The innate immune system is a fundamental and universal defense system of the host against pathogens. Pathogen recognition relies on the detection of unique motifs called pathogen-associated molecular patterns (PAMPs) present in their structure. Immune cells, as well as epithelial, endothelial, and fibroblast cells, possess specific sensors called pattern recognition receptors (PRRs), which activate signaling cascades leading to the elimination of pathogens or infected cells. This system enables a rapid response to a diverse range of pathogens, including viruses. Viral nucleic acids, such as RNA and DNA, are crucial PAMPs recognized by PRRs. Successful viral recognition triggers an anti-viral immune response, resulting in the production of type I interferons (IFNs) and proinflammatory cytokines. Due to the complexity of the innate immune response, precise regulation is necessary to avoid detrimental outcomes, such as encephalitis, chronic inflammatory bowel diseases, or multiple sclerosis. PRR-induced responses are regulated by phosphorylation, ubiquitination, and ADP-ribosylation, with proteins responsible for these post-translational modifications acting as checkpoints in PRR signaling cascades. One such potential checkpoint is the DTX3L ligase, which possesses E3 ubiquitin ligase activity and the ability to poly ADP-ribosylate proteins.

This project aims to elucidate the role of the DTX3L ubiquitin ligase in the signaling pathways activated by PRRs during viral infections. While DTX3L has been primarily studied as a modulator of the DNA damage response and has been found to be elevated in various solid tumors, recent literature suggests its involvement in modulating the antiviral immune response. Preliminary results from our research show increased production of type I interferons and pro-inflammatory cytokines in DTX3L-deficient cells infected with influenza B virus compared to cells with normal DTX3L expression. Thus, DTX3L appears to prevent excessive induction of the antiviral response. This novel finding warrants further investigation to elucidate the underlying mechanism. Our research will involve using different viruses or equivalent ligands to activate various classes of PRRs and determine the involvement of DTX3L in the induced immunological response. Additionally, we will investigate the regulatory mechanisms of PRR signaling pathways by DTX3L. The results obtained from cell line experiments will be validated using an *in vivo* mouse model.

Understanding the molecular mechanisms through which DTX3L modulates the antiviral immune response will provide valuable insights into immune signaling pathways. Furthermore, identifying the DTX3L-regulated agent responsible for triggering the type I interferon response holds significant implications for the development of new antiviral therapies. Moreover, our research hypothesis suggests that manipulating the levels/activity of DTX3L could increase endogenous IFNβ production, potentially offering an alternative immunomodulatory therapy that does not require the intravenous administration of recombinant interferon.