Metastasis is the most devastating phase of cancer. While most of the research effort to date has been focused on analysing the primary tumour, there is a lack of information on how the tumour microenvironment influences metastasis and pre-metastatic niche formation. The mechanisms underlying the evolution of the tumour microenvironment during metastasis may hold the key to converting cancer from a deadly disease to a manageable one. Prominent roles for stromal cells, such as fibroblasts, endothelial cells, lymphatic endothelial cells, bone marrow-derived cells, soluble factors and secreted vesicles have been established during pre-metastatic niche formation. Our novel studies suggest that tumour-secreted exosomes can fuse specifically to stromal cells acting locally in pre-metastatic niches and systemically reinforcing metastasis.

“Our work has highlighted that tumour-secreted exosomes promote the ’education’ of the tumour microenvironment, thus reinforcing metastasis.”

**Role of tumour-derived exosomes in pre-metastatic niche formation**

We have demonstrated that exosomes are biomarkers and functional contributors to pre-metastatic niche formation in metastatic organs. Exosomes can serve as vehicles for horizontal transfer of oncogenes, thus promoting additional modifications in the tumour and metastatic microenvironments. We showed that melanoma-derived exosomes expressing c-MET influence bone marrow-derived cell mobilisation and recruitment to pre-metastatic and metastatic niches, thus promoting metastasis in a process that we have termed ’education’ (Peinado et al., Nature Med, 2012). More recently, we have observed that pancreatic cancer-derived exosomes expressing macrophage migration inhibitory factor (MIF), preferentially acted upon Kupffer cells (Costa-Silva et al., Nat Cell Biol, 2015). Strikingly, MIF and c-MET levels in plasma exosomes demonstrate the potential of using exosomal protein levels as an early biomarker for liver pre-metastatic niche formation and for predicting patient outcomes, respectively.

**Tumour-derived exosomes define metastatic organotropism**

Our studies demonstrated that tumour exosomes are a major tumour-derived factor that acts systemically to promote bone marrow-derived cells (BMDCs) recruitment to the tumour and metastatic microenvironments (Peinado et al., Nature Med, 2012). Our recent results demonstrate that tumour-derived exosomes are uptaken by organ-specific cells preparing the pre-metastatic niche. These exosomes revealed distinct integrin expression depending on their specific organ of metastasis. Therefore, we postulate that exosome integrins could serve as a ’ZIP’ code for exosomes to home in metastatic organs triggering local effects reinforcing organ-specific metastasis. Our clinical data indicate that the profiling of integrins in circulating exosomes could be used to predict organ-specific metastasis (Hoshino et al., Nature, 2015).

**RESEARCH HIGHLIGHTS**

- **Overview**
  - **Role of tumour-derived exosomes in pre-metastatic niche formation**
  - **Tumour-derived exosomes define metastatic organotropism**

**AWARDS AND RECOGNITIONS**

- **Spanish National Cancer Research Centre (CNIO)**
- **Molecular Oncology Programme**
- **Junior Group**
- **Senior Group**
- **Graduate Students**
- **Undergraduate Students in Practice**
- **Research Faculty**
- **Molecular Oncology Programme**
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