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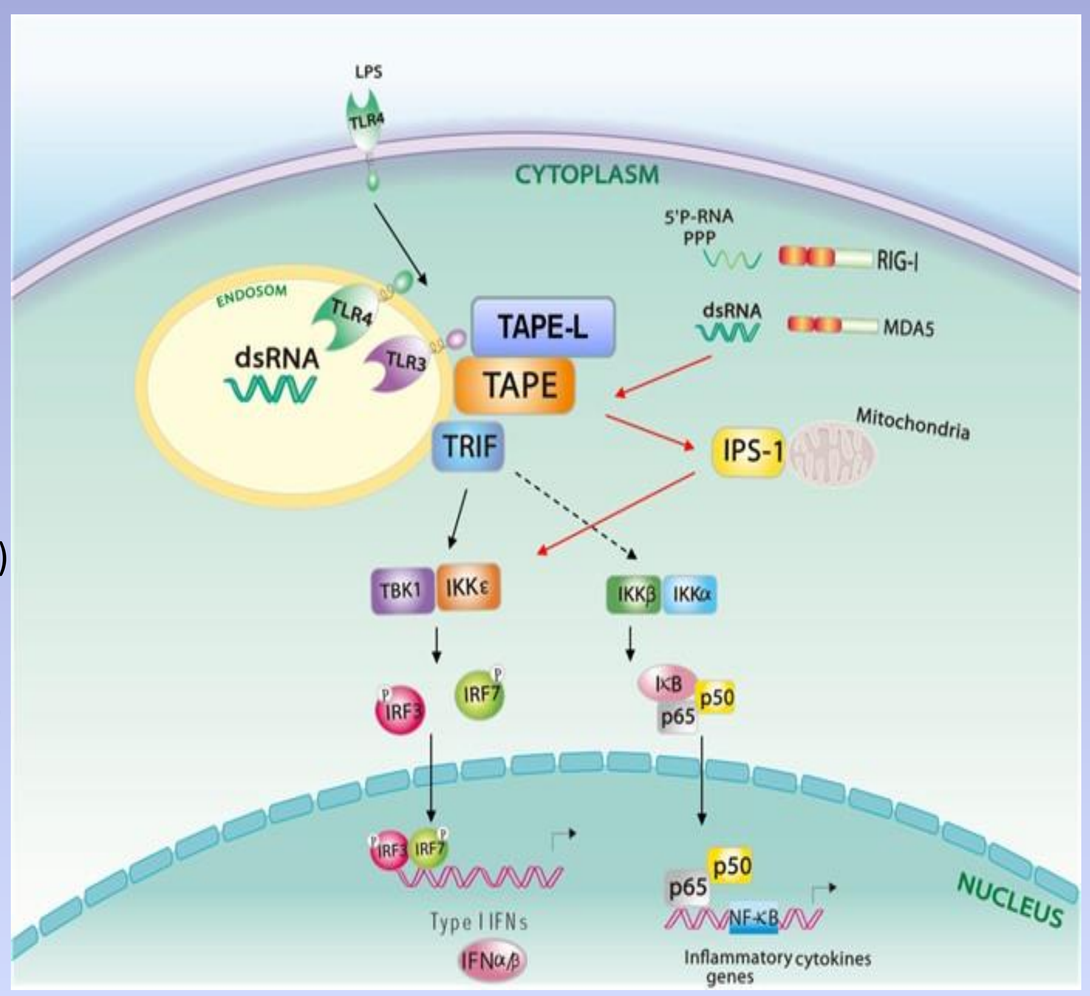
Research Interests

