Metabolic and physiological rearrangements in bladder cancer cells transitioning from adherent to spheroid cultures

Ducci G.[1,2], Pasquale V.[1,2], Campioni G.[1,2], Servidio F.[1], Gigliotti G.[1], Bonanomi M.[1,3], Ciufolini G.[4], Petrella G.[4], Galuzzi B.[1,2], Piazza R.[1], Cicero D.[4], Gaglio D.[1,3], Damiani C.[1,2], Elena S.[1,2], Vanoni M.[1,2]

Email: g.ducci@campus.unimib.it
[1] Department of Biotechnology and Biosciences, University of Milano-Bicocca, Milan, Italy
[2] Sysbio-ISBE-it, Europe, Milan, Italy
[3] Institute of Molecular Bioimaging and Physiology, National Research Vouncil, Segrate, Milan, Italy
[4] Department of Chemical Science and Technologies, University of Roma "Tor Vergata", Rome, Italy

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Abstract:
Bladder cancer is one of the most common malignancies worldwide. Therefore, identifying new markers contributing to patients' stratification is crucial to direct them to more effective and less toxic targeted treatments, improve prognosis, and avoid relapses[1]. Energy metabolism reprogramming is an established cancer hallmark, and altered metabolic pathways can represent attractive clinical targets exploitable in new therapeutic strategies[2].
Here we use 3D cultures (spheroids), that better simulate the architectural complexity of a tumor mass in vivo, to characterize the metabolic and physiological rearrangements induced by spheroid formation in a panel of six bladder cancer cell lines at different stages and grades. Using a systems metabolomic approach, integrating omics analyses, and morpho-functional assays (including analysis of metabolic fluxes by Seahorse technology[3]) with mathematical models of metabolism[4], we show that 3D growth induces a profound stage- and grade-independent gene expression rearrangement indicative of a proliferative rate decrease, differentiation, EMT transition, and alteration of sensing processes. These changes correlate with a significant downregulation of folate metabolism, biosynthesis of purines and pyrimidines, serine and glycine metabolism, and alteration of the tricarboxylic acid cycle. However, cell line- and stage-specific differences accompany the transition from 2D to 3D: notably, in two cell lines, glycolysis is down-regulated in spheroids compared to adherent-growing cells. A mathematical model of metabolism integrates different omics data[5] highlighting the possible regulatory layers controlling metabolic rewiring in spheroids, with the final aim to contribute to the identification of novel clinical targets for precision medicine[6].

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