Glucose and glutamine play different roles in 2D and 3D breast cancer models

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Abstract: Metabolic rewiring is a complex and dynamic hallmark of cancer, and its comprehension can be exploited for targeted therapeutic interventions. Breast cancer (BC) represents the most frequent and deadly tumor in women and, although the development of targeted therapies for the most common subtypes have improved patients' survival, relapses and therapeutic failures often occur [1]. *In vitro* bi-dimensional (2D) cultures present some limitation in fully mimicking the tumor *milieu*, while in vitro three-dimensional (3D) cultures, such as cell line-derived spheroids, are believed to better recapitulate the tumor architecture, representing more valid models of cancer disease [2]. In our study, we have developed 3D cultures (spheroids) of three breast cancer cell lines (MCF7 – luminal subtype, MDA-MB-231 and SUM155PT – triple negative subtype) and compared their metabolic profile with the 2D cultures by mean of Seahorse technology [3]. The basal metabolic profile of 3D models undergoes a shift compared to 2D models, but the direction of this change is not the same for the three cell lines: MCF7 become more glycolytic, while the MDA-MB-231 and SUM155PT cell lines become metabolically less active. Then, we evaluated the effect of metabolic perturbation, i.e., nutritional deprivation and pharmacological treatments, on 2D cell proliferation and on the process of spheroid formation by mean of a high throughput imaging system, Operetta CLS. We observed that 2D cultures proliferation is more affected by glutamine deprivation, while the spheroid formation is stronger inhibited by glucose metabolism perturbation. In future we prospect to expand our studies developing 3D heterotypic models of the main BC subtypes by co-culturing BC cell lines with normal human mammary fibroblasts, in order to identify specific metabolic interactions occurring in these models of the tumor microenvironment to be exploited for therapeutic scopes.

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