microscopy images of lung 24 hours after injection of mouse breast cancer cells. Green, CMFDA-labeled E0771-LG breast cancer cells; red, CD11b; blue, nuclei; arrow head, interaction between myeloid cells and cancer cells. Dotted line indicates the interaction between macrophage and tumor cell. Bars, 10 µm.

This study identifies a novel prometastatic chemokine cascade that promotes lung metastasis in breast cancer. Although the concept of chemokine crosstalk has been described previously, this work demonstrates, for the first time, the existence of the CCL2–CCL3 cascade in vivo and its contribution to tumor metastases. It appears that CCL2 is primarily responsible for macrophage migration, whereas CCL3 is primarily responsible for macrophage retention. It also seems likely that CCL2-induced CCL3 expression is specific to the prometastatic macrophage, which raises the exciting possibility of more effective identification and targeting of MAMs. However, the molecular mechanism by which CCL3 activates macrophages and promotes their interaction with tumor cells needs to be elucidated. CCL3 is known to have potent effects on neutrophil extravasation and activation. Although neutrophils may not play a major role in the breast tumor models used in this study, the potential involvement of neutrophils in other models and in patients requires further analysis.

This study presents a more refined picture of the role of macrophages in metastases than has been appreciated to date, and it suggests that more precise targeting of macrophages may allow us to curtail the development of metastases.

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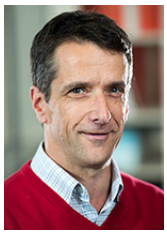
CD99: An endothelial passport for leukocytes

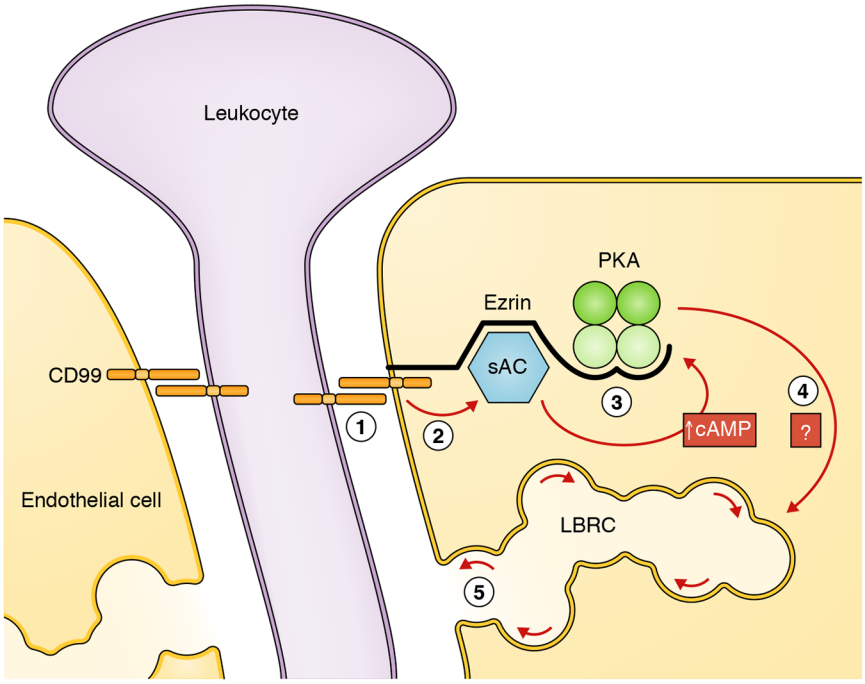


Insight from Michael Hickey

It has long been understood that the endothelium is not simply a passive barrier to leukocyte transendothelial migration (TEM). Complex cellular responses within endothelial cells involving signaling, membrane trafficking, and remodeling of cell–cell junctions are necessary for leukocytes to cross the endothelium and exit the vasculature. Inhibition or absence of junctional molecule CD99 has been shown to trap leukocytes midway through TEM, indicating an essential role for this molecule. However, the mechanisms by which CD99 contributes to TEM have been unclear. In this Issue, Watson et al. describe the signaling pathway activated by CD99 and demonstrate an important role for soluble adenylyl cyclase (sAC) in TEM.

Using an elegant imaging-based assay, Watson et al. show that CD99 inhibition prevents movement of the lateral border recycling compartment (LBRC) to the site of TEM, whereas CD99 cross-linking can restore this response, providing evidence of a role for CD99 in signaling for LBRC recycling. Using a comprehensive array of in vitro and in vivo analyses, the authors show that CD99 forms a complex at the endothelial cell junction with sAC, the scaffolding protein ezrin, and protein kinase A (PKA). Engagement of CD99 leads to activation of sAC and release of cAMP, which subsequently activates PKA, promoting LBRC recycling and facilitating leukocyte TEM. This is the first demonstration of a role for sAC in TEM and of the signaling pathway activated by CD99.

The key question to emerge from this study is: can this information be useful therapeutically? Inhibition of leukocyte recruitment is now established as a viable therapeutic approach for several inflammatory diseases, although it is not without risks in terms of susceptibility to infection. CD99 inhibition may be worth investigating as an additional strategy for inhibition of leukocyte recruitment. However, it remains to be determined how universal this mechanism is within the microvasculature. The current studies were performed using human umbilical vein endothelial cells and mouse dermal microvessels. It is now clear that the mechanisms of leukocyte recruitment can differ markedly in different microvascular beds. Detailed imaging-based analysis of important vascular beds such as the gastrointestinal tract, lung, and brain will be necessary to determine whether CD99 retains this function throughout the microvascular system. In addition, the mechanism whereby PKA promotes LBRC recycling remains to be determined. Unquestionably, the molecular complexity of transmigration will continue to engage the efforts of researchers for many years to come.



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A model of how CD99 signals during TEM. Under resting conditions, CD99, sAC, PKA, and ezrin form a signaling complex at endothelial junctions. During TEM, homophilic engagement of endothelial CD99 with leukocyte CD99 (1) signals through soluble adenylyl cyclase (2) to elevate cAMP (3), to activate PKA, which works through an unknown mechanism (4) to induce LBRC membrane trafficking to sites of leukocyte–endothelial contact (5).

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