Department of Chemistry

The main focus of our study is on the innate immune system. Innate immunity is conserved throughout multicellular organisms and plays important roles 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 through 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 (1-5).

1) The two-component regulatory system

We examined the transcriptional promoter strength of every 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 (1).

2) The sigma subunit of bacterial RNA polymerase

The DNA-dependent RNA polymerase of *E. coli* is a multisubunit holoenzyme and one of seven species of the promoter-recognizing subunit sigma. We found 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 (2).

3) RNA chaperone-non coding RNA complex

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 (5).

2. Phagocytic elimination of bacteria and altered self

Phagocytes have a role in cellular innate immunity by eliminating microbes 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 (6-12).

1) Phagocytic elimination of apoptotic cells

We found two phagocytic pathways with receptor Draper/MEGF-10 and Integrin alpha3-betanu/Integrin alpha3-beta5 (Drosophila/human) recognized both apoptotic and virus-infected cells. Their ligands are membrane lipid phosphatidylserine (PS) and PS-binding proteins (7-12).

2) Cell wall molecules of bacteria for interaction with host immunity

We found S. aureus provides cell wall components teichoic acid and peptidoglycan to ligands for phagocytic receptors and immune receptor Toll (flies) and Toll-like receptors (mammals) (7).

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. The surfactant contains two collectins called surfactant proteins A and D (SP-A and SP-D). These collectins play important 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 homeostasis.

1) Innate immune functions

Pulmonary collectins are involved in the elimination of infectious pathogens in the innate immune system. We examined the roles of collectins in host defense against *Legionella pneumophila*, an intracellular pathogen. Also, we are interested in innate immune functions of collectins expressed in tissues other than the respiratory system (13).

The functions of pulmonary collectins are influenced by their structure. For instance, acrolein-modification disrupts structural and functional features of SP-A (14). Studies on structure-function relationships of collectins are ongoing.

2) Other functions

Recently, we found that SP-A interacts with human β-defensin 3 (hBD3), an antimicrobial peptide, and regulate its functions (15). SP-A attenuated chemoattractant activity and cytotoxicity of hBD3. Interestingly, SP-A did not affect antimicrobial activity of hBD3. More detailed studies are underway to apply SP-A as a regulatory molecule of hBD3 function.

Pulmonary collectins also affect the epidermal growth factor (EGF) signaling through interaction with the EGF receptor (16, 17). Our data suggest that pulmonary collectins contribute to the suppression of lung cancer progression..

