Overview for the distinguished achievements of Shizuo Akira

Immunity is a biological defense system designed to avoid infectious diseases or cancers. Immunology is a biomedical science that studies various aspects of the immune system. The mammalian immune system is comprised of two branches: innate and acquired immunity.

The innate immune system is the first line of host defense against pathogens, and is characterized by "simple phagocytes" called macrophages and dendritic cells (DCs).
Compared to innate immunity, acquired immunity eliminates pathogens in the late phase of infection. Acquired immunity is characterized by the words "T cell", "B cell", "antigen-specificity" and "gene rearrangement" (Figure 1). It is these properties of acquired immunity that have worked for the development vaccine.

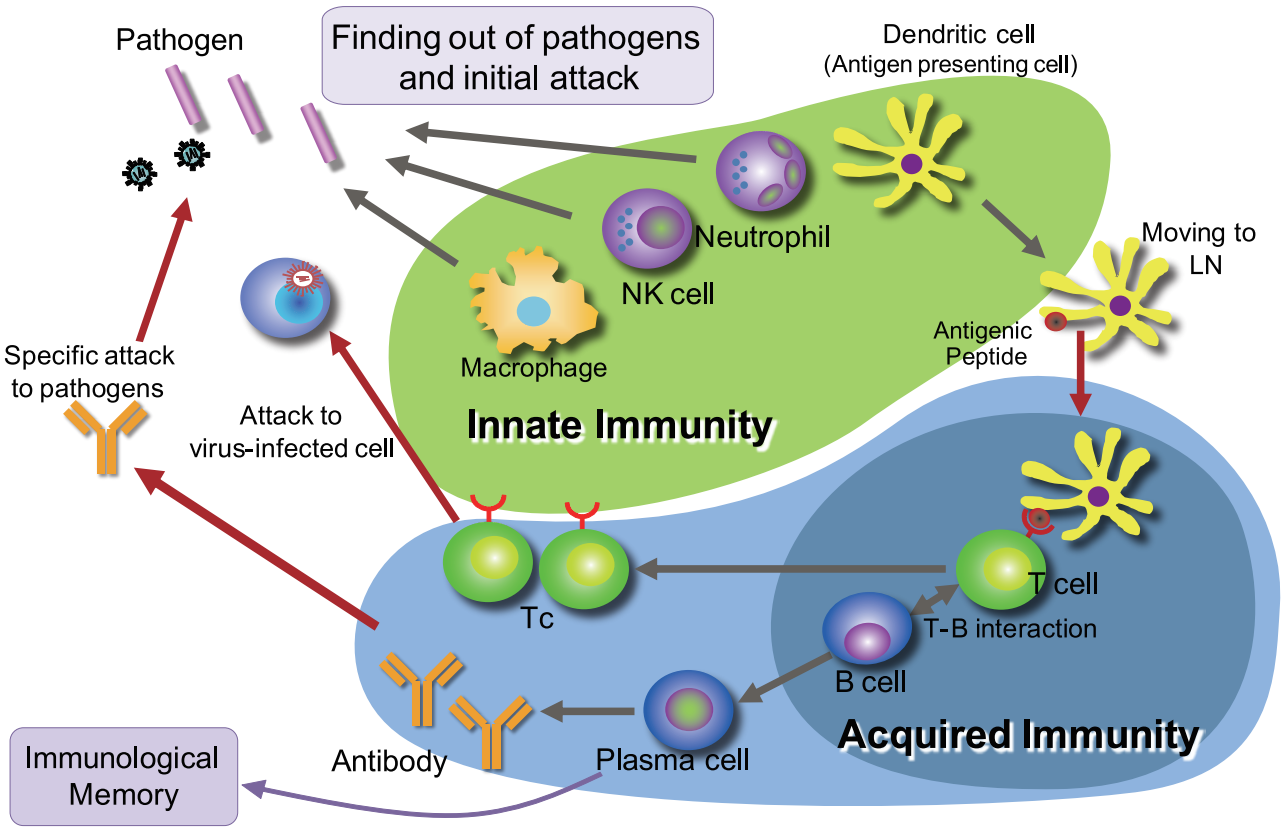

Fig. 1 Interaction between innate & acquired immunity

Shizuo Akira, Director of Immunology Frontier Research Center (WPI-IFReC) did the breakthrough studies in innate immunology. Akira and his research group have unlocked the importance of innate immunology by the functional analysis of Toll-like Receptors (TLRs), existing in innate cells (macrophages, DC).

("Toll" means "Great" or "wonderful" in German.)

