Chemistry

The main focus of our study is on the innate immune system. Innate immunity is conserved throughout multicellular organisms and plays an important role as the first line of host defense. We are examining the functions of surfactant proteins in innate immunity and the process of phagocytic elimination of bacteria and altered-self cells. Concerning pathogens, they change their gene expression pattern to evade the host immune system. We are also interested in factors that trigger the alteration in the gene expression of pathogens.

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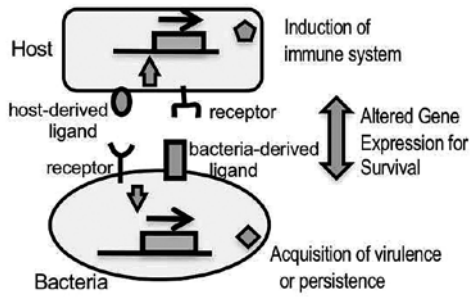
1. Regulation of bacterial gene expression under infectious conditions

There are three systems by which bacteria adapt themselves to host environments by altering gene expression patterns. One is a two-component regulatory system to control signal transduction in bacteria. Another is by means of the promoter-recognizing subunit sigma of bacterial RNA polymerase that plays a major role in the selection of genes to be transcribed. The third consists of the complex of RNA chaperon proteins and small noncoding RNA facilitating their binding to target mRNA for the alteration of translation efficiency and stability. We examined the roles of these factors in bacterial adaptation to hosts using genetically tractable organisms, *Escherichia coli* and *Staphylococcus aureus*, as pathogens and *Drosophila melanogaster*, the immune system of which is conserved in humans as well as mammals as hosts.



a) The two-component regulatory system

We examined the transcriptional promoter strength of all genes coding sensor kinases and response regulators of *E. coli* in the host. Among these, we found a signaling system consisting of EnvZ, a sensor kinase, and OmpR, a transcription factor, activated in the host and reduced bacterial virulence.

b) The sigma subunit of bacterial RNA polymerase and RNA chaperon

The DNA-dependent RNA polymerase of *E. coli* is a multisubunit holoenzyme and one of seven species of promoter-recognizing subunit sigma. We discovered that the repertoire of the seven sigma subunits changed upon infection and enhanced levels of sigma38 in the host-induced expression of catalases for persistent infection. An RNA chaperone of *E. coli* called Hfq forms a complex with small noncoding RNA. We found that Hfq contributes to persistent infection of *E. coli* by maintaining the expression of sigma38, a type of sigma subunit in RNA polymerase.

2. Phagocytic elimination of apoptotic cells and cancer cells

The role of phagocytes in cellular innate immunity is to eliminate microbes, virus-infected cells, and altered-self cells. There are two evolutionarily conserved phagocytosis pathways in species ranging from nematodes to humans, including phagocytic receptors in phagocytes and their signaling molecules. We discovered that two phagocytic pathways with receptor Draper/MEGF-10 and Integrin alphaPS3-betanu/Integrin alpha3-beta5 (Drosophila/human) recognized both apoptotic and virus-infected cells. Their ligands are membrane lipid phosphatidylserine (PS) and PS-binding proteins. Phagocytosis of cancer cells prevents neoplastic transformation in multicellular organisms.

3. The functions of pulmonary collectins

The surface of alveoli is covered with pulmonary surfactant, a mixture of lipids and proteins, which reduces surface tension to keep alveoli from collapsing. Pulmonary surfactant contains two collectins called surfactant proteins A and D (SP-A and SP-D). These collectins play vital roles in host defense in the lung. Furthermore, the collectins bind to host proteins and regulate their functions. The aim of our study is to clarify multiple functions of pulmonary collectins

in host defense and lung homeostasis.

a) Innate immune functions

Pulmonary collectins consist of a collagen-like domain, a neck region, and a C-type lectin domain. These collectins bind various microbes and are involved in innate immunity against infectious pathogens. The functions of pulmonary collectins are affected by their oligomeric structure. We are interested in the structure-function relationship of pulmonary collectins.

Pulmonary collectins are also expressed in several tissues other than the respiratory system. We are examining the immune functions of these collectins expressed in non-pulmonary tissues.

b) Interaction with host proteins

We are also examining the regulatory effects of pulmonary collectins as a result of interaction with host proteins. For instance, SP-A binds human b-defensin 3 (hBD3) and attenuates its cytotoxicity against host cells. Interestingly, SP-A does not affect the antimicrobial activity of hBD3. More detailed studies are under way to apply SP-A as a regulatory molecule of hBD3 functions. Pulmonary collectins also interact with cell-surface receptors and modulate signal transduction. We especially focus on interaction with receptor tyrosine kinases involved in host cell proliferation.

List of Main Publications (September 2018 to August 2023)

See 2D Barcode below