Instituto de Medicina Molecular João Lobo Antunes

Master Project Proposal

Title: Onco-immuno-microbial profiling of the breast tumour microenvironment for therapeutic targeting

Synopsis:

Breast cancer (BC) is the most commonly diagnosed cancer type and the leading cause of cancer-related death in women worldwide. The tumour microenvironment (TME) is now recognized as an active player in cancer progression and response to treatments. A multi-dimensional network of non-malignant cells populate the TME, including fibroblasts, adipose and immune cells, namely T cells and macrophages. Evidence suggests that immune cells (ICs) play an ambiguous role in regulating both protumour and antitumor immune responses in BC. Strikingly, a pan-cancer study found that BC has a particularly rich and diverse microbiome compared to other cancer types [1]. This suggests that intra-tumoural bacteria exist, are active, and more provocatively that they may play key roles in cancer pathogenesis and response to therapy. Indeed, some of these tumour-associated bacteria can activate immune responses against tumours, while others produce enzymes able to hamper chemotherapy, helping cancer cells escape from the immune system [2]. Nevertheless, the complex interaction between microbiota, the immune system and malignant cells is still poorly described, as are the mechanisms by which they modulate immunity and therapy response. Thus, a more comprehensive understanding of these mechanisms will be a step forward to discover novel targets in BC treatment and prevention. We hypothesize that the microbiome interacting with tumour cells as well as the host's immune system may be a key determinant *in situ*, constituting an independent component of the TME.

We therefore propose a computational biology MSc project aimed at deciphering new rules illustrating the interaction between BC cells and their TME components, namely ICs and tumour-associated microbiota, as they have been found to independently act on tumour progression, response to therapy, and patient survival. The student will, for instance, mine and analyse publicly available and clinically annotated BC whole-genome and RNA sequencing datasets and participate in the development of a computational framework to characterise the tumour-associated microbiota. Using dimensionality reduction combined with machine learning methods, novel associations between specific bacteria species, immune silent or active TME, and unfavourable or favourable clinical outcome in the various BC subtypes will be uncovered. By dissecting the crosstalk between those different layers, this project will unravel novel molecular signatures of BC progression and provide novel insights with implications for BC prognosis and personalized therapy.

This project will be integrated in the iMM-Laço Hub initiatives and benefit from the collaborative and interdisciplinary environment of iMM and host teams. Observations from computational analyses of omics data will be subsequently validated in diagnostic biopsies and surgical samples from an independent local cohort of BC patients. Moreover, this project will trigger hypotheses about the tripartite onco-immuno-microbial crosstalk in BC that will be functionally tested *in vitro* and *in vivo*.

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Bibliography:

[1] Nejman, D. *et al.* The human tumor microbiome is composed of tumor type-specific intracellular bacteria. *Science* **368,** 973–980 (2020).

[2] Geller, L. T. *et al.* Potential role of intratumor bacteria in mediating tumor resistance to the chemotherapeutic drug gemcitabine. *Science* **1160,** 1156–1160 (2017).