The potential of orphan G-protein coupled receptors as novel therapeutic targets

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Although G-protein coupled receptors (GPCRs) are the most successful drag targets, 30% of the FDA-approved drugs targeting GPCRs act on only 10% of the entire human GPCRome. In humans, around 160 receptors have unknown ligands and functions and therefore are termed orphan GPCRs. The expression of GPCRs in the pancreatic beta cells is critical in the regulation of glucose-stimulated insulin secretion (GSIS) therefore the characterization of novel metabolic pathways involving the functions of orphan GPCRs remains a key target in academia and the pharma industry for promoting novel therapeutic strategies for type-2-diabetes. Our previous work has demonstrated the existence of negative and positive metabolic loops that inhibit and enhance GSIS by involving two major metabolites, acetate and 20-hydroxyeicosatetraenoic acid (20-HETE) acting on the FFAR1, FFAR2, and FFAR3 (1-2) receptors, respectively. Next studies were focused on the role of orphan GPCRs that are expressed in both the pancreatic beta cells and neurons in the regulation of GSIS. GPR27 and GPR75 receptors are expressed in the pancreatic beta-cells and various neuronal populations. By employing a combination of reverse pharmacology, mouse genetics, and cell signaling techniques we demonstrated that GPR27 is an atypical receptor that can recognize a major metabolite and plays a significant role in the regulation of GSIS. In addition, GPR27 expressed in insulinoma cells has significant effects on cellular proliferation. GPR75 is also expressed in the pancreatic beta-cells. *In vivo* studies using a mouse model of *Gpr75* deficiency showed its implication in metabolism, particularly in regulating body weight.

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