Metastasis

Major finding: VCAM-1 promotes lung metastasis by tethering breast cancer cells to lung TAMs.

Mechanism: Juxtacrine activation of a VCAM-1–Ezrin–PI3K/AKT pathway promotes survival.

Impact: Antibodies blocking the VCAM-1–α4-integrin interaction may decrease metastatic potential.

VCAM-1 BINDS MACROPHAGES TO PROMOTE SURVIVAL OF LUNG METASTASES

Disseminated tumor cells must receive survival signals upon infiltration of a distant organ for metastatic colonization. Based on previous work identifying *vascular cell adhesion molecule-1* (*VCAM-1*) as part of a gene signature expressed in lung-metastatic breast cancer cells, Chen and colleagues hypothesized that VCAM-1 is required for lung metastasis. Interestingly, knockdown of VCAM-1 in breast cancer cells had no effect on lung invasion but led to a striking reduction of metastatic colonies associated with an increase in apoptotic cells. To identify the lung stromal cell types that VCAM-1–expressing cells encounter, the authors prepared single-cell suspensions from lung nodules, incubated the cells with VCAM-1, and used specific cell markers to identify and quantify interacting cells by flow cytometry. VCAM-1 bound specifically to macrophages, which expressed high levels of cell surface α4-integrin and comprised approximately 7% of the total cell population of metastatic nodules. Furthermore, binding of VCAM-1 to α4-integrin was required for the anti-apoptotic effect of VCAM-1. The authors found that VCAM-1–α4-integrin engagement specifically activated Ezrin and induced PI3K/AKT signaling to suppress apoptosis, indicating that tumor-associated macrophages (TAM) act in a juxtacrine manner to promote the survival of metastatic breast cancer cells upon lung invasion. Collectively, these data suggest that VCAM-1–expressing cancer cells have a survival advantage in leukocyte-rich organs such as the lungs, an observation that was supported by a bioinformatic analysis of breast tumors showing that a leukocyte expression signature was specifically associated with lung metastasis and high expression of VCAM-1. Because targeted therapies such as natalizumab that disrupt the interaction between endothelial VCAM-1 and leukocyte α4-integrins are already in use for such diseases as multiple sclerosis, these findings suggest that similar approaches may be effective in elimination of residual disease following primary tumor resection. ■

Chen Q, Zhang XH-F, Massagué J. Macrophage binding to receptor VCAM-1 transmits survival signals in breast cancer cells that invade the lungs. Cancer Cell. 2011;20:538–49.

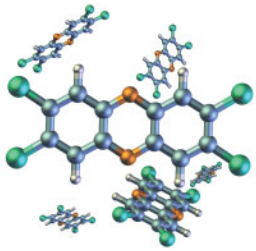
Immune Evasion

Major finding: Kyn is an endogenous ligand of AHR that is generated by TDO in tumors.

Impact: Kyn-dependent AHR activation promotes tumor growth and immunosuppression.

Clinical relevance: TDO and AHR may be promising therapeutic targets for glioma therapy.

TUMORS ACTIVATE THE ARYL HYDROCARBON RECEPTOR



Activation of the aryl hydrocarbon receptor (AHR) caused by exposure to toxic environmental xenobiotics has been implicated in carcinogenesis and immune suppression, but a mechanistic link between these 2 phenomena has been lacking. Further, no endogenous ligand capable of activating the AHR has been identified in a physiologically relevant disease setting. Opitz and colleagues report the surprising discovery that kynurenine (Kyn), a catabolite of tryptophan (Trp) excessively produced by glioma cells, binds and activates the AHR. They show that glioma cells release high micromolar amounts of Kyn due to specific overexpression of tryptophan-2,3-dioxygenase (TDO), an enzyme normally expressed in the liver that regulates systemic Trp levels. Glioma sections with high TDO expression displayed decreased immune cell infiltration, which the authors linked to Kyn-dependent inhibition of T-cell proliferation. Kyn was also shown to promote the survival and motility of glioma cells, and microarray and pathway analyses revealed that the most highly Kyn-induced genes were all regulated by the AHR. AHR was required for both the autocrine effect of Kyn on glioma cell growth and motility and the paracrine effect on T-cells in TDO-expressing glioma xenografts. In primary human gliomas, TDO expression was correlated with AHR and AHR target gene expression, and Kyn-dependent expression of AHR gene targets predicted poor survival in glioma. Collectively, these findings identify a mechanism of endogenous AHR activation by constitutive Trp catabolism and suggest that the TDO-Kyn-AHR signaling pathway is an important mediator of tumor growth and immune suppression. ■

Opitz CA, Litzenburger UM, Sahm F, Ott M, Tritschler I, Trump S, et al. An endogenous tumour-promoting ligand of the human aryl hydrocarbon receptor. Nature 2011;478:197–203.