

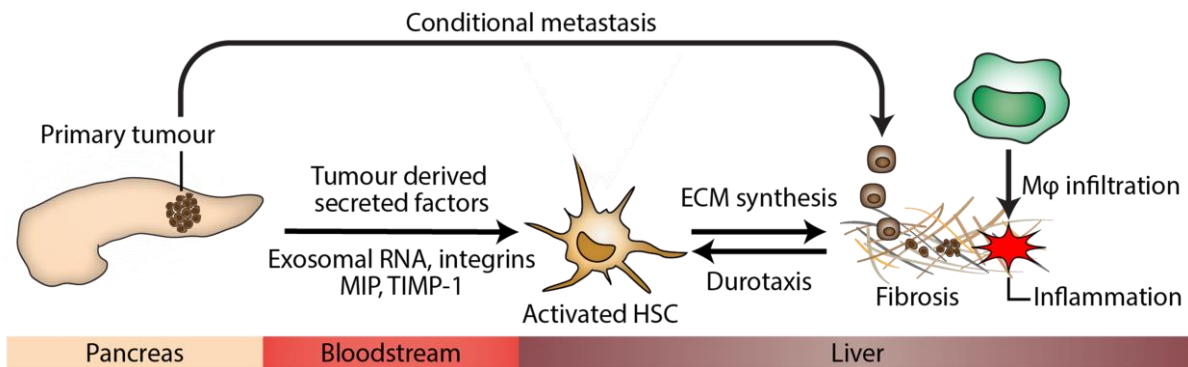
Title of the project: Biomechanical regulation of the pre-metastatic niche formation in the liver for pancreatic cancer colonisation

Supervisor: Dr. Armando E. Del Río Hernández

Cellular and Molecular Biomechanics laboratory: <http://biomechanicalregulation-lab.org/>

Department: Bioengineering/ South Kensington Campus

email: a.del-rio-hernandez@imperial.ac.uk



Project Description:

Pancreatic ductal adenocarcinoma (**PDAC**) is the most common type of pancreatic cancer, and the fourth leading cause of cancer-related death in the developed world. Around 10,000 people are diagnosed each year in the UK[1, 2]. It constitutes a “death sentence” to those afflicted by this devastating disease leading to rapid death of all patients. The 5-year survival-rate of pancreatic cancer is only 3% in the UK and this figure has not changed over the past four decades[1, 2]. Importantly, this is the only cancer reported so far, in which metastasis (in the liver) precedes the formation of the primary tumour[3, 4]. One of the reasons for the poor prognosis of PDAC is its high metastatic potential, being metastasis the leading cause of PDAC-associated death[4]. Therefore, a better understanding of the initial steps leading to PDAC metastasis, is urgently needed to improve disease intervention. Metastasis is difficult to investigate because it involves a series of stochastic events and its mechanisms vary depending on the tissue type that is being colonised. The concept of formation of **metastatic niche** to adapt and prepare the foreign tissue for a second tumour growth at distant sites, has been proposed since more than 130 years ago by Steven Paget’s ‘seed and soil’ hypothesis[5]. More recently, advances in the understanding of cancer exosomes have reverberated the field of cancer metastasis and in particular pancreatic cancer metastasis in the liver.

Exosomes are nanovesicles of around 150 nm that have emerged as key mediator of intercellular communication between cancer cells and the microenvironment through transfer of information via their cargo (proteins, DNAs, mRNAs). Integrin molecules in the surface of these tumour borne exosomes determine organotropic metastasis[6]. These tumour-derived exosomes bind the surface of specific cells in the host organ in an integrin dependent manner, and ‘educate’ the cells to create a pre-metastatic niche favourable for further cancer cells colonisation. In the case of exosomes secreted by pancreatic cancer cells, they have abundant $\alpha v \beta 5$ integrins that fuse with the Kupffer cells in the liver and reprogram the genetic profile of these cells to make them upregulate the production of tumour growth factor beta (TGFB), and expression of the pro-inflammatory gene S100-A8. $\alpha v \beta 5$ integrins uptake by the Kupffer cells also activates Src phosphorylation. Furthermore, the upregulation of TGFB by the Kupffer cells activates hepatic stellate cells, which increase fibronectin (FN) secretion and deposition in the ECM producing a fibrotic microenvironment[4]. This increased rigid microenvironment promotes the recruitment, of bone marrow-derived macrophages. Macrophage migration inhibitory factor (MIF) was highly expressed in PDAC-derived exosomes, and its blockade prevented liver pre-metastatic niche formation and metastasis. Collectively these data suggest that the preparation of pre-metastatic niche and liver colonisation by PDAC are driven by exosomes that modulate the function of host cells to create a fibrotic matrix that primes metastasis colonisation. Thus, therapies that target the mechanobiology pathways in these cells may be used effectively to hamper liver colonisation by PDAC.

The student that chooses this project will join a team of senior PhD students in our group working in this overarching aim. To discuss the specific project please send an email to: **Dr. Armando E. Del Río Hernández**

Key techniques: Biophysical and cell biology techniques: Magnetic tweezers, immunofluorescence, Western blot, tissue culture, organotypic cultures, elastic pillars.

References:

1. UK, C.R. *Pancreatic cancer survival statistics*. 2015; Available from: <http://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/pancreatic-cancer/survival#ref-0>.
2. UK, C.R. *Pancreatic cancer statistics*. 2015; Available from: <http://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/pancreatic-cancer#heading-Six>.
3. Rhim, A.D., et al., *EMT and dissemination precede pancreatic tumor formation*. *Cell*, 2012. **148**(1-2): p. 349-61.
4. Costa-Silva, B., et al., *Pancreatic cancer exosomes initiate pre-metastatic niche formation in the liver*. *Nat Cell Biol*, 2015. **17**(6): p. 816-26.
5. Psaila, B. and D. Lyden, *The metastatic niche: adapting the foreign soil*. *Nat Rev Cancer*, 2009. **9**(4): p. 285-93.
6. Hoshino, A., et al., *Tumour exosome integrins determine organotropic metastasis*. *Nature*, 2015. **527**(7578): p. 329-35.