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Role of extracellular ATP in immune mechanisms against infection

Lalitha Tadala

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Fakultetsopponent: Mikael Sellin, PhD

Uppsala Universitet, Uppsala, Sverige.

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Author
Lalitha Tadala

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Abstract
Inflammation is driven either by infection with pathogens or sterile stimuli, such as tissue damage or autoimmune diseases. Upon tissue damage, ATP is released passively from the dead or compromised cells. During stress, ATP can be secreted from the cells. Extracellular ATP (eATP) acts as a endogenous danger signal. An increase in eATP is sensed by cell surface purinergic receptors and regulates the onset and resolution of inflammation. Extracellular ATP is an important inflammatory mediator during sterile inflammation. On the other hand, the role of eATP is poorly studied during infection, both bacterial and viral. In this thesis, I present the molecular mechanisms underlying ATP secretion during bacterial infections and the role of eATP in human hantaviral infections.

During infection with certain enteropathogenic Gram-negative bacteria, intestinal epithelial cells secrete ATP via connexin hemichannels as an alert signal to activate the immune system, which triggers acute inflammation in the gut. However, neither what triggers ATP secretion nor the molecular mechanisms of ATP secretion were known. Pharmacological, genetic and microscopy-based evidence shows that during invasive bacterial infections, the plasma membrane ruffles act as mechanical immune stimuli and activate the inherently mechanosensitive plasma membrane channel PIEZO1. Mechanically activated PIEZO1 leads to the influx of Ca^{2+} ions and concurrent ATP secretion. In addition, PIEZO1 also activates protective transcriptional responses. Thus, PIEZO1 acts as a sensor for invasive infection using mechanical stimuli, unlike the so far described immune sensors of infection, which all recognize microbial components by chemical interaction.

During human hantavirus infection, the humoral immune responses is poorly studied. Our collaborators found that atypical B cells, which do not have the surface marker CD27, show increased frequency in a cohort of hantavirus-infected patients. CD27 shedding in murine lymphocytes had been previously linked to eATP-dependent activation of a purinergic receptor$_7$. To test whether ATP levels in the circulation of hantavirus-infected patients are elevated, an approach to perform same-day eATP quantifications in human plasma was developed. This assay was used to establish the normal eATP concentration in plasma in a cohort of healthy volunteers and to show that eATP levels are elevated in the acute and convalescent stages of hantavirus infection. Further, addition of ATP to isolated human B cells recapitulated the observed CD27 shedding via a metallomatrix proteinase-8-dependent (MMP8) mechanism. Together, these projects provide an evidence for the importance of eATP in bacterial and viral infectious diseases.

Keywords
Extracellular ATP, invasive bacteria, *Shigella*, *Listeria*, plasma membrane ruffle, PIEZO1, infection, immune response, Hanta virus

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