Three-dimensional models for the study of breast cancer metabolism

Pasquale V.[1,2]*, Campioni G.[1,2]*, Ducci G.[1,2], Savore A.[1,2], Sacco E.[1,2] and Vanoni M.[1,2]
E-mail: valentina.pasquale@unimib.it
[1] Department of Biotechnology and Bioscience, University of Milano-Bicocca, Milan 20126, Italy
[2] SYSBIO, Centre of Systems Biology, Milan 20126, Italy
* VP and GC equally contributed to this manuscript.

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Abstract: Breast cancer (BC) is the first cause of cancer-related death in women. It presents a high degree of heterogeneity, though a tailored approach is required to improve therapy response. Triple negative breast cancer (TNBC) 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 high rate 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. Understanding of metabolic phenotype could unravel the diversity of BC, but a reliable model is needed. We developed three-dimensional models, spheroids from breast carcinoma cell lines and organoids from patient derived xenografts, to perform a better analysis of BC metabolism. Spheroids have been generated from three immortalized cell lines: SUM159PT and MDAMB231, (TNBC), and MCF7 (estrogen receptor-positive BC).
Firstly, we set up optimized protocols for the development of organoids and spheroids, using confocal microscopy to characterize the three-dimensional structure; 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. Then, we evaluated metabolic features of cell lines using Seahorse technology, able to deliver a real-time measure of bioenergetics variations of live cells, and flow cytometry to assess mitochondrial function. A different metabolic profile for the three BC cell lines emerged: TNBC cell lines 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 TNBC.
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