J Clin Cell Immunol 2018, Volume 9
DOI: 10.4172/2155-9899-C3-055

Exosomes-based cell-cell communication role in metastatic organotropism

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In the last 15 years, research on the metastatic progression of cancer has shown that tumors can modify normal tissues at a distance, by releasing extracellular vesicles that travel in the blood stream, bind to distant cells and transfer oncoproteins that ultimately promote the formation of microenvironments prone to receive and support metastatic lesions, formed even before the arrival of the first metastatic cells, known as pre-metastatic niches. We discovered that pancreatic cancer-derived exosomes carring high levels of macrophage migration inhibitory factor (MIF) bind preferentially to Kupffer cells in the liver, inducing production of inflammatory mediators such as TGF-B, which in turn promote extracellular matrix remodeling by hepatic stellate cells that supports accumulation of bone marrow-derived macrophages, which ultimatelly contribute to the attachment and growth of metastatic pancreatic cancer cells in the liver. Compared with patients whose pancreatic tumors did not progress, MIF was markedly higher in exosomes from stage I PDAC patients who later developed liver metastasis, suggesting that exosomal MIF may be a prognostic marker for the development of PDAC liver metastasis. Furthermore, we have also shown that exosomal patterns of integrins expression dictates the tissue affinity of tumor exosomes, which in turn determines the location of pre-metastatic niches formation and the tumor metastasis organ distribution. Our clinical data indicate that exosomal integrins could be used to predict organ-specific metastasis, helping to answer one of the greatest unsolved mysteries of metastatic cancer regarding the biological basis of organotropism.

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