40P Regulation of glucose transporters by protein kinases in cancer cells

A.A. Henriques, P. Matos, P. Jordan

Human Genetics Department, Instituto Nacional de Saúde Doutor Ricardo Jorge, Lisbon, Portugal

Background: Cancer cells require increased glucose supply to sustain proliferation. One mechanism involves increased expression of glucose transporter (GLUT) genes. But insulin has revealed that protein phosphorylation is another key mechanism in glucose uptake regulation: insulin binding to responsive cells triggers a signalling cascade with phosphorylation of TBC1D4, a negative regulator of endosomal GLUT trafficking,

so that more transporters are inserted into the plasma membrane. Previous work from the host lab has identified the family of WNK protein kinases and shown that WNK1 can also phosphorylate TBC1D4 and promote GLUT translocation to the cell surface. Our objective is to understand the contribution of WNK1 to glucose uptake in colorectal cancer cells. Our objective is to understand the contribution of WNK1 to glucose uptake in colorectal cancer cells.

Methods: To characterize the role of WNK1, various colorectal cell lines were first cultivated with different glucose concentrations. Levels of GLUT1 at the cell surface were compared under these conditions and the effect of depleting WNK1 expression by siRNA determined.

Results: For selected conditions, key cell cycle or apoptotic marker proteins were analysed by Western blot and revealed higher apoptotic and cell-cycle arrest phenotypes in WNK1-depleted cells cultured in low glucose medium. In order to dissect key phosphorylation events involved in GLUT1 regulation, mass spectrometry analysis revealed that WNK1 phosphorylates TBC1D4 and the functionally related TBC1D1 at unique Serine residues. The corresponding phospho-mimetic mutants are currently being tested for their ability to increase GLUT1 translocation.

Conclusions: Together, these studies will elucidate the molecular details regulating the translocation of glucose transporters in cancer cells and have the potential to identify novel therapeutic targets.

Legal entity responsible for the study: Peter Jordan

Funding: Fundação para a Ciência e Tecnologia BioISI - Biosystems and Integrative Sciences Institute

Disclosure: All authors have declared no conflicts of interest.