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When GPCR signaling pathway crosses trafficking pathway: how NTR1/miR-133a/AFTPH pathway regulates colitis development

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Neurotensin receptor 1 (NTR1) is a high-affinity G protein-coupled receptor (GPCR) for neurotensin (NT), a neuropeptide/hormone secreted by cells in ileum and colon. NT/NTR1 interactions promote proliferation and inflammation of colonocytes and angiogenesis in colon. We first studied how NTR1 is regulated in colonocytes, and showed that NTR1 is recycled back to cell surface through early endosomes to achieve re-sensitization during sustained NT stimulation. Furthermore, our results demonstrated that NT/NTR1 signaling was dependent on the functioning of early endosomes and the efficiency of recycling. We next investigated whether this re-sensitization mechanism is regulated by epigenetic modulators, such as microRNAs (miRNAs). Interestingly, we identified miR-133a, a proposed anti-oncogene, as a downstream target of NT/NTR1 signaling and further demonstrated that aftiphilin (AFTPH), a protein expressed in endosomes and trans-golgi network (TGN), to be a direct target of miR-133a and NTR1 recycling was modulated via NTR1/miR-133a/AFTPH axis. Importantly, we provided evidence that miR-133a/AFTPH axis also played significant role in colitis development in experimental colitis models and their expression were dysregulated in colonic tissue samples taken from patients with ulcerative colitis (UC). Previous research has shown that AFTPH not only bound to clathrin/Adaptor protein-1 (AP-1) complex, a protein complex that mediates transport between endosomes and TGN, but to non-muscle myosin 2 (NMMII), an important component in actomyosin ring adjacent to tight junction protein (TJP) complex that is crucial in maintaining intestinal epithelial integrity. This newfound evidence suggested that NT/NTR1 signaling might also play a role in regulating intestinal epithelial permeability via its association with NMMII. Along this line, our latest research showed that AFTPH regulates intestinal epithelial permeability potentially through modulating myosin light chain kinase (MLCK) activity in vitro. In this presentation, we will present latest findings in this project and discuss how studying organelle interactions may be crucial to understand pathophysiology of ulcerative colitis.

Biography

Ivy (Ka Man) Law, PhD, MPhil, is a researcher studying pathophysiology of Inflammatory Bowel Disease (IBD). Her research focuses on inflammatory response and epithelial cell permeability in colonic epithelial cells. She has also studied non-coding RNA, including micro-RNAs, long non-coding RNAs, and their role in epithelial cell biology. She has published more than 20 research articles in peer-reviewed journals including Gut, Scientific Reports, and Journal of Biological Chemistry. She is a member of the American Gastroenterological Association. She is also a biomedical science educator involved in undergraduate medical education (UME).

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