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Talk Title: **Ciliary Control of Metabolic Signaling**

Abstract:
Cilia are ancient signaling organelles with evolutionary roots in unicellular organisms that use beating flagella to sense and respond to nutrients via highly conserved and amplified sensory mechanisms. In mammals, primary cilia have evolved to non-motile structures that use these conserved sensory mechanisms to respond to neuroendocrine, olfactory, and metabolic signaling hormones. Cilia are also present on many stem cells to control fate determination and regeneration of these sensory cells. Many cells in specific tissues are ciliated including neuroendocrine cells, regenerative ductal cells, neurons, glia, and many stem cells including all mesenchymal steps. Recent work has shown that regeneration of muscle stem cells and *de novo* expansion of preadipocytes requires ciliation. Combining endocrine signaling and regeneration of metabolic tissues, recent human genetic and GWAS studies show that cilia have a clinically important role in metabolic diseases including obesity and diabetes.

Recent genetic studies show that loss of cilia disrupt β-cell endocrine function, but the molecular drivers are unknown. Single cell expression profiles show multiple G protein coupled receptors (GPCRs) are expressed in pancreatic islet cells, but most have unknown functions. Using functional expression, we identified multiple GPCRs localized to cilia in mouse and human islet α- and β-cells, including FFAR4, PTGER4, DRD5, ADRB2, KISS1R, and P2RY14. We find that free fatty acid receptor 4 (FFAR4), the w-3 fatty acid receptor, and prostaglandin E receptor 4 (PTGER4) agonists stimulate ciliary cAMP signaling and promote glucose-stimulated glucagon and insulin secretion (GSGS and GSIS) by α- and β-cell lines, and in isolated mouse and human islets. Transport of GPCRs to primary cilia requires *TULP3*, whose knockdown in primary human and mouse islets relocalized ciliary FFAR4 and PTGER4, and impaired regulated glucagon or insulin secretion, without affecting ciliary structure. Using a ciliary cAMP reporter, we show that ciliary FFAR4 signaling stimulates localized ciliary cAMP increase over ~100 seconds). FFAR4 stimulation of GSIS required cAMP effectors protein kinase A and EPAC and cooperated with calcium signaling trigger via FFAR1, a non-ciliary w-3 fatty acid receptor. The effects of FFAR4 signaling were comparable in magnitude to GLP1 receptor agonists. FFAR4 agonist strongly cooperate with GLP1 agonists, suggesting new therapeutic strategies for GLP1 resistant diabetes. We find that cilia are important to amplify GPCR signaling, and our new data suggests that cilia also organize basal repression of ciliary signaling. Our findings provide index evidence

that regulated hormone secretion by islet α- and β-cells is controlled by ciliary GPCRs providing new targets for diabetes.

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