VALERI Nicola EOI 2022 – Imperial

Project title: Mechanistic exploration of cell-free tumour DNA (ctDNA) shedding into circulation using microfluidic vascularised organoid-on-chip models

Project Summary:
Colon cancer (CC) is the second cause of cancer-related deaths worldwide. The presence of ctDNA in the circulation of stage II-III CC patients is considered a bio-marker of minimal residual disease (MRD). Although the presence of ctDNA is widely accepted as a surrogate for MRD in resected CC patients, a potential hurdle to the clinical adoption of ctDNA in this space is the variability of this biomarker among patients. A significant proportion of patients with MRD have undetectable levels of ctDNA in peripheral blood samples. Given the sensitivity of current ctDNA detection methodologies, it is likely that these findings can be explained, at least in part, by differences in the shedding of ctDNA into the circulation from MRD. Unfortunately, little is known about the physical and biological mechanisms responsible for the shedding or release of DNA from tumour cells into circulation. This is contributed by our lack of good in vitro platforms capable of modelling MRD and the transport of shed molecules into the general circulation. Here we aim to study the molecular dynamics and the biology behind tumours' ability to shed mutant DNA fragments in the circulation using microfluidic models of vascularised tumour organoids. We will integrate molecular data gathered on primary colon cancer tissues from ctDNApositive and ctDNAnegative cases with results on ctDNA fragmentation obtained from patients and pre-clinical models to characterise origins and kinetic of ctDNA. We will compare activation of pathways involved in apoptosis, necrosis, active release, phagocytosis, exocytose and ETosis observed in tissues with doubling time, proliferation index, apoptosis, caspase-activated DNase and lysosomal DNase II in Patient-Derived Organoids (PDOs) from ctDNApositive and ctDNAnegative patients. Building on our expertise in angio-organoid co-cultures we will model organoid vascularisation ex vivo in co-cultures of PDOs and vascular endothelial cells using organ-on-a-chip technologies. Using PDOs from ctDNApositive and ctDNAnegative patients we will compare vasculature formation ability and gene-expression changes induced in endothelial cells by PDOs and compare them with molecular signatures observed in patients. The extent of vascularisation and fluid flow through vessels will be varied in these systems to determine how these physical factors influence the transport of ctDNA from MRD models to the vasculature. We envision that our project will generate a framework to understand and model ctDNA shedding in colon cancer and will eventually result in improved detection and treatment of early(er) cancers.

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Clinical Specialities: Medical Oncology, Surgery