Study the operation modes of the innate immune system

The mammalian innate immune system serves the first line of host defenses against pathogen infection meanwhile bridges to the activation and programming of adaptive immune responses, leading to the full spectrum immune protection. The host innate immune system detects invading pathogens by so-called pattern-recognition receptors (PRRs) through recognizing conserved microbial components known as pathogen-associated molecular patterns (PAMPs). Several families of PRRs have emerged in the innate immune system, including Toll-like receptors (TLRs), RIG-I-like receptors (RLRs), NOD-like receptors (NLRs), C-type lectin receptors (CLRs) and cytosolic DNA sensors. Cytosolic innate immune regulators help relay the PRR signals to the major downstream pathways, including NF-κB, MAPK, and/or IRF3/7, which in turn induce the production of inflammatory cytokines and/or type I interferons (IFNs) for mounting innate immune responses. Insights from studying the innate immune system have transformed our understanding of Immunology, and have also made a great impact on other biomedical fields like infectious disease, inflammatory disease, cancer and vaccine development. The operation modes of the innate immune system are complicated and have much yet to be explored. Better understanding its operations and its interplays with the adaptive immune system and other physiological systems may provide critical insights toward the development of vaccines and novel treatments of infectious and inflammatory diseases in the near future.



1. **Identification and characterization of innate immune regulators TAPE and TAPE-L.** TBK1 is a key protein kinase linking TLR3, TLR4, cytosolic RLRs and DNA sensors to type I IFN production. Our work first uncovered a novel TBK1-interacting protein termed TAPE (TBK1-Associated Protein in Endolysosomes), also known as CC2D1A /Freud-1/Aki-1, which acts as an innate immune regulator implicated in regulating the endosomal TLR3 and TLR4 pathways. Further, we extended the biological role of TAPE to the regulation of the viral sensor RLR pathways during RNA virus infection. To our knowledge, TAPE is the first innate immune regulator involved in both the TLR and RLR pathways at the early stage. In addition, we have identified a TAPE paralog in the human and mouse genomes, termed TAPE-like (TAPE-L). Our initial biochemical analyses showed that TAPE-L was a potent NF-κB activator and was able to regulate the TLR and RLR pathways. Thus, our long-term objective is to determine the roles of these TAPE family adaptors in innate immune regulation. To this main goal, we employ biochemical, cell biology and genetic knockout approaches to investigate the regulatory roles of TAPE family adaptors in innate immunity.

2. **Explore interactions between the host innate immune system and pathogens.** To better understand the pathogenesis of pathogen infection, it is important to elucidate the interactions between the host immune system and invading pathogens. In particular, the innate immune system provides the first contact with invading pathogens at the early stage of infection. The quality and quantity of innate immune responses during early pathogen infection could affect the subsequent adaptive immune responses. Also emerging evidence indicates that many pathogens develop the strategies to counteract the innate immune operations at different steps to help them establish the successful infection. These intricate interactions between the innate immune system and pathogens become a critical issue to be explored. In collaborations with other faculty in NCKU campus and other institutions, we are interested in exploring how the innate immune system interacts with several viruses at the early stage of infection, including Influenza A virus (IAV), Dengue virus (DV) and Enterovirus 71 (EV71). Our long term goal aims to determine how specific innate immune pathways and pathogenic factors contribute to the outcomes of pathogen infection and infectious diseases.

Publications

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3. Lin LH, Ling P, Liu MF. 2011. The potential role of interferon-regulatory factor 7 among Taiwanese patients with systemic lupus erythematosus. The Journal of Rheumatology 38: 1914-9
4. Chang CH, Lai LC, Cheng HC, Chen KR, Syue YZ, Lu HC, Lin WY, Chen SH, Huang HS, Shiau AL, Lei HY, Qin J, Ling P. 2011. TBK1-associated protein in endolysosomes (TAPE) is an innate immune regulator modulating the TLR3 and TLR4 signaling pathways. The Journal of Biological Chemistry 286: 7043-51
5. Li ZH, Li CM, Ling P, Shen FH, Chen SH, Liu CC, Yu CK. 2008. Ribavirin reduces mortality in enterovirus 71-infected mice by decreasing viral replication. The Journal of Infectious Diseases 197: 854-7