Fields of Life Sciences

Achievement

Discovery of the nucleic acid sensing mechanism by the innate immune system

Prof. Shizuo Akira (Japan)

Born: January 27, 1953 (Age: 72)
Specially Appointed Professor
Center for Advanced Modalities and DDS (CAMaD),
The University of Osaka

Prof. Zhijian "James" Chen (USA)

Born: January 1, 1966 (Age: 60)
Professor of Molecular Biology
University of Texas Southwestern Medical Center

Activating the immune system through nucleic acid recognition

Humanity has survived to this day by fighting off pathogenic infections caused by viruses and bacteria. The mechanism that identifies pathogens in the body as "foreign" and defends the body is called the immune system.

The immune system has two sub-systems called the "innate immune system," in which the central role is played by macrophages and dendritic cells, and the "adaptive immune system," in which T cells and B cells play the central role. (See Figure 1.) Innate immune cells swiftly detect pathogens that have invaded the body, whereupon they produce cytokines and present pathogen-derived antigens on the surface of the cell. These two actions induce the adaptive immune system to activate cells with characteristics that match the pathogen, and to produce antigen-specific antibodies. Antibody-producing cells differentiate into memory cells that remain in the body for a long period of time, which allows them to rapidly produce antibodies and prevent infection whenever the same pathogen invades the body again.

It was already known that part of the immune response was the activation of the immune system by nucleic acids such as pathogen-derived DNA and RNA, but how that led to the activation of the adaptive immune system remained a major immunological mystery.

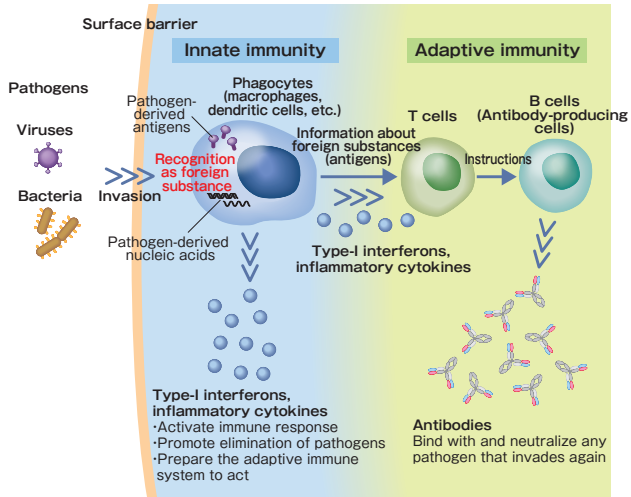


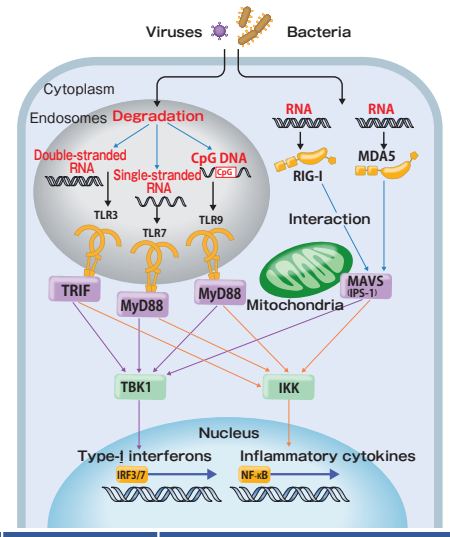
Figure 1: Mechanisms of the immune system

In the innate immune system, phagocytes recognize pathogen-derived nucleic acids as foreign substances, whereupon they release type-I interferons and inflammatory cytokines. This activates an immune response in the surrounding area, eliminating the foreign substance at the same time as it prepares for the adaptive immune system to begin working. This induces adaptive immunity; B cells are activated via T cells, and antibodies are produced.

Establishing the basic principles of nucleic acid recognition in innate immunity

Phagocytes ingest and degrade pathogens and play a central role in innate immunity, but how do they identify substances as pathogens? The end of the 20th century saw the publication of numerous studies that solved this mystery by showing that phagocytes have "sensors" that are able to detect pathogens. (See Figure 2.) A prime example of those sensors are the proteins called "toll-like receptors" or TLRs.

In 2000, Prof. Akira revealed that a TLR called TLR9 recognizes bacterial DNA, and in 2002, he revealed that TLR7 recognizes single-stranded viral RNA. In addition, he contributed to the overall understanding of how TLR signaling works by elucidating downstream molecules such as adaptor proteins, kinases, and transcription factors. These discoveries demonstrated for the first time the fundamental



Symbols used in figure above	Name	Function
	Sensor	Recognizes viral/bacterial DNA and RNA
	Adaptor protein	Binds to sensors and transmits information it receives to other molecules
	Kinase	An enzyme that turns substrates on or off through phosphorylation
	Transcription factor	Activates cytokines and other immune-related genes

Figure 2: Sensors and signaling used for nucleic acid recognition in the innate immune system

Phagocytes ingest pathogens that have invaded the body and detect pathogen-derived nucleic acids in the phagocytic endosomes and cytoplasm. TLRs on the endosomal membrane detect double-stranded viral RNA(TLR3), single-stranded RNA (TLR7), and unmethylated CpG sequences specific to bacterial DNA (TLR9), while RIG-I and MDA5 detect viral RNA in the cytoplasm. These sensors use adaptor proteins and kinases to activate transcription factors, which results in the production of type-I interferons and inflammatory cytokines.

principles through which innate immunity works: by directly identifying pathogen-derived nucleic acids and triggering an immune response.

