Imperial Prize and Japan Academy Prize to:

Shizuo Akira

Professor, Research Institute for
Microbial Diseases, Osaka University

for "Pathogen Recognition by Innate Immunity and its Signaling"

Outline of the work:

Immune system is largely categorized in innate and acquired immunity. The acquired immunity produces a huge number of receptors with an almost infinite range of specificities by way of DNA rearrangement in T and B lymphocytes, and is a unique system present only in vertebrates to recognize pathogens, foreign substances, and non-self. On the other hand, the innate immunity is a phylogenetically conserved defense system shared from lower organisms to higher animals, and was formerly considered as a non-specific immune system which is involved only in engulfment and digestion of pathogens by phagocytes. However, recent studies have revealed that the innate immunity can specifically distinguish between self and pathogens via Toll-like receptors (TLRs). The study on TLR originated from the finding by Jules Hoffmann and his colleagues in France in 1996 that Toll plays a critical role in fungal immunity of Drosophila. Next year Charles Janeway's group in USA reported the presence of human homolog (human Toll, also called TLR4) of Drosophila Toll, and at the end of 1998 Bruce Beutler and his colleagues showed that TLR4 recognizes lipopolysaccharide (LPS), one of cell wall components in Gram-negative bacteria that has a potent immunostimulatory activity and is a causative agent of endotoxin shock. Dr. Akira has shown by generating knockout mice of TLR family which consist of 12 members that individual TLRs recognize different microbial components and established the role of TLR family as pathogen recognition receptors, and further clarified the whole picture of their signaling pathways. Particularly, Dr. Akira's finding that TLR7 and TLR9 recognize RNA and DNA of pathogens, respectively is highly appreciated because this finding confirmed that activation of innate immunity by TLR plays a critical role in induction of acquired immunity, and also gave the scientific background on tumor immunotherapy and allergy treatment using a variety of nucleic acids and their derivatives, and is now accelerating the clinical application. Furthermore, this is the first demonstration that TLRs are involved in viral recognition in addition to bacterial recognition. Moreover, this finding modified the previous idea that only pathogen-specific molecules are recognized by TLRs, and shows that the common molecules present both in host and pathogens are recognized by TLRs. This idea developed into the subsequent studies showing that TLR7 and TLR9 are involved in development of autoimmune diseases. As described above, through the discovery of TLRs and analyses of their function, it has become evident that even the innate immunity harbors pathogen sensing receptors that recognize pathogen components such as lipopolysaccharide, lipoproteins, DNA and RNA, and then trigger the host defense against invading pathogens. Among immune cells, so-called phagocytes including macrophages, leukocytes, and dendritic cells express TLRs abundantly. These phagocytes induce inflammatory as well as immune responses through TLR activation when they engulf and digest invading pathogens. The more important point is that pathogen recognition by TLRs also induces activation of acquired immunity that is regulated by T

and B lymphocytes. The discovery that TLRs are essential to initial recognition of pathogens and subsequent induction of acquired immunity has drastically changed our idea about the immune response, which was so far derived from the studies of acquired immunity solely. Furthermore, this led to modification of the previous concept of pathogenesis of a variety of immune-associated diseases as well as immunotherapy against cancers and allergy. Dr. Akira has made a great contribution to establishment of importance of innate immunity and he has been given the Robert Koch Prize, the most prestigious international medical award in Germany together with Jules Hoffmann in France and Bruce Beutler in USA. His work on TLRs are highly evaluated world-wide, and he has given a lecture in a variety of international conferences including Keystone Symposia, Gordon Conference, Nobel Forum, and many meetings dealing with immunology and infectious diseases in various countries. He has authored over 500 papers, and is one of the most cited immunologists. In 2006 and 2007 he was twice recognized the first hottest scientist who had published the greatest number of Hot Papers over the preceding two years.

Selected original papers

[1] Adachi, O., Kawai, T., Takeda, K., Matsumoto, M., Tsutsui, H., Sakagami, M., Nakanishi, K., and *Akira, S.* Targeted disruption of the MyD88 gene results in loss of IL-1- and IL-18-mediated function. **Immunity** 9:143-150, 1998

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[5] Takeuchi, O., Hoshino, K., Kawai, T., Sanjo, H., Takada, H., Ogawa, T., Takeda, K., and *Akira, S.* Differential roles of Toll-like receptor (TLR) 2 and TLR4 in recognition of Gram-negative and Gram-positive bacterial cell wall components. **Immunity** 11:443-451, 1999

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[9] Yamamoto, M., Sato, S., Hemmi, H., Hoshino, K., Kaisho, T., Sanjo, H., Takeuchi, O., Sugiyama, M., Okabe, M., Takeda, K., and *Akira, S.* Role of adaptor TRIF in the MyD88-independent Toll-like receptor signaling pathway. **Science** 301:640-643, 2003

[10] Yamamoto, M., Sato, S., Hemmi, H., Uematsu, S., Hoshino, K., Kaisho, T., Takeuchi, O., Takeda, K., and *Akira, S.* TRAM is specifically involved in the Toll-like receptor 4-mediated MyD88-independent signaling pathway. **Nat. Immunol**. 4:1144-1150, 2003

[11] Yamamoto, M., Yamazaki, S., Uematsu, S., Sato, S., Hemmi, H., Hoshino, K., Kaisho, T., Kuwata,

H., Takeuchi, O., Takeshige, K., Saitoh, T., Yamaoka, S., Yamamoto, N., Yamamoto, S., Muta, T., Takeda, K., and *Akira, S.* Regulation of Toll/IL-1-receptor-mediated gene expression by the inducible nuclear protein IkBzeta. **Nature** 430:218-222, 2004

[12] Kawai, T., Sato, S., Ishii, K.J., Coban, C., Hemmi, H., Yamamoto, M., Terai, K., Matsuda, M., Inoue, J., Uematsu, S., Takeuchi, O., and *Akira, S.* Interferon-α induction through Toll-like receptors involves a direct interaction of IRF7 with MyD88 and TRAF6. **Nat. Immunol**. 5:1061-1068, 2004

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[14] Kawai, T., Takahashi, K., Sato, S., Covan, C., Kumar, H., Kato, H., Ishii, K.J., Takeuchi, O., and *Akira, S.* IPS-1, an adaptor triggering RIG-I and Mda5-mediated type I interferon induction. **Nat. Immunol**. 6:981-988, 2005

[15] Ishii, K.J., Coban, C., Kato, K., Takahashi, K., Torii, Y., Takeshita, F., Ludwig., H., Sutter, G., Suzuki, K., Hemmi, H., Sato, S., Yamamoto, M., Uematsu, S., Kawai, T., Takeuchi, O., and *Akira, S.* A Toll-like receptor-independent antiviral response induced by double-standed B-form DNA. **Nat. Immunol**. 7:40-48, 2006

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Review articles

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[2] Takeda, K., Kaisho, T., and *Akira, S.* Toll-like receptors. **Annu. Rev. Immunol**. 21:335-376, 2003

[3] *Akira, S.* Toll-like receptor signaling. **J. Biol. Chem**. 278:38105-38108, 2003

[4] *Akira, S.*, and Takeda, K. Toll-like receptor signalling. **Nat. Rev. Immunol**. 4:499-511, 2004

[5] *Akira, S.*, Uematsu, S., and Takeuchi, O. Pathogen recognition and innate immunity. **Cell** 24:783-801, 2006