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Cortisol upregulated the expression of iNOS, a marker previously suggested as an indicator of poor survival in breast cancer.³ Induction of chronic stress in a syngeneic mouse model of breast cancer had no effect on the growth of the primary tumour; however, inhibition of NOS in stressed mice significantly decreased tumour volume compared to stress alone. A significant increase in tumour microvasculature was observed in the primary tumours, as there was an increase in metastatic sites per mouse in stressed mice, compared to the control. This was also reversed through the inhibition of NOS.

This study indicated that stress may impact tumourigenic progression through the induction of DNA damage, mediated by the release of NO. Inhibition of NOS was able to negate the effects of stress on tumour growth and metastasis, providing an insight into the potential benefits of NOS inhibitors in breast cancer treatment. However, presentation of this research at the ESMO congress raised some potential implications of inhibition of NO signalling. Primarily, these included the effects of NOS inhibition on haemodynamics, because L-NAME has been used previously in a clinical setting to increase blood pressure. In future studies, this limitation could be resolved through cotreatment with antihypertensives, as was the case in a previous study that demonstrated the growth inhibitory effects of iNOS inhibition in breast cancer.⁴

Discussion also focussed on the effects of glucocorticoid signalling in the immune system, since previous research has demonstrated that

stress can adversely affect the immune response in breast cancer models, and in patients.^{5,6} Furthermore, an increase in the expression of the GR has been observed to correlate with poor prognosis in oestrogen receptor-negative breast cancer patients, indicating that glucocorticoid-mediated signalling can influence cancer progression.⁷ As such, current trials using novel GR inhibitors in breast cancer patients are underway. Future perspectives for this work would seek to use pharmacological therapeutics, including using selective GR inhibitors in combination with NOS inhibitors, in highly stressed patients with breast cancer.

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REGULATION OF GLUCOSE TRANSPORTERS BY PROTEIN KINASES IN CANCER CELLS

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Reprogramming of energy metabolism is one of the hallmarks of cancer, since tumour cells need to fuel their high proliferation rates.¹ Warburg et al.² first observed that cancer cells largely limit their method of energy production to glycolysis only. In order to compensate for lower ATP yields, cancer cells often upregulate expression of glucose transporters, typically GLUT1, which substantially increases extracellular glucose import into the cytoplasm.³

In normal physiology, insulin-responsive cells rapidly increase their glucose uptake 10-20-fold by translocating glucose transporter vesicles (specifically GLUT4) from intracellular storage

compartments to the plasma membrane. In adipocytes, insulin activates the protein kinase AKT to phosphorylate the Rab GTPase activating protein, TBC1D4. This protein normally maintains Rab GTPases in their inactive state so that storage vesicles containing the glucose transporter remain cytoplasmic. Upon phosphorylation, TBC1D4 becomes inactive, allowing the translocation of GLUT vesicles so that more transporters are inserted into the plasma membrane.⁴ In muscle cells, the highly homologous Rab-GTPase activating protein TBC1D1 is predominantly expressed but also becomes phosphorylated by AKT in response to insulin.

Previous work from our laboratory described that the protein kinase WNK1 also participates in the regulation of TBC1D4. WNK1 forms a protein complex with TBC1D4 in human embryonic kidney (HEK293) cells and phosphorylates it *in vitro*.

