招待講演

Innate Immune Protection of the Ear: Roles of Toll-Like Receptors (TLRs) and Antimicrobial Innate Immune Molecules (AIIMs)

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Remarkable progress has been made in recent years concerning the cellular and molecular mechanisms involved in the innate immunity and its importance as a first line of defense as well as an immune modulator for adaptive immunity. The discovery of Toll-like Receptors (TLRs) as Pattern Recognition Receptors (PRRs), which recognizes Microorganism-Associated Molecular Patterns (MAMPs) helped to redefine complex interplay between the innate immunity and the adaptive immunity. Once the host cells sense the presence of pathogens through PRRs, the host cells immediately respond by mobilizing or inducing Antimicrobial Innate Immune Molecules (AIIMs), in order to defend against the invading pathogens.

There has been an alarming increase of antibiotic resistance among major otitis media (OM) pathogens in recent decades. Thus, there is an urgent need to develop new and innovative non-antibiotic therapeutics to prevent and manage OM and OM-induced inner ear injury. We have demonstrated for the first time that a number of mucosal AIIMs show a potent bactericidal activity against OM pathogens. Furthermore, we recently showed that deficiency of lysozyme, one of the AIIMs elaborated in the tubotympanum, increases a susceptibility to experimental pneumococcal OM. Important progress in establishing the involvement of TLRs and their cell signaling pathways in OM pathogen-induced up-regulation of AIIMs has been made and sheds a new light on understanding OM pathogenesis. We also showed that β-defensin 2, one of the AIIMs, is up-regulated by IL-1α via a Src-dependent Raf-MEK1/2-ERK signaling pathway. These findings led us to explore a host's receptor and its associated adaptor molecule involved in NTHi-induced β-defensin 2 up-regulation. We recently showed that bacterial molecule(s) of NTHi up-regulate(s) β-defensin 2 via a TLR2-dependent MyD88-IRAK1-TRAF6 signaling pathway in the middle ear epithelial cells. We further showed that middle ear epithelial cells release IL-1α upon exposure to the NTHi molecules and that this cytokine acts synergistically with NTHi to up-regulate

β-defensin 2, pointing to the complexity of the signaling pathways that regulate the AIIMs.

Very little is known about the innate immunity of the inner ear. Our recent investigation confirmed that spiral ligament fibrocytes (SLFs) induce a number of chemokines that are responsible for infiltration of leukocytes in the inner ear following exposure to OM pathogens. Moreover, we demonstrated that TLR2-dependent NF-κB activation is required for NTHi-induced MCP-1 up-regulation in SLFs. Thus, it is believed that SLFs play a central role in innate immunity of the inner ear. In addition, our preliminary results showed that lysozyme and Bin1b, a member of β-defensin family antimicrobial peptide are highly potent in inhibiting/killing OM pathogens and are expressed in the endolymphatic sac (ES) epithelial cells. Considering that macrophages and intraepithelial T-cells are resident in the ES, we believe that the ES is an immune organ of the inner ear, equipped with both innate and adaptive immune system, in addition to a regulator of the inner ear ion/fluid homeostasis.

Resolution of inflammation requires an orchestrated process in which initial inflammation clears the invading pathogens and is then down-regulated before inflammation-mediated pathology occurs. Thus, an important area of innate immune regulation is the negative feedback system that modulates the inflammatory response as well as the delicate balance between up-regulation and down-regulation of the AIIMs. Dysregulation of the innate immune modulation/regulation could result in inflammatory disorders including autoimmunity. A conceptual framework of the proposed functioning of the innate immune system in the ear and its role in the immune-mediated ear diseases will be discussed.