

Thy-1 (CD90)-Induced Metastatic Cancer Cell Migration and Invasion Are β_3 Integrin-Dependent and Involve a Ca^{2+} /P2X7 Receptor Signaling Axis

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Abstract

Cancer cell adhesion to the vascular endothelium is an important step in tumor metastasis. Thy-1 (CD90), a cell adhesion molecule expressed in activated endothelial cells, has been implicated in melanoma metastasis by binding to integrins present in cancer cells. However, the signaling pathway(s) triggered by this Thy-1-Integrin interaction in cancer cells remains to be defined. Our previously reported data indicate that Ca^{2+} -dependent hemichannel opening, as well as the P2X7 receptor, are key players in Thy-1- $\alpha_v\beta_3$ Integrin-induced migration of reactive astrocytes. Thus, we investigated whether this signaling pathway is activated in MDA-MB-231 breast cancer cells and in B16F10 melanoma cells when stimulated with Thy-1. In both cancer cell types, Thy-1 induced a rapid increase in intracellular Ca^{2+} , ATP release, as well as cell migration and invasion. Connexin and Pannexin inhibitors decreased cell migration, implicating a requirement for hemichannel opening in Thy-1-induced cell migration. In addition, cell migration and invasion were precluded when the P2X7 receptor was pharmacologically blocked. Moreover, the ability of breast cancer and melanoma cells to transmigrate through an activated endothelial monolayer was significantly decreased when the β_3 Integrin was silenced in these cancer cells. Importantly, melanoma cells with silenced β_3 Integrin were unable to metastasize to the lung in a preclinical mouse model. Thus, our results suggest that the Ca^{2+} /hemichannel/ATP/P2X7 receptor-signaling axis triggered by the Thy-1- $\alpha_v\beta_3$ Integrin interaction is important for cancer cell migration, invasion and transvasation. These findings open up the possibility of therapeutically targeting the Thy-1-Integrin signaling pathway to prevent metastasis.

Author keywords

breast cancer
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