Mammals have about ten kinds of TLRs, and their various functions have been revealed by Akira's group (Fig. 2). Some distinguished discoveries by Akira's group are as follows.

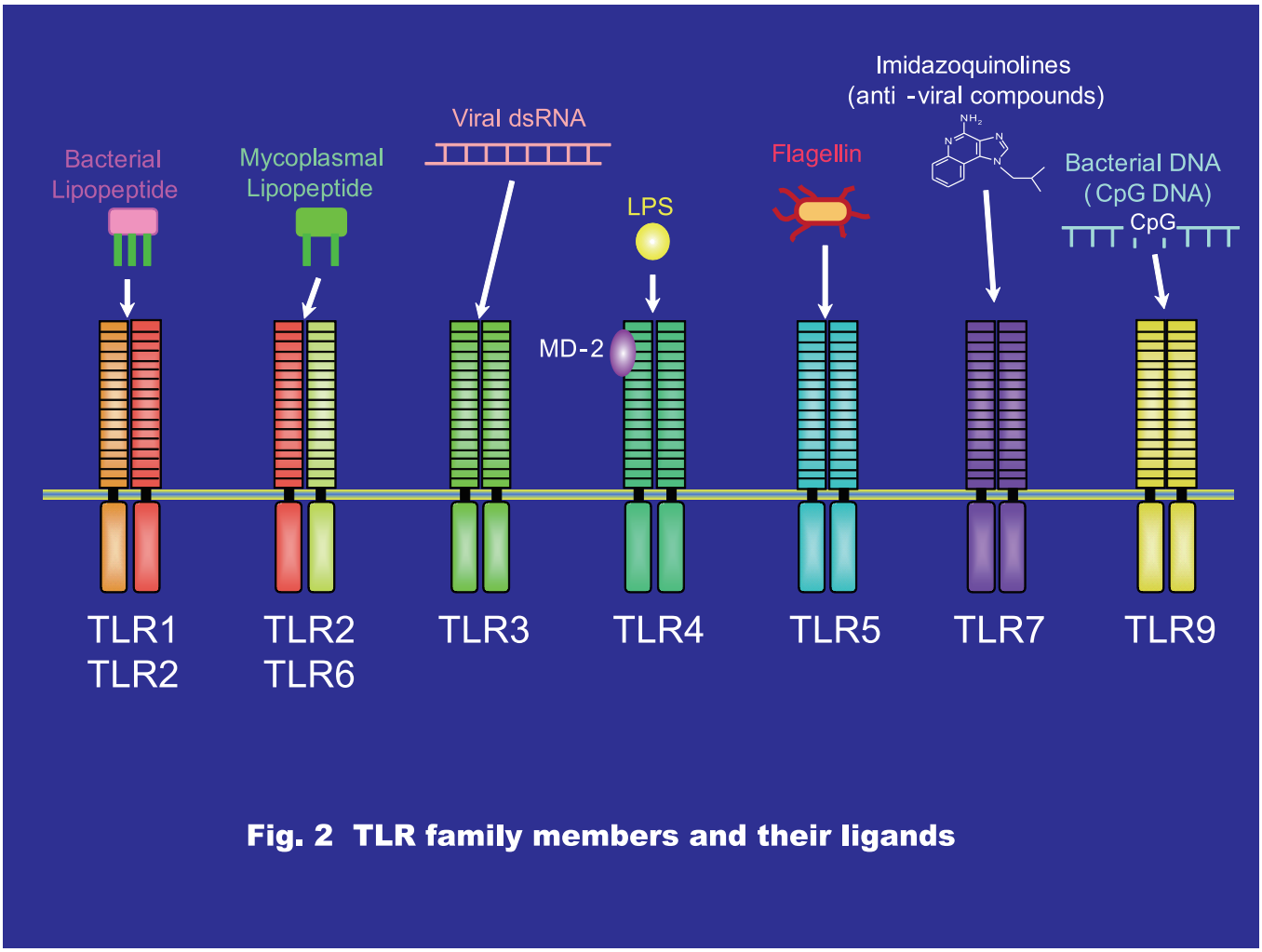

Fig. 2 TLR family members and their ligands

LPS recognition by TLR4

Bacteria are classified into two major groups depending on the different staining characteristics of their cell walls, Gram-positive and -negative bacteria. Lipopolysaccharide (LPS) is a surface component of Gram- negative bacteria known to be an endotoxin. From the experiments using TLR4 knockout mice, TLR4 was identified as the receptor for LPS by Akira's group.

