Instituto de Medicina Molecular João Lobo Antunes

Master Project Proposal

Title: Crosstalk between RANK signalling and expression of hormone receptors in breast cancer

Synopsis:

The receptor activator of the nuclear factor-κB ligand (RANKL)/RANK signaling pathway was identified in the late 1990s and is the key mediator of bone remodeling. Targeting RANKL with the antibody denosumab is part of the standard of care for bone loss diseases, including bone metastases. Over the last decade, evidence has implicated RANKL/RANK pathway in hormone and HER2-driven breast carcinogenesis and in the acquisition of molecular and phenotypic traits associated with breast cancer (BCa) aggressiveness and poor prognosis. This marked a new era in the research of the therapeutic use of RANKL inhibition in BCa. Previous work from the Lab implies RANK signalling in the modulation of hormone receptors in breast cancer, which may have an impact in the efficacy of hormone therapy. We also have extensive data supporting that pharmacological inhibition of RANK pathway may overcome RANK-mediated resistance to therapy (Gomes et al. 2023, in revision). The purpose of the project to be developed by the Master student is to evaluate the expression of hormone receptors - estrogen, progesterone and androgen receptors -, in cell lines with or without functional RANK protein expression. RANK pathway will be inactivated by point mutation, KO and/or pharmacological approaches; and the expression of RANK, hormone receptors, and downstream mediators assessed by RT-qPCR, Western blot, immunocytochemistry and/or flow cytometry, as appropriate. The student will derive hormone therapy-resistant cell lines, and RANK pathway status will be quantified as described above. Sensitivity to hormone-receptors' targeted therapies, with or without RANK pathway inhibition, will be assessed by Alamar bluer and clonogenic assay. If in vitro data substantiates the use of hormone therapy plus RANK pathway inhibition to treat hormone therapyresistant BCa, efficacy will be tested in vivo, using xenograft models.

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