Title: The role of 5' adenosine monophosphate-activated protein kinase in the chemo-sensitivity and metabolic behaviour of breast cancer cells exposed to hypoxia and hyperglycaemia.

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Abstract

Background: 5' adenosine monophosphate-activated protein kinase (AMPK) is a key enzyme for maintaining energy homeostasis in the cell and is associated with many downstream targets of metabolic processes such as mTORC1, p53 and fatty acid synthase (FASN) and insulin-like growth factor binding protein-2 (IGFBP-2).

Aim: To investigate the interactions between AMPK, FASN and IGFBP-2 and how the activity of AMPK affects the metabolism and response of breast cancer cells to chemotherapy with changes in oxygenation and under different glucose concentrations.

Methods: MCF-7 breast cancer cells were exposed to different glucose levels (5mM and 25mM) in the presence or absence of doxorubicin under normoxic and hypoxic conditions with and without AMPK silenced using siRNA. Changes in protein abundance were monitored using Western Immunoblotting. Cell death was measured by the Muse® Cell Analyser using a count and viability assay. Hypoxia was chemically induced using cobalt chloride or with low levels of oxygen (2%). Lactate and citrate levels were measured using commercially available kits.

Results: With normoxia, AMPK activity was higher in normal compared with high levels of glucose. Under hypoxic conditions AMPK phosphorylation remained high in 5mM glucose with levels in 25 mM glucose being equivalent. Upregulation of AMPK in normoxic and hypoxic conditions was associated with a reduction in FASN and IGFBP-2 and a better response to chemotherapy. In normoxic conditions in high, compared with lower glucose conditions the cells increased their production of lactate and reduced that of citrate. Silencing AMPK under normoxic conditions or inducing hypoxia promoted a more glycogenic phenotype. However, silencing AMPK under hypoxic conditions reduced levels of lactate comparable to normoxic levels. The citrate profile was unaffected by silencing AMPK or altering levels of oxygen.

Conclusions: AMPK plays an important role in regulating metabolic signalling and this alters the sensitivity of breast cancer cells to chemotherapy.

Biography

Dr. Al-Qahtani received her Ph.D. in Medical Oncology from Bristol University where she later worked in collaboration with Southmead Hospital on various breast cancer projects. She currently works as a Clinical Researcher at King Fahd Medical City in Riyadh, Saudi Arabia. Dr. Al-Qahtani has published many scientific articles and conference papers, and became a scientific reviewer for the journal, *Oncotarget*. She also received many different awards including RED, PLuS and Colston Society Research Awards.

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Session name/ number: Cancer Cell Biology

Category: Oral presentation