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Biased G protein-coupled receptor agonism and mammalian neuraminidase 1-mediated glycosylated receptor signaling platform

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Overactivity of the renin-angiotensin system (RAS) involving angiotensin II (ANG II) produced from this system can induce insulin resistance. It has also been linked to the pathophysiology of type 2 diabetes mellitus, hypertension and cancer. ANG II binds to angiotensin receptors, AT1 and AT2, which belong to a class of G protein-coupled receptors (GPCR). The molecular mechanism of ANG II induced insulin resistance and other pathologies is unknown. We have reported a novel neuromedin B (NMBR) GPCR-signaling platform controlling mammalian neuraminidase-1 (Neu1) and matrix metalloproteinase-9 (MMP9) cross-talk in the activation of the insulin receptor (IR) through the modification of the IR glycosylation in human IR-expressing hepatoma (HTC) cells. This novel organizational signaling platform linked to glycosylated receptor tyrosine kinases (RTK) (e.g., EGFR, TrkA, insulin) and TOLL-like (TLR) receptors is identified to regulate receptor activation process, all of which are known to play major roles in pathologies. This signaling paradigm proposes that ligand binding to its receptor on the cell surface induces a conformational change of the receptor to initiate GPCR and matrix metalloproteinaser-9 (MMP-9) activation to induce Neu1. Activated Neu1 hydrolyzes α-2,3-sialyl residues linked to β-galactosides, which are distant from the ligand binding sites. These findings predict a prerequisite desialylation process by activated Neu1 enabling the removal of steric hindrance to receptor association. Here, we reasoned that there might exist a biased GPCR agonism as diffusible small molecules in the circulation involved in the activation of Neu1-mediated glycosylated receptor signaling platform contributing to type 2 diabetes mellitus, hypertension and cancer.

Biography

For the past 35 years Dr. Szewczuk is Full Professor of Immunology and Medicine, Queen's University, Kingston, Ontario Canada. He received his B.Sc. (Hon) in Chemistry (U. of Guelph), M.Sc. in Biochemistry (Guelph), PhD. in Immunochemistry (U. of Windsor) and post-doctoral training with Gregory W. Siskind, M.D. in cellular immunology at Cornell University Medical College, NYC. Dr. Szewczuk's recent research has focused on the role of glycosylation in receptor activation with a particular focus of TOLL-like, nerve growth factor Trk, EGFR and insulin receptors. He has discovered a novel receptor-signaling platform and its targeted translation in multistage tumorigenesis and engineered drug delivery systems.

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