HBP activation as a metabolic sensor during epithelial to mesenchymal transition

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Oncogenic transformation is usually accompanied by changes in cell glycophenotype. The reprogramming of metabolic pathways is an important hallmark of the physiological changes in cancer and recent evidence suggests that tumor cells redirect glucose flux through the hexosamine biosynthesis pathway (HBP). Most cancers arise from epithelia, which is believed to undergo differentiation to mesenchymal phenotype, a process termed epithelial-mesenchymal transition (EMT), a key step to metastasis. The purpose of this work is to study the importance of the HBP in tumor cells undergoing EMT. The glycoconjugates present on the surface of A549 cells treated or not with TGF-β were compared using specific lectins to oligosaccharides commonly found in mammalian cells. The aberrant glycosylation is an universal feature of tumor cells and the lectins have been applied as a tool for detecting abnormalities in the carbohydrate units of many types of cancer involved in malignant transformation, differentiation of tumor cells, adhesion and metastasis. We observed that TGF-β treatment of A549 cells induces an increase an increase of glycoconjugates decorated with α2-6Neu5Ac with concomitant increase of N-glycans wherein the N- acetylglucosamine linked to the protein core is decorated with α1-3- or α 1-6fucose and the α-mannose of the saccharide core was branched with β1-6 N-acetylglucosamine, generating a triantennary N-glycans. N-linked structures containing mannose residues and poly-N-acetyl-lactosamine were also increased. There is also a 2-fold increase in intracellular glycosylation (O-GlcNAc). The GFAT activity, the rate limiting enzyme of the HBP, was increased about 30 % after 24 h and 48 h of TGF-β treatment. However, a 3 fold and 5-fold increase of GFAT protein levels were detected after 24h and 48h respectively. These results confirm our hypothesis that the glucose flux through HBP is increased during the EMT, which reflects in glycophenotype changes with possible effects on the phenotype of malignancy.

Palavra chave: HBP, EMT, O-GlcNAc

Patrocínio: FAPERJ, CNPq and CAPES