PREFACE

I came to know the word *immunity* in Chinese for the first time when I was given a shot of vaccine during my childhood in my hometown, a small town called Poyang Town, named after the largest freshwater lake of China, Poyang Lake, near the middle of Yangtze River, in Jiangxi province, China. After elementary school, middle school, and high school in Poyang, I was admitted to Sun Yat-sen University (SYSU), my first alma mater. At university, I had a chance to learn the basic terms of immunology, such as *antibody* and *antigen*, with a major in biology. After graduating from SYSU, I was awarded a government scholarship to study in the United States in 1985, and was eventually admitted to the PhD program of Immunogenetics at the University of Illinois at Urbana-Champaign (UIUC) in 1986. Under Dr Harris Lewin's supervision, I became fascinated by the complexity and diversity of animal and human immunity, which prompted me to question how this immunity originated and how it was formed during the evolutionary process. In addition to my scientific curiosity, my way of thinking about scientific questions and conducting scientific experiments was completely established by my PhD mentor's hard training, which has influenced my scientific career ever since. After graduating from UIUC, my second alma mater, with both MS and PhD degrees, I was fortunate to work with a world-famous physician scientist, Dr Helen M. Ranney, a professor in the Department of Medicine, University of California San Diego (UCSD), in 1992 as her last postdoctoral student. I then went with Dr Ranney to work at a San Diego–based pharmaceutical company, Alliance Pharmaceutical Corporation, after completing my postdoctoral research. Dr Ranney has also had a great influence on my scientific career, like Dr Lewin. In 1996, in consultation with these two important persons in my scientific career, I decided to come back to China to join the faculty of the Department of Biochemistry, College of Life Sciences.

The first thing I decided to do for my scientific research after returning to China was to start something new that could use my scientific training in the United States and explore new avenues in the field of immune research. I had many ideas about my new research direction, and one of the most important for me was to understand the origin and evolution of human immunity. However, I had no idea about which model species to use in pursuit of this very important goal. It took me 1 year to figure out that amphioxus was *the* model organism to address my question best, and another 2 years to establish a laboratory-based aquaculture system of amphioxus and the infection model for understanding the host immune response to infection. This made my laboratory a global pioneer in the study of amphioxus immunity, although this species had been an iconic model for evolutionary biology for more than 200 years. Instead of using conventional immunological methods only, my laboratory combined traditional immune methods

with cellular, biochemical, and molecular approaches, particularly a genomic approach, to conduct a comprehensive survey on the immune response of amphioxus to bacterial infection from the beginning. This gave us a quick opening for this brand new field. For last 15 years, my laboratory has contributed more than 50 papers related to amphioxus immunity. In summary, our contributions to the field of amphioxus immunity, with the aim of understanding the origin and evolution of vertebrate immunity, especially human immunity, can be briefly described as follows:

1. Genomic analysis of the immune gene repertoire of amphioxus reveals extraordinary innate complexity and diversity, suggesting that our chordate ancestors had a remarkably elaborate innate immune system, but this system was somehow reduced in the vertebrate lineage. This finding provides obvious evidence for the so-called "immunological big bang" to explain the origin of vertebrate immunity.
2. Functional analyses of important innate immune genes in amphioxus involved in two basic forms of innate immune signaling, TLR and TNF signaling, suggest that the basic frameworks for these two signaling pathways were established at the basal chordate, which have laid the foundation for the eventual formation of these two pathways in vertebrates.
3. Identification of lymphocyte-like cells, along with related transcription factors and signaling molecules for lymphoid proliferation and differentiation, indicates the emergence of adaptive immunity for vertebrates along with some basic components for adaptive immunity. The finding of an extrinsic apoptosis pathway in amphioxus further substantiates the claim for the beginning of adaptive immunity in the basal chordate, because the extrinsic apoptosis pathway is generally believed to have coevolved with adaptive immunity. Most recently, the two key genes for the V-D-J rearrangement of immunoglobulin, RAG 1- and RAG 2, were identified in amphioxus and found to have a similar fanction like their vertebrate counterparts.
4. In addition to tracing the origin of the existing system for immune response and regulation in vertebrates, including humans, we may be able to reveal a novel mechanism involved in immune regulation, which has never been described in other organisms by studying this animal model. It includes finding novel molecules for immune recognition and novel mechanisms for immune regulation epigenetically by alternative 3' UTRs.
5. In the immune signaling system, most proteins have characteristic and conserved multiple domains that exert specific functions in proteins so as to interact with specific molecular partners. Our studies on amphioxus immune signaling molecules indicate that different combinations of these domains (e.g., CARD, TIR, DFD, DEATH) are the evolutionary sources for the generation of new signaling molecules that can result in interaction specificity. Understanding the evolutionary mechanisms of these domains and their shuffling for the generation of new proteins, with new functions, should provide a novel vista for synthetic

biology and insights that may help in the treatment of diseases associated with mutated protein activity.

Finally, I would like to thank all my students who have made significant contributions to our understanding of amphioxus immunity. I would not have come this far without their diligent and intelligent work on this research. I would also like to thank Professors Xu Xun of the Third Institute of Oceanography, State Oceanic Administration of China, Zhang Shicui of Ocean University of China, Zhang Hongwei of Shandong University, Zhang Peijun of Institute of Oceanology, Chinese Academy of Sciences (CAS), Wang Yiquan of Xiamen University, Chen Junyuan of Nanjing Institute of Geology and Palaeontology, CAS, Gao Fu of the Institute of Microbiology, CAS, Peng Xuanxian of Sun Yat-sen University, and Liu Xiaolong of Shanghai Institutes for Biological Sciences, CAS, for their scientific comments and academic discussions on my research. I would also like to thank Professors Linda and Nick Holland of the Institute of Oceanography, University of California, San Diego, David Schatz of Yale School of Medicine and Hector Escriva of CNRS UMR, UPMC University of Paris, Banyuls, France, for their academic communication and exchanges about my research. In particular, I would like to thank Professor Max Cooper of Emory University School of Medicine, Atlanta, GA, USA, for his long-time enthusiastic support to my research; his important foreword to my book is deeply appreciated.

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