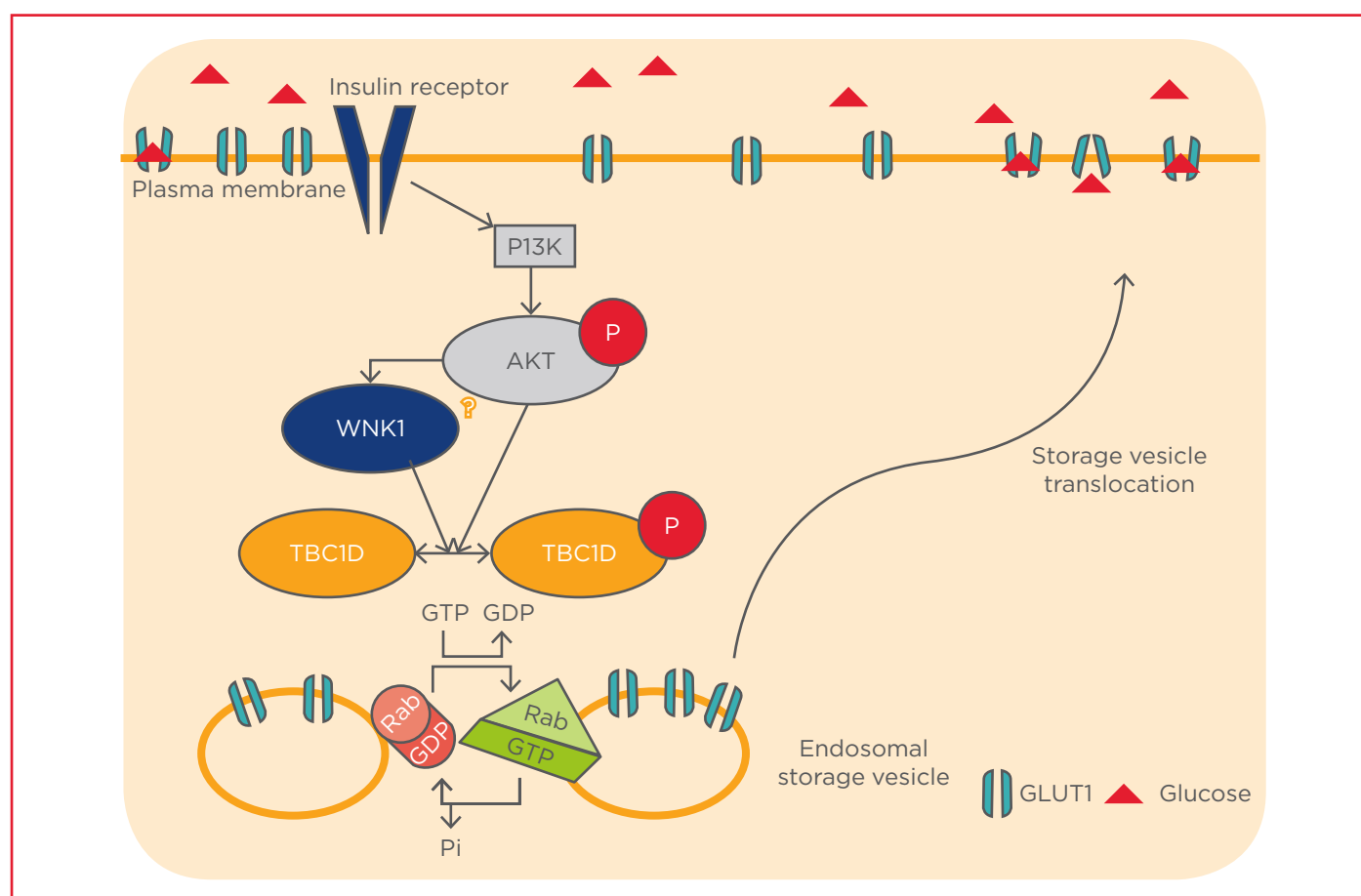


Figure 1: The regulation of cell surface expression of GLUT1.

GLUT1: glucose transporter 1; PI3K: phosphoinositide 3-kinase.

Phosphorylation by WNK1 was found to increase the binding of TBC1D4 to regulatory 14-3-3 proteins and to reduce its interaction with the exocytic small GTPase, Rab8A. This novel pathway regulates the cell surface expression of GLUT1 (Figure 1).⁵

The subfamily of WNK protein kinases belongs to the superfamily of 518 human protein kinase genes.^{6,7} WNK1 and WNK4 were shown to regulate the cell surface expression and activity of a variety of renal ion channels.⁷ The finding that WNK1 regulated GLUT1 showed, for the first time, that it is also involved in the cell surface expression of other plasma membrane transport proteins.⁵ Besides the catalytic domain, WNK1 contains coiled-coil domains, which, together with the large size of the protein, suggests that WNK1 also has scaffolding functions and may be involved in multiple cellular signalling processes.⁶⁻⁸ Interestingly, AKT can phosphorylate WNK1 at residue Thr60.⁹

Our goal was to characterise the role of protein kinase WNK1 in the phosphorylation network that regulates cellular glucose uptake in cancer cells. WNK1 expression was depleted by small interfering RNA in various colorectal cancer cell lines and key cell cycle proteins were analysed by a western blot in the presence of different glucose concentrations. WNK1-depleted cells showed higher apoptotic and cell cycle arrest phenotypes when cultured in low glucose medium.

In order to determine how WNK1 regulates GLUT1 translocation, key phosphorylation events were identified by mass spectrometry analysis, which

revealed unique serine residues specifically phosphorylated by WNK1 in both TBC1D4 and the functionally related TBC1D1. The respective phosphomimetic mutants are currently being tested for their ability to modulate GLUT1 translocation. Together, these studies will contribute to an increased knowledge of the signalling pathways involved in the control of glucose uptake in cancer cells and will potentially allow the identification of novel therapeutic targets.

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