
Preface

All living organisms are continuously exposed to foreign entities including food, microorganisms, and unnecessary self-metabolites, thus creating a need to discriminate dangerous non-self from safe self entities, particularly life-threatening microorganisms that invade the body. The vertebrate immune system has evolved two arms of defense against invading pathogens: innate (natural) immunity and adaptive (acquired) immunity. A great deal of immunology research revealed that adaptive immunity has two sophisticated systems designated self- and non-self-discrimination by which T and B cells, both of which express highly diverse antigen receptors generated through DNA rearrangement, are thereby able to respond to a wide range of potential antigens.

In contrast, innate immunity had been regarded as a relatively non-specific system whose two main roles were engulfing and destroying pathogens. The innate system also triggers pro-inflammatory responses and is involved in antigen presentations to prime adaptive immune responses.

Recent studies have shown that the innate immune system has a greater degree of specificity than was previously thought. The system has a highly developed ability to discriminate between self and foreign entities, including microorganisms and unnecessary self molecules including proteins, and lipids, as well as nucleic acids that constitute the main topic of this book. Why and how the innate immune system discriminates self and non-self nucleic acids will be discussed in particular detail by the groups of Wagner and Stacey (DNA) and Kariko, Diebold, Hornung, Bauer, and Colonna (RNA).

This discrimination relies, to a great extent, on pattern-recognition receptors (PRRs) including Toll-like receptors (TLRs), Nod-like receptors (NLRs) and the recently described RIG-I-like receptors (RLRs) that play a crucial role in early host defenses against invading pathogens, as described in the chapters contributed by the groups of Wilson, Kawai, Kato, Kaisho and Krug. These germ line-encoded PRRs are expressed constitutively on both immune and non-immune cells, and recognize conserved microbial components known as pathogen-associated molecular patterns (PAMPs).¹ After recognition, each PRR activates specific signaling pathways, leading to robust but highly defined innate immune responses, followed by protective adaptive (antigen-specific) immune responses to pathogens.

PAMPs have triggered considerable interest in nucleic acids in the field of immunology. While nucleic acids such as DNA and RNA are essential components of all living organisms, accumulating evidence over the last several decades suggests that nucleic acids function as essential ultimate units of life and also stimulate the immune system when they are released from pathogens.^{2,3} Their connection to pathogens attracted little attention in the past, but the link is in the limelight after the recent discovery of TLRs.^{4,5}

Structure- and sequence-dependent immune recognitions of nucleic acids by TLRs were shown to play an important role in both innate and adaptive immune

responses to infectious organisms, including bacteria, viruses, and parasites.^{6,7} Novel therapeutics include nucleic acid-based agonists and antagonists via TLR-mediated immunomodulation, and including the use of CpG DNA as a potent TLR9 agonist are under development for multiple applications to prevent or treat infectious diseases, allergic disorders, and cancers (detailed by Krieg, Verthelyi, Klinman and Broide).

On the other hand, the innate immune system that fights infection also seems to have an important role in clearing unnecessary or abnormal host molecules including nucleic acids. In fact, the system possesses specialized sets of genes including TLRs that facilitate clearance in cases of trauma, tumor, and autoimmune diseases,^{8,9} as summarized in the chapter by Rothstein. This role of the innate immune system is important. Initial dogma dictating that the system including TLRs discriminates infectious non-self from non-infectious self nucleic acids has been challenged by findings that host (self) nucleic acids are no longer inert in the immune system under certain conditions. Thus, the one or more elements within DNA and RNA (sequence, modification, structure) recognized by the innate immune system constitute an important issue that must be clarified to further explain this system. This book reviews recent advances in our understanding of the innate immune recognition of nucleic acids, and describes the resulting immune modulation through TLR-dependent or -independent pathways.

We would like to acknowledge some of the pioneering works that appeared long before the studies in this book were published. In 1963, two independent groups, including one led by Alick Isaacs who discovered interferon, reported that DNA and RNA derived from pathogens or host cells activated chicken and mouse fibroblasts to produce interferon (IFN).¹¹ The other pioneering work in 1984 by Tokunaga and colleagues showed that a DNA fraction isolated from BCG activated both human and mouse non-B, non-T cells to produce type I IFNs.¹² They also demonstrated that bacterial, and not mammalian, DNAs are immunostimulatory and can be reproduced by short, single-stranded (ss) oligodeoxyribonucleotides (ODNs) containing palindromic GC-rich sequences.¹³

Finally, we hope that our book will provide insight into the new areas of immunology, nucleic acid recognition, and regulation by innate immune systems.

Ken J. Ishii and Shizuo Akira

Research Institute for Microbial Diseases
Osaka University

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Dr. Ishii is currently a professor at the Research Institute for Microbial Diseases of Osaka University in Japan. He is also affiliated with the Japan Science and Technology Agency where he serves as a group leader of the Akira Innate Immunity Project. Dr. Ishii graduated from the medical school of Yokohama City University, now in Japan. After years of clinical work, he joined the United States Food and Drug Administration where he worked as an immunologist and reviewer for vaccine clinical trials. Since then, his research has focused on how the immune system can recognize various agents, including RNA and DNA, and the physiological relevance of RNA and DNA to infectious diseases, allergies, cancer, and autoimmune diseases.

Dr. Ishii is also interested in developing vaccine and/or immunotherapies including various viral infections, allergic, metabolic, and autoimmune diseases. He was singled out in September 2007 as a Rising Star by Thomson Scientific, Inc. (Optimize for Scientific Information) after achieving the highest percentage increase in total citations in the immunology field. He was recently named an expert and member of the Independent Peer Review Panel of the National Institutes of Health in 2007.

Dr. Shizuo Akira is currently a professor at the Research Institute for Microbial Diseases of Osaka University, and a group leader of the Akira Innate Immunity Project of the Japan Science and Technology Agency. He was recently appointed a director of the Frontier Immunology Research Center at Osaka University.

Dr. Akira is a leading immunologist and has made many contributions establishing the importance of innate immunity. He has received many awards in Japan and abroad, including the Robert Koch Prize. His work on Toll-like receptors is highly regarded worldwide, and he has lectured at a number of international conferences including Keystone Symposia, Gordon Conferences, Nobel Forum, and meetings dealing with immunology and infectious diseases. He has published over 500 papers, and is one of the most cited immunologists. He was recognized in 2006 and 2007 by the Institute for Scientific Information as the scientist who published the greatest number of "hot papers" during the preceding two years.