4. List of Main Publications from 2013 to 2018

1) Pukklay P, Nakanishi Y, Nitta M, Yamamoto K, Ishihama A, Shiratsuchi, A. Involvement of EnvZ-OmpR two-component system in virulence control of *Escherichia coli* in *Drosophila melanogaster*. ***Biochem Biophys Res Commun*** 438: 306-311 (2013)
2) Shiratsuchi A, Osada Y, Nakanishi, Y. Differences in the mode of phagocytosis of bacteria between macrophages and testicular Sertoli cells. ***Drug Discov Ther*** 7: 73-77 (2013)
3) Nonaka S, Nagaosa K, Mori T, Shiratsuchi A, Nakanishi Y. Integrin αPS3/βν-mediated phagocytosis of apoptotic cells and bacteria in *Drosophila*. ***J Biol Chem*** 288: 10374-10380 (2013)
4) Shiratsuchi A, Shimamoto N, Nitta M, Tuan TQ, Firdausi A, Gawasawa M, Yamamoto Y, Ishihama A, Nakanishi Y. Role for sigma38 in prolonged survival of *Escherichia coli* in *Drosophila melanogaster*. ***J Immunol*** 192: 666-675 (2014)
5) Nainu F, Tanaka Y, Shiratsuchi A, Nakanishi Y. Protection of insects against viral infection by apoptosis-dependent phagocytosis. ***J Immunol*** 195: 5696-5706 (2015)
6) Kong Q, Nakai Y, Kuroda N, Shiratsuchi A, Nagaosa K, Nakanishi, Y. Peptidoglycan recognition protein-triggered induction of *Escherichia coli* gene in *Drosophila melanogaster*. ***J Biochem*** 157: 507-517 (2015)
7) Shiratsuchi A. Mechanim and role for phagocytosis of apoptotic cells and bacteria as the innate immune reaction. **Kagaku to Seibutu** 53: 38-41 (2015)
8) Shiratsuchi A, Nitta M, Kuroda A, Komiyama C, Gawasawa M, Shimamoto N, Tran Quoc T, Morita T, Aiba H, Nakanishi Y. Inhibition of phagocytic killing of *Escherichia coli* in *Drosophila* hemocytes by RNA chaperon Hfq. ***J Immunol*** 197: 1298-1307 (2016)
9) Ekowati H, Arai J, Puput ASD, Nainu F, Shiratsuchi A, Nakanishi Y. Protective effects of *Phaseolus vulgaris* lectin against viral infection in *Drosophila*. ***Drug Discov Ther*** 11: 329-355 (2017)
10) Nonaka S, Ando Y, Kanetani T, Hoshi C, Nakai Y, Nainu F, Nagaosa K, Shiratsuchi A, Nakanishi Y. Signaling pathway for phagocyte priming upon encounter with apoptotic cells. ***J Biol Chem*** 292: 8059-8072 (2017)
11) Nainu F, Shiratsuchi A, Nakanishi Y. Induction of apoptosis and subsequent phagocytosis of virus-infected cells as an antiviral mechanism. (review) ***Front Immun***8: 1220 (2017)
12) Nonaka S, Shiratsuchi A, Nagaosa K, Nakanishi Y. Mechanisms and significance of phagocytic elimination of cells undergoing apoptotic death. (review) ***Biol Pharm Bull*** 40: 1819-1827 (2017)
13) Hashimoto J, Takahashi M, Saito A, Murata M, Kurimura Y, Nishitani C, Takamiya R, Uehara Y, Hasegawa Y, Hiyama Y, Sawada N, Takahashi S, Masumori N, Kuroki Y, Ariki S. Surfactant protein A inhibits growth and adherence of uropathogenic *Escherichia coli* to protect the bladder from infection. ***J Immunol.*** 198: 2898-2905 (2017).
14) Takamiya R, Uchida K, Shibata T, Maeno T, Kato M, Yamaguchi Y, Ariki S, Hasegawa Y, Saito A, Miwa S, Takahashi H, Akaike T, Kuroki Y, Takahashi M. Disruption of the structural and functional features of surfactant protein A by acrolein in cigarette smoke. ***Sci Rep.*** 7: 8304 (2017).
15) Uehara Y, Takahashi M, Murata M, Saito A, Takamiya R, Hasegawa Y, Kuronuma K, Chiba H, Hashimoto J, Sawada N, Takahashi H, Kuroki Y, Ariki S. Surfactant protein A (SP-A) and SP-A-derived peptide attenuate chemotaxis of mast cells induced by human β-defensin 3. ***Biochem Biophys Res Commun.*** 485: 107-112 (2017).
16) Hasegawa Y, Takahashi M, Ariki S, Saito A, Uehara Y, Takamiya R, Kuronuma K, Chiba H, Sakuma Y, Takahashi H, Kuroki Y. Surfactant protein A downregulates epidermal growth factor receptor by mechanisms different from those of surfactant protein D. ***J Biol Chem.*** 292: 18565-18576 (2017).
17) Hasegawa Y, Takahashi M, Ariki S, Asakawa D, Tajiri M, Wada Y, Yamaguchi Y, Nishitani C, Takamiya R, Saito A, Uehara Y, Hashimoto J, Kurimura Y, Takahashi H, Kuroki Y. Surfactant protein D suppresses lung cancer progression by downregulation of epidermal growth factor signaling. ***Oncogene*** 34: 838-845 (2015).