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2008





CRE Role

Molecular aspects of insulin resistance, cell signaling pathways and breast cancer in relation to obesity

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Introduction

Breast cancer is prevailing as the most diagnosed cancer in women. Obesity and its co-morbidities, including type-II diabetes, are increasing to epidemic proportions.

A pathological link between obesity, breast cancer risk and mortality has been established recently¹.

Insulin resistance is a pre-malignant indicator of type-II diabetes and closely linked with obesity. Its molecular implications result in chronically elevated circulating insulin plasma levels.

Here we examine the effect of high insulin levels on cell proliferation, activation of PI3-kinase and MAP-kinase cell signalling pathways in estrogen-receptor negative (ER-) breast cancer cells (MDA-MB-231) and on normal breast epithelial cells (MCF-10a).

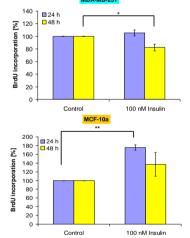
Objectives

- 1. To examine the effects of high insulin levels (100 nM) on cell proliferation in MDA-MB-231 and MCF-10a cells.
- To examine activation of PI3-kinase and MAP-kinase cell signalling pathways after insulin treatment
- To examine the role of PI3-kinase and MAPkinase cell signalling pathways in insulinmediated cell proliferation.

Pasults

Effects of high insulin levels on cell proliferation

BrdU-incorporation was used to measure DNA-synthesis after 24 and 48 h treatment with 100 nM insulin

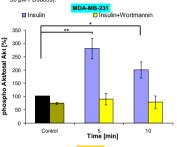


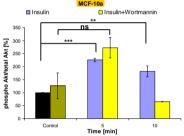
High insulin concentrations increased cell proliferation in normal breast epithelial cells, but not in ER- breast cancer cells.

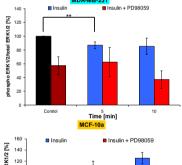
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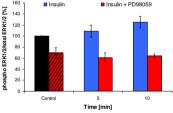
Effect of high insulin levels on activation of PI3kinase and MAP-kinase cell signalling pathways

ELISA kits were used to measure Akt and ERK1/2 phosphorylation after 5 and 10 min treatment with 100 nM insulin and with/without pre-treatment (100 nM wortmannin or $50\,\mu M$ PD98059).







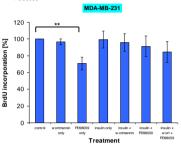


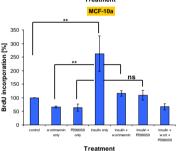
High insulin concentrations activated the Pl3-kinase, but not the MAP-kinase cell signalling pathway in ER-breast cancer cells and in normal breast epithelial cells

Paculte

Inhibition of cell signalling pathways and effects on cell proliferation after insulin stimulation

DNA-synthesis was measured during 24 h treatment with 100 nM insulin following cell signalling pathway inhibition by 1 h pre-treatment with 100 nM wortmannin and/or 50 µM PD98059





Inhibition of the MAP-kinase pathway reduced cell proliferation in ER- breast cancer cells. In normal breast epithelial cells, inhibition of MAP-kinase pathway reduced insulin-induced cell proliferation.

Conclusions

- Further preliminary results indicate an activation of MAP-kinase cell signalling pathway after 15 min of insulin treatment in MCF-10a cells (data not shown).
- Insulin may initiate carcinogenesis of breast epithelial cells by increasing cell proliferation (MCF-10a), rather than increasing cancer progression of existing tumours (MDA-MB-231).
- These effects may be mediated by insulin activating the MAP-kinase pathway.
- The MAP-kinase pathway may be a future target for breast cancer prevention in obese women.

References

 Calle, E.E., Rodriguez, C., Walker-Thurmond, K. and Thun, M.J. (2003) Overweight, obesity and mortality from cancer in a prospectively studied cohort of U.S. adults. N. Engl. J. Med., 348, 1625-1638.

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