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Title: Role of insulin and IGF-1 receptors in bronchial epithelial cancer cells

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Body: Background: Inhalable insulin was developed in order to avoid daily injections in diabetes therapy. However, there are safety concerns as this route of application results in high local insulin concentrations which may trigger mitogenic effects via activation of the IGF-I receptor (IGF-1R). To find out whether this hypothesis is true, the present study aimed to explore the role of insulin receptor (IR) and IGF-1R and their downstream signaling in human bronchial epithelial cancer (HBEC) cell lines H292, H226 and H460. Methods: Cell proliferation was assessed by [^{3}H]thymidine incorporation. Activation of Extracellular signal-regulated kinases/ Mitogen-activated protein kinases (ERK/MAPK) was detected by phosphoprotein Western blot analysis. To knockdown (KD) receptors, cells were transduced with lentivirus encoding shRNAs (LV-sh-IR or LV-sh-IGF-1R). Results: Treatment of H292 cells with 10nM insulin and 10nM IGF-1 increased proliferation by 44±4% and 121±7%, respectively. Similar effects were seen in H226, whereas there was no response in H460 cells. Correspondingly, insulin and IGF-1 increased the rate of phospho-ERK by ~50% in H292 and H226, but not in H460 cells. 4 days after transduction of H292 with LV-sh-IR (KD ~70%) a decrease of cell viability by 92% and a reduction of basal phospho-ERK by 40% was observed. In contrast, transduction with LV-sh-IGF-1R (KD ~50%) induced a mesenchymal phenotype, associated with a 3 fold up-regulation of N-cadherin and fibronectin mRNA expression. Conclusion: In HBEC cells insulin and IGF-1 activate MAPK and increase proliferation in a tumour specific manner. Functional IRs appear to be crucial for survival, whereas IGF-1Rs seem to suppress mesenchymal characteristics.