Extended Abstract Journal of Molecular and Cellular Biochemistry 2021
Vol.5 No.1

Metabolomics, transcriptomics and functional glycomics reveal bladder cancer cells plasticity and enhanced aggressiveness facing hypoxia and glucose deprivation

Andreia Peixoto
University of Porto, Portugal

Abstract

Bladder cancer constitutes one of the deadliest genitourinary diseases, especially when diagnosed at late stages.These tumours harbour micro environmental niches characterized by low levels of oxygen (hypoxia) and limited glucose supply due to poor vascularization. However, the synergic contribution of these features to disease development is poorly understood. Here, we demonstrated that cells with distinct histopathological and molecular backgrounds responded similarly to such stimuli. Cancer cells arrested proliferation, significantly increased invasive capacity in vitro and enhanced tolerance to cisplatin-based chemotherapy. Reoxygenation and access to glucose restored basal proliferation and invasion levels without triggering stress-induced apoptosis, denoting significant cellular plasticity in adapting to microenvironmental cues. Whole transcriptomics showed major molecular reprogramming, supporting main functional alterations. Metabolomics evidenced fatty acids β-oxidation as main bioenergetic pathway rather than anaerobic glycolysis generally adopted by hypoxic cells. Joint pathway analysis also suggested relevant alterations in mucin-type O-glycan biosynthesis. Glycomics confirmed a major antagonization of O-glycosylation pathways, leading to simple cell glycophenotypes characterized by the accumulation of immature short-chain O-glycans such as Tn and STn antigens at the cell surface. Glycoengineered models reflecting simple cell glycophenotypes were developed and functional studies in vitro and in vivo showed that Tn and STn overexpression decreased proliferation and promoted chemoresistance, reinforcing their close link with tumour aggressiveness. Collectively, we have demonstrated that hypoxia and glucose deprivation trigger more aggressive cell behaviours, in what appears to be an escape mechanism from microenvironmental stress. We propose that, altered glycosylation may be used to target these subpopulations, paving the way for precision oncology.

This work is partly presented at 11th world Glycobiology Congress on May 17-18, 2021, Webinar

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