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Akt Signaling and Coordinated Changes in the Distribution and Expression of Akt-Regulating Phosphatases

AKADEMISK AVHANDLING

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ABSTRACT

Cancer is one of the major causes of death worldwide. The PI3K/Akt signaling pathway is up-regulated in a variety of human cancers. Akt is an important signaling molecule in cellular survival pathways. Activated Akt (pAkt) is able to induce protein synthesis pathways, and is therefore a key protein involved in growth and prevention of apoptosis. Several lipid or protein phosphatases exist that inhibit Akt signaling. Nuclear localization of pAkt is crucial for its activity and function.

Previously, it was demonstrated that cholesterol-lowering and anti-carcinogenic drugs, statins, rapidly depleted nuclear pAkt. We focused on the mechanism behind this rapid nuclear pAkt depletion. In paper I our results showed that statins or extracellular ATP induced a complex and coordinated response in insulin-stimulated A549 cells leading to depletion of nuclear pAkt. This involved lipid/protein phosphatases PTEN, PHLPP1 and -2, PP2A and calcineurin. Purinergic P2X7 receptor was identified to be a mediator of this effect.

In study II, the rapid nuclear pAkt depletion was further investigated and the possible role of a PI3K subunit, p110 β , was elucidated. This subunit has been associated with aggressive prostate cancer, and studies on mouse embryonic fibroblast cells and cancer cells showed that p110 β is essential for nuclear pAkt depletion.

EHBP1 and P-Rex1 have been involved in protein transport and membrane recruitment of proteins, and both of these proteins have been associated with aggressive or invasive prostate cancer. In paper III we found that P2X7 correlated with aggressive prostate cancer and that P2X7-mediated rapid nuclear pAkt depletion is dependent of both EHBP1 and P-Rex1. Moreover, pharmacological concentrations of statins decreased nuclear pAkt in non-transformed prostatic cells, suggesting that the anticancer effect of statins might be mediated by inhibition of the Akt pathway.

In Paper IV we characterized crosstalk between PHLPPs and PTEN, two proteins that down-regulate Akt activity. This crosstalk was seen in cancer cells and TGF β -1-activated prostate stem cells, and had an impact on cellular invasiveness. The P2X4 receptor was identified to be a mediator of crosstalk induction. Downstream of P2X4 epigenetic and transcriptional factors were activated.

Overall, these studies show a novel mechanism leading to nuclear pAkt depletion. We also provide evidence for a role of P2X7-EHBP1-Akt axis in prostate cancer development and that inhibition of Akt may affect the invasive capacity of the cancer cells. A crosstalk between Akt phosphatases regulates Akt and affects invasiveness.