Development of computational and *in vitro* breast cancer models in a nutrient-dependent context to simulate the tumor microenvironment

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Abstract:
Tumors exhibit high metabolic plasticity that depends on cancer cells features (i.e. metabolic phenotype, genetic characteristics) and their position within the tumor mass, which affects access to oxygen and nutrients. Consequently, the tumor microenvironment (TME) plays a pivotal role in shaping tumor progression [1]. Tumor growth scenarios can be simulated experimentally and computationally to gather complementary insights for understanding the biological mechanisms of interest and making predictions. Our work consists in the development of experimental and computational 2D and 3D tumor cell models in which a nutrient gradient is maintained to simulate a specific accessibility to nutrients and investigate the response of cells to these conditions. The experimental models designed for this project foresee the co-culture of breast tumor cell lines with different metabolic phenotypes (MDA-MB-231, glycolytic, and MCF7, oxidative [2]) and normal human mammary fibroblasts. In the 2D model specific microfluidic plates are used, in which a gradient of nutrients can be generated around the cell growth chamber: obtainable results concern the speed of cell migration (induced by the nutrient gradient) and growth rate, as well as bulk omics data. For the 3D cellular models, we will develop heterotypic spheroids, in which the formation of a nutrient gradients between the outermost and innermost cell layers is physiological. Also in this case, analyses on the energetic metabolism of cells through transcriptomics, metabolomics, IBEX method and two-photon microscopy can be performed. The computational model will be used in a complementary manner to the experimental models, allowing the simulation of growth conditions and metabolites exchanges between cells and the TME, aiming to make predictions on cancer cells survival and proliferation, that will be validated in both 2D and 3D systems [3]. We will use a Python code based on Cellular Potts Model and Flux Balance Analysis. In this model, metabolic parameters of the cell types involved, the growth medium with nutrients, the metabolites produced, the adhesion and movement of the cells can be set. Moreover, inputs of transcriptomic and metabolomic data can be adapted to predict the behavior of the cells in any desired growth environment. This kind of approach that integrates experimental and computational models will allow us to deepen our understanding of the interactions between tumor cells and the TME.

[1]: Parri, M. et al., 2020, DOI 10.1016/j.copbio.2020.03.001
[2]: Campioni, G. et al., DOI 10.3390/cells11050866
[3]: Maspero, D. et al., DOI 10.3233/FI-2020-1883