Prof. Akira also genetically modified mice to clarify the roles of RIG-I and MDA5, which detect viral RNA in cytoplasm, and the molecules that act downstream of them. He discovered that pathogen-derived DNA in cytoplasm is detected not by TLRs but by distinct sensors that induce the immune response, which laid the foundation for research into the DNA response system that was later developed and clarified by Prof. Chen and other researchers. (Further explanation below.)

These discoveries have advanced our understanding of immune-system-related diseases to a significant extent. Furthermore, identifying the mechanisms by which nucleic acids activate the innate immune system led to the development of nucleic-acid-based adjuvants (substances used in vaccines to enhance an immune response) and provided a molecular foundation for the mRNA vaccines developed during the COVID-19 pandemic.

The cGAS-STING pathway: sensing cytoplasmic DNA

The research of Prof. Akira established the fundamental principles through which nucleic acids are recognized in the innate immune system. However, the key unsolved point in that framework was the sensor that detects pathogen-derived DNA in cytoplasm. Prof. Chen was able to provide a clear answer to that as-yet unresolved puzzle, and in doing so, he pushed research into innate immunity to the next stage.

In 2013, Prof. Chen identified a sensor protein that detects cytoplasmic DNA called cGAS. (See Figure 3.) He went on to unravel the cGAS-STING pathway, through which cGAS detects DNA and produces cGAMP, which then triggers an immune response via a protein called STING. This pathway was thus revealed to be an important defense mechanism against infection by DNA viruses.

The cGAS-STING pathway also plays a role in triggering an immune response through detecting DNA abnormalities in cancer cells. This pathway can currently be artificially activated using small molecules, and investigations are actively underway into how this pathway can be targeted in cancer immunotherapy.

It was later discovered that bacteria also use a DNA recognition system similar to cGAS when detecting phage virus infections. This illustrates that the mechanism of sensing nucleic acids to initiate immune responses is an evolutionarily conserved defense strategy that is universal.

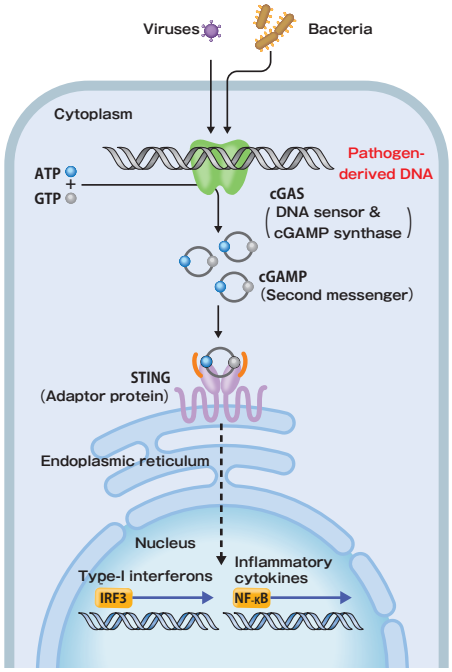


Figure 3: The cGAS-STING pathway

When pathogen-derived DNA exists in cytoplasm, it is detected by cGAS, which produces the second messenger cGAMP. cGAMP then binds to STING and activates it, which induces the production of type-I interferons and inflammatory cytokines.

How these discoveries have contributed to medical research

It is evident that the research efforts of Professor Shizuo Akira and Professor Zhijian "James" Chen have complemented each other in clarifying how nucleic acids are recognized in innate immunity. (See Figure 4.) Their discoveries transformed our overall grasp of innate immunity, significantly advanced our understanding of infectious diseases and immunology, and have opened new avenues of study for vaccine research.

Their research has directly contributed to improving the health and welfare of humanity, and it is already being used in vaccine development and other aspects of medical care. Their research is expected to lead to even more innovative applications in the treatment of autoimmune diseases and cancer in the future.

	Prof. Shizuo Akira's Research	Prof. Zhijian Chen's Research
2000	Identification of TLR9, which recognizes bacterial DNA	
2002	Discovery of RNA-like compounds (imidazoquinoline compounds) which activate immune response via TLR7	
2005	Identification of MAVS (IPS-1) downstream of the RIG-I and MDA5 pathway in cytoplasmic virus response	Identification of MAVS (IPS-1) downstream of the RIG-I and MDA5 pathway in cytoplasmic virus response
2006	Clarification of the role of cytoplasmic RIG-I and MDA5, which recognize different viral RNAs	
2013		Discovery of cGAS, which recognizes cytoplasmic DNA, and clarification of the cGAS-STING pathway

Figure 4: Major achievements by these two researchers that clarified the mechanisms of nucleic acid recognition