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OXYGEN-SENSITIVE INTERACTIONS BETWEEN GLYCOLYTIC ENZYMES AND A CANCER-TESTIS ANTIGEN ESTABLISHED SIGNALLING SCAFFOLD ARE REGULATED BY LYSINE ACETYLATION

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Reactivation of the male gametogenic expression program is tightly associated with the most malignant and metastasis-prone tumours and the emergence of aggressive sub clones of tumour cells, which are highly resistant to stress-induced apoptosis. While the cancer-testis antigens (CTAs) CABYR and AKAP3/4 roles during gamatogenesis and their importance for flagellar movement have gradually emerged, their function in cancer cells have remained obscure. In this study, we combine immunoprecipitation (IP), mass spectrometry (MS) and Western blot (WB) analysis to unravel their functional roles in therapy resistant lung and ovary adenocarcinoma cells by identifying their interaction partners. CABYR variants were shown to oligomerize and interact with AKAP proteins to generate a HMW signal scaffold structure, which was found to bind several glycolytic enzymes and signal transducers. Forward and reverse IP experiments followed by WB confirmed interactions between CABYR and LDH, ALDO, PFK, TPI-1, GAPDH, ENO-1 and GSK3b. Transistion from normoxic to hypoxic growth conditions disrupted the associations between glycolytic enzymes and the CABYR-AKAP signaling scaffold in the cancer cells, leading to a 3.2-fold increase in their production and secretion of lactic acid. Hypoxic growth conditions resulted in increased acetylation of lysine residues in both CTAs, and triggered deacetylation of lysines in LDH and aldolase. Treatment with resveratrol prevented hypoxia-induced dissociations, suggesting that the regulation of oxygen-sensitive protein interactions within the CABYR-AKAP-glycolysome complex involve changes in the acetylation of lysines in the engaged proteins. MS analysis of IPs finally revealed interactions between CABYR and proteins associated with the cancer cells contractile cytoskeleton. Based on these findings, it is tempting to speculate that hypoxia-induced release and subsequent local activation of glycolysomes from cytoskeleton-associated CABYR-AKAP scaffold structures might be instrumental for cancer cells ability to maintain a steady energy supply to their contractile cytoskeleton and thereby sustain their migratory and invasive capability despite encountering severe reductions in environmental oxygen levels.

Biography

Soren Naaby Hansen has graduated as MD from Copenhagen University in 1991. Following Residential Training, he went on to train as a Postdoctoral Fellow at the Department of Cell Biology, University of Virginia (1993), where he later became Group Leader in Proteomics. In 1999, he became Assistant Member and Head of Biochemical Proteomics, Ludwig Institute for Cancer Research, Royal Free and University College London Medical School, UK. He became Lecturer in Biochemistry and Molecular Biology, University College London, in 2000. In 2006, he returned to Denmark where he was appointed as Senior Scientist at the Department of Clinical Immunology, Aarhus University Hospital, Aalborg. He completed a Doctorate in Medical Sciences at Aarhus University in 2012, and is currently employed at the Department of Psychiatry, Aalborg University Hospital, where he directs a study of the pathophysiology underlying depression disorders.

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