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# Exosomes-based cell-cell communication role in metastatic organotropism

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## Abstract

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.

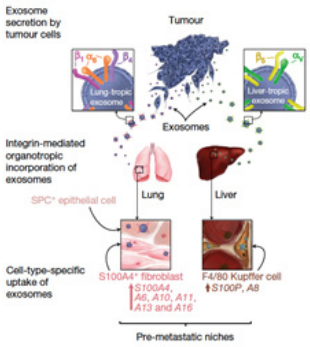


Figure 1. Tumor-derived exosomes role in metastatic organotropism. Exosomal integrin composition drives exosomes preferential accumulation in lungs (Integrins Alpha 6 Beta1/4) or liver (Integrin Alpha V Beta 5). Once in these specific sites, exosomes elicit pre-metastatic niche setup, which provides support to metastatic seeding (Adapted from Hoshino, Costa-Silva and Shen, et al. Nature, 2015)

## Biography

Dr Costa-Silva obtained his PhD in Oncology at the Ludwig Institute for Cancer Research and AC Camargo in São Paulo, Brazil, working on pre-metastatic niches induction by tumor-derived exosomes. Then he moved to Weill Cornell Medical College in New York for his post-doc at Dr. Lyden´s laboratory, where he spearheaded studies on the role of exosomes in cancer pathogenesis, specifically in metastasis of pancreatic cancer. Since 2016 he moved to Lisbon where he is leading the Systems Oncology group at the Champalimaud Foundation. He currently leads several projects on exosomes-based cell-cell communication and tumor microenvironment.

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