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Unraveling mechanism(s) of interaction between tumor cells and microenvironment components relevant for triple negative breast cancer progression

Triple negative breast cancer (TNBC) is a major focus of BC research due to the lack of targeted therapies and the high rate of relapse. This has led to the discovery that TNBC, which has a higher degree of stromal and intratumoral tumor-infiltrating lymphocytes among BC subtypes, is more likely to respond to immunotherapy than other types of BC, but its response rates remain low. Thus, novel strategies to reduce local immunosuppression and implement the response to immunotherapy are needed.

Adipocytes are the main stromal cells in the breast and nowadays there is growing evidence that they can be modified by tumor cells, becoming cancer associated adipocytes (CAAs) and supporting tumor progression. Our recent observations revealed the ability of CAAs to recruit neutrophils and an enrichment of immunosuppresive cells (Treg and MDSC) were found associated with CAAs. A specific tumor-associated microbiota has been also identified in the mammary tumor microenvironment and in a TNBC preclinical model we recently observed the presence of bacteria with high inflammatory activity that were associated with an increased level of Tregs.

We hypothesize that tumor-modified adipocytes and a microbiota shaped by cancer during its progression partecipate in inducing an immunosuppressive microenvironment by the release of metabolic and inflammatory mediators. This effect may represent a novel undescribed mechanism of resistance to T-cell-based cancer immunotherapies.

The project aims to elucidate the intricate and yet unexplored relationship between CAAs, mammary tumor-associated microbiota and tumor-infiltrating suppressive immune cells and to prove that strategies that interfere in their crosstalk are fundamental to improve the efficacy of immunotherapies currently explored in clinical practice.