Flagellin recognition by TLR5

Flagellin is the major protein constituent of bacteria flagella, the motility apparatus used by many microbial pathogens, and is a potent activator of innate immune responses. Akira and his group discovered that TLR5 is responsible for the detection of flagellin (collaborative research with Alan Aderem). TLR5 is expressed by epithelial cells, monocytes, and immature DCs. Since TLR5 is basolaterally expressed on intestinal epithelia, flagellin is recognized by the host only when bacteria have invaded across the epithelia.

Viral ssRNA and chemical substances recognition by TLR7

Akira's group discovered that TLR7 recognizes synthetic antiviral imidazoquinoline components

(R848, Imiquimod, etc.). TLR7 is expressed within the endosomal membrane, and recognizes ssRNA. Many enveloped viruses traffic into the cytosol through the endosomal compartment. The phagolysosome is a highly acidified environment containing abundant degradation enzymes that may damage the viral particles leading to ssRNA release and recognition by TLR7.

Bacterial DNA recognition by TLR9

Bacterial genomic DNA is also an immunostimulant and is recognized by TLR9. Its stimulatory effect is due to the presence of unmethylated CpG dinucleotides (CpG-DNA). In contrast, the methylated CpG motif does not activate mammalian immune cells. The expression of TLR9 in intracellular compartments is important to distinguish non-self DNA from self DNA. The discovery of the function of TLR9 was a most important works of Akira's group, and the article (Hemmi et al., Nature 2000) has been cited more than 2700 times (as of March, 2011).

Furthermore, the group showed that TLRs are necessary for maturation and activation of T cells. Essentially, TLRs behave as "bridges" between innate and acquired immunity (Figure 3).

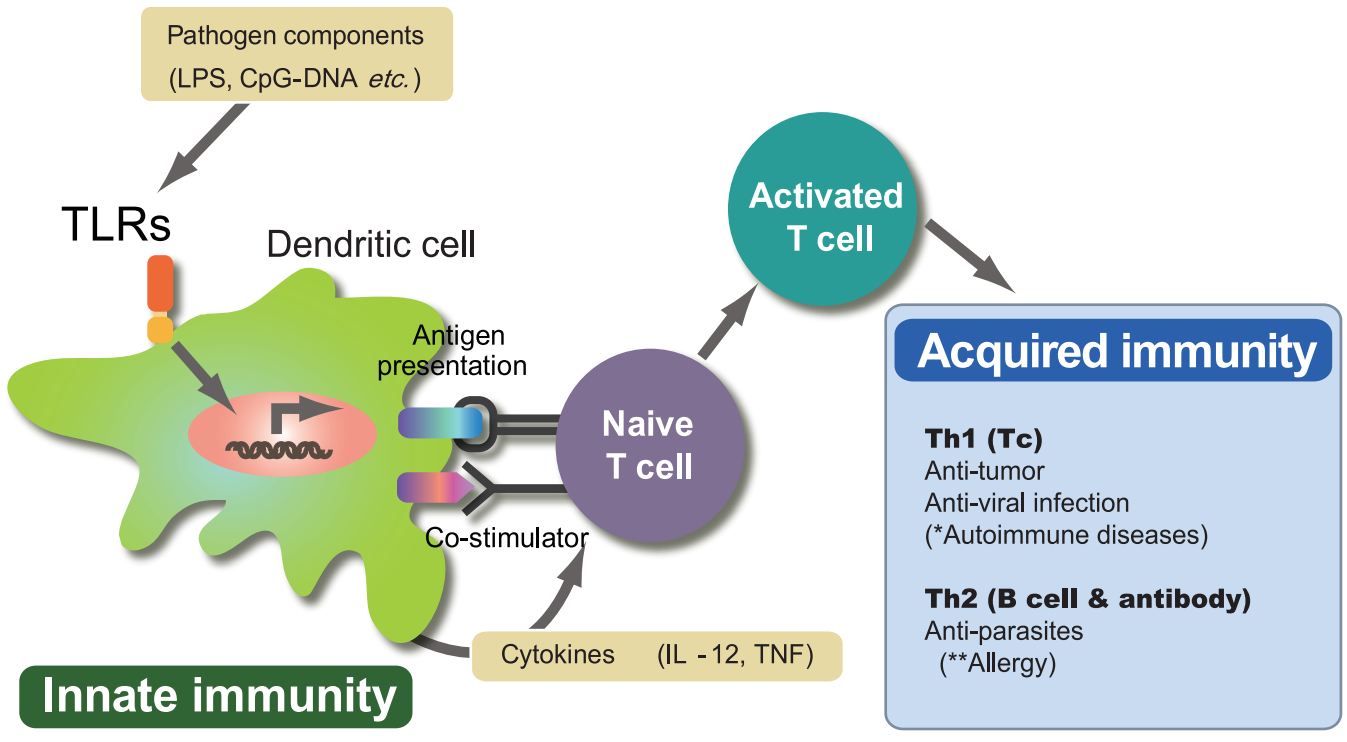

Fig. 3 TLRs are "bridges" between innate and acquired immunity.

