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Novel Cancer Therapeutics: Glycosylation, GPCRAgonism, Insulin Receptor and Metabolic Syndrome

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Insulin signaling, as mediated through the insulin receptor (IR), plays a critical role in metabolism. Aberrations in this signaling cascade lead to several pathologies, the majority of which are classified under the umbrella term "metabolic syndrome". Although many of these pathologies are associated with insulin resistance, the exact mechanisms are not well understood. One area of current interest is the possibility of G-protein-coupled receptors (GPCRs) influencing or regulating IR signaling. This concept is particularly significant, because GPCRs have been shown to participate in crosstalk with the IR. More importantly, GPCR signaling has also been shown to preferentially regulate specific downstream signaling targets through GPCR agonist bias. This signaling 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. Although GPCR-IR cross-talk has previously been established, the notion that GPCRs can regulate the activation of the IR is particularly significant in relation to metabolic syndrome and other pathologies that develop as a result of alterations in IR signaling. As such, an overview of the physiological and pathophysiological roles of the IR within metabolic syndrome and its related pathologies will be presented. Furthermore, we propose that the GPCR-biased agonism may perhaps mediate some of the downstream signaling effects that further exacerbate these diseases for which the mechanisms are currently not well understood.

Biography:

Dr. Myron R Szewczuk is Full Professor of Immunology and Medicine for over 38 years, Queen's University, Kingston, Ontario Canada. Dr. Szewczuk's research has focused on the role of glycosylation in receptor activation with a particular focus of Toll-like, neurotrophin Trk, EGFR and insulin receptors. A novel receptor-signalling platform was discovered and its targeted translation in multistage tumorigenesis. He is now in the development of engineered drug delivery systems.