MECHANOBIOLOGY OF CANCER PROGRESSION

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Context of the research

Female breast cancer is currently the most diagnosed cancer, with an estimated 2.3 million new cases per year. Breast cancer is known to be initiated by the mutation of specific oncogenes. It has been recently proven, however, that progression of the tumour is dictated by changes in the mechanical microenvironment of the mutated cells [1]. Breast cancer aggressiveness correlates specifically with fibrosis involving the deposition of a collagen matrix by stromal fibroblasts. Tumour-infiltrating immune cells like macrophages secrete signals that further increase collagen deposition and progressive tumour stiffening. This extracellular matrix acts as a progressive diffusive barrier. To overcome the progressive tumour resistance to anticancer treatments, it would be transformative for the field to understand and control how the tumour fibrotic environment evolves.

Background

The key mechanical/mass transport parameters of tumour stiffening are the fibrillar collagen matrix properties (e.g. stiffness, density, diffusion coefficient) and the microvascular network properties (e.g. geometry, permeability). These properties determine interstitial fluid pressure and blood flow velocity in the tumour, which modulate pH, diffusion (of endogenous molecules as soluble signals, nutrients, gases, metabolic products and of anticancer agents), cancer cell response (proliferation, motility, metabolism) and infiltration in the tumour of non-cancer cells (endothelial cells, macrophages, fibroblasts). Microfluidic-based platforms can recreate complex functional aspects of this mechanical environment *in vitro*. However, microvascular networks generated *in vitro* aren't stable enough in terms of hierarchy and permeability, to reproduce physiological profiles of luminal flows.

Recent Advances

The embryonated avian egg experimental model allows to measure *in vivo* the effect of therapeutic agents injected in the embryonic circulation, on a structure called chorioallantoic membrane and/or on the embryo. This model has also been used to monitor *in vivo* the invasive features of human ovarian, thyroid, and skin cancer cells. My group has recently replicated the human microvascular niche and relevant druggability *in vivo* using this model [2].

Future directions

We will use human breast cancer cells adhering to 3D polymeric micro scaffolds to create arrays of tumour

micro environments. We will implant the arrays *in vivo* in the chorioallantoic membrane of an embryonated avian egg, to elicit a foreign-body fibrotic reaction. We will vary the micro scaffolds geometry to condition tumour infiltration by the host's vessels and cells. We will predict mass transport of solutes and anticancer agents by computational modelling. To validate the platform, we will quantify *in vivo* the dose-dependent efficacy and cancer specificity of therapeutic agents whose success is known to depend on the fibrotic stage of tumours.
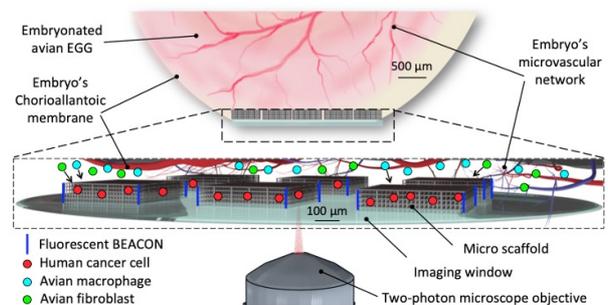

Figure 1: Scheme of idea of exploiting the innate immune system of an avian embryo to induce a foreign-body reaction able to recreate tumour fibrotic micro environments, with variable levels of matrix stiffness and vascularity, to embed human breast cancer cells.

References

1. Metcalf et al., J Clin Invest, 131:6, 2021.
2. Conci et al., Adv Optical Mater, 2101103, 2022.

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