Three-dimensional models for the study of breast cancer metabolism

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Keywords: breast cancer, metabolism, three-dimensional models.

Breast cancer is the first cause of cancer-related death in women. It is characterized by a high degree of heterogeneity, though a tailored approach is needed to obtain better responses to treatments. In particular, triple negative breast cancer is the most aggressive among mammary carcinoma subtypes, due to the lack of a targeted therapy (contrarily to more common ER/PR and HER2-positive subtypes) and the frequent development of metastasis and relapses.

Metabolic reprogramming is one of the main hallmarks of cancer: cancer cells remodel the metabolic network to maintain their transformed state and survive in the tumor microenvironment. The study of tumor metabolic phenotype can help to describe the diversity of breast cancer by leading to the development of novel precision medicine approaches. However, considering the complexity of this heterogeneous pathology, the main challenge is to build up a reproducible and easy to handle *in vitro* model that can recapitulate the architectural structure of carcinoma. For this purpose, three-dimensional models, such as spheroids from breast adenocarcinoma cell lines and organoids from patient derived xenografts, have been developed to perform a better analysis of breast cancer metabolism. Spheroids have been generated from three immortalized cell lines: SUM159PT and MDAMB231, derived from triple-negative tumor breast tissue, and MCF7 derived from estrogen receptor-positive breast cancer.

The first part of this project aims to set up optimized protocols for the development of organoids and spheroids, using confocal microscopy to characterize the three-dimensional structure. The second part aims to evaluate metabolic features of tumor cell lines using Seahorse technology, able to deliver a real-time measure of bioenergetics variations of live cells, and to asses mitochondrial function by flow cytometry.

Among the different culture methods tested, the drip-culture technique (growth on a thin layer of Matrigel) has proved to be the most effective method for organoids maintenance and proliferation, while the not treated plates for adherent cell culture provided the most stable and healthy spheroids.
A different metabolic profile for the three breast cancer cell lines emerged from the Seahorse and flow cytometry analysis: triple-negative breast cancer cell lines - SUM159PT and MDAMB231 - presented a typical glycolytic phenotype with a decreased mitochondrial respiration and activity, while MCF7 cell line showed a more aerobic metabolism.

The study of spheroid metabolism, as well as the evaluation of stem cell traits such as chemoresistance, could be useful to provide information for the discovery of novel targeted therapies for triple negative breast cancer.