As mentioned above, the group of Akira has revealed that each TLR has the specific function that recognizes the type of "invader" and induces the acquired immune responses. These results are greatly praised and expected to contribute to the therapies of immunological diseases in the future.

These discoveries by Akira and his group have changed the position of innate immunity. Mammals protect their bodies by two stages of immune system, innate immunity and innate-acquired immunity. We can say the discoveries by Akira's group gave paradigm shift to the concept of immunity (Figure 4).

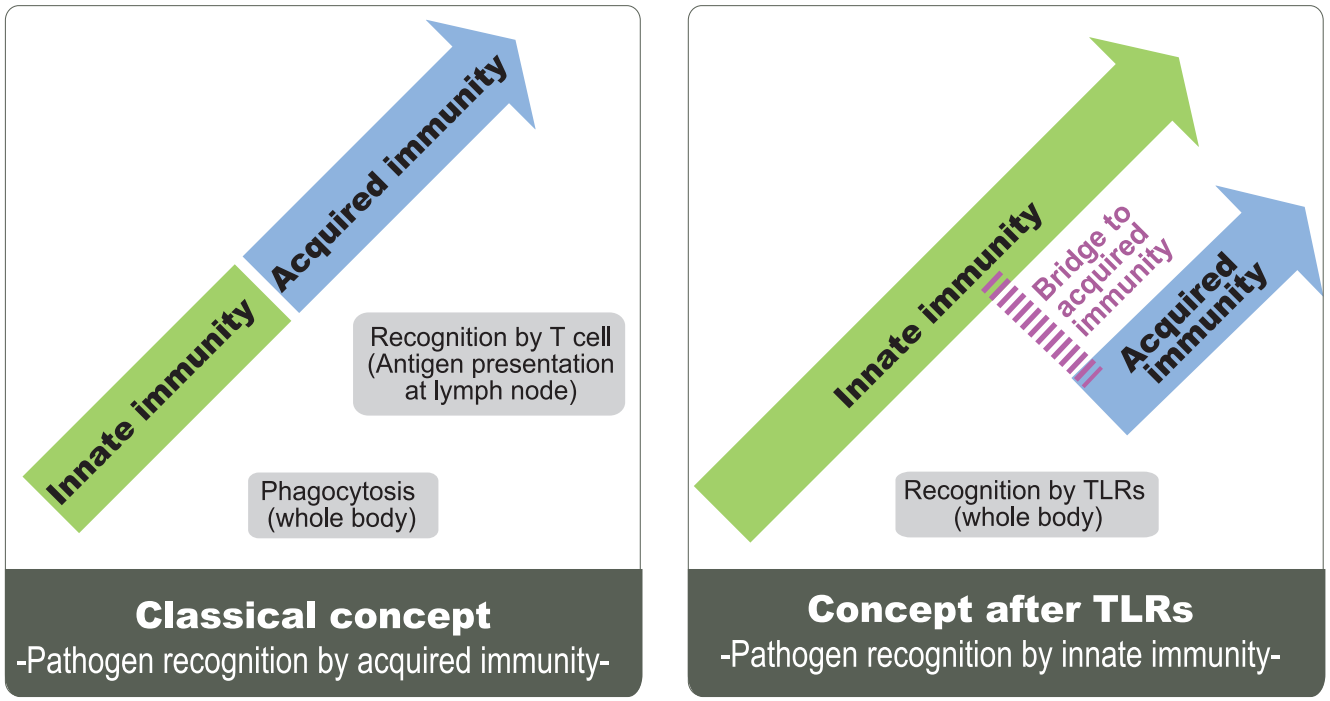

Fig. 4 Concept change in immune system

References on TLRs

- Akira, S., Uematsu, S., and Takeuchi, O. Pathogen Recognition and Innate Immunity. Cell 124, 783-801 (2006).
- Hemmi, H., Takeuchi, O., Kawai, T., et al. A Toll-like receptor recognizes bacterial DNA. Nature 408, 740-745 (2000).