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Activation of human insulin receptors is regulated by G protein-coupled receptor signaling and neuraminidase-1 sialidase

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G protein-coupled receptors (GPCR) can participate in a number of signaling pathways, and this property led to the concept of biased GPCR agonism. Agonists, antagonists and allosteric modulators can bind to GPCRs in different ways, creating unique conformations that differentially modulate signaling through one or more G proteins. A unique neuromedin B (NMBR) GPCR-signaling platform controlling mammalian neuraminidase-1 (Neu1) and matrix metalloproteinase-9 (MMP9) crosstalk has been reported in the activation of the insulin receptor (IR) through the modification of the IR glycosylation. Here, we propose that there exists a biased GPCR agonism as small diffusible molecules in the activation of Neu1-mediated insulin receptor signaling. GPCR agonists bombesin, bradykinin, angiotensin I and angiotensin II significantly and dose-dependently induce Neu1 sialidase activity and IR activation in human IR-expressing rat hepatoma cell lines (HTC-IR), in the absence of insulin. Furthermore, the GPCR agonist-induced Neu1 sialidase activity could be specifically blocked by the NMBR inhibitor, BIM-23127. Protein expression analyses showed that these GPCR agonists significantly induced phosphorylation of IRβ and insulin receptor substrate-1 (IRS1). Among these, angiotensin II was the most potent GPCR agonist capable of promoting IRβ phosphorylation in HTC-IR cells. Interestingly, treatment with BIM-23127 and Neu1 inhibitor oseltamivir phosphate were able to block GPCR agonist-induced IR activation in HTC cells in vitro. Additionally, we found that angiotensin II receptor (type I) exists in a multimeric receptor complex with Neu1, IRβ and NMBR in naïve (unstimulated) and stimulated HTC- IR cells with insulin, bradykinin, angiotensin I and angiotensin II. This complex suggests a molecular link regulating the interaction and signaling mechanism between these molecules on the cell surface. These findings uncover a biased GPCR agonist-induced IR transactivation signaling axis, mediated by Neu1 sialidase and the modification of insulin receptor glycosylation.

Biography

Fiona Haxho has special interest and expertise in the glycosylation of human cancer cells, specifically the transient modifications in sialylation patterns of malignant cells. Her research has shown that the removal of terminal sialic acid residues from growth factor receptors on the surface of malignant cells, including insulin receptors and, epidermal growth factor receptors among others, is highly regulated by and dependent on perquisite G protein-coupled receptor signaling. Drug targeting of these protein complexes, particularly neuraminidase-1 and GPCR, has important implications for the development of novel molecular therapies in the treatment of human cancer.

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