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Non B cell-Derived Immunoglobulins

The Structure, Characteristics and the Implication on Clinical Medicine

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Foreword

The earliest studies of adaptive immunity focused on the analysis of serum immunoglobulin (Ig) produced in response to challenges from pathogens. Ig was first discovered as an antibody, and it has long been regarded as an immune defense molecule; its non-antibody activity has been neglected. The origin and generation mechanism of Ig have been a mystery, and a number of hypotheses regarding the mechanism of Ig production, including the template hypothesis, natural selection hypothesis, and clonal selection hypothesis, were proposed and accepted at different periods in immunology history. It was discovered only in the 1960s that B cells, not other immune cells, were found to be able to produce high-level antibodies. Susumu Tonegawa revealed that Ig gene recombination is a necessary condition for the generation of Ig in B cells at the end of the 1970s; thereby, the concept that Ig is only produced by B cells has been established and widely accepted. Prof. Qiu from Peking University revealed that Ig can also be widely produced by non-B cells; these Igs display not only antibody activities but also cellular biological activities under physiological conditions. Moreover, it has been documented that these Igs maintain the basic life activities of cells by promoting cell proliferation and adhesion. In addition, Ig produced by non B cells directly participates in the pathological process of malignant tumours and immune-related diseases, such as kidney disease; importantly, Igs were proven for the first time to be produced by malignant tumours, and this type of Ig has a strong tumour cell growth-promoting effect. Prof. Qiu's finding has been supported by more results from different labs around the world. The initial discovery of the existence of non B-derived Igs has evolved into a comprehensive study on non B-Ig, not only for its role in basic immunology but also for its potential clinical applications.

The book covers non B-Ig-related basic immunology and the fundamental principles relating to clinical immunology. It is designed for immunologists, clinicians, and postgraduate students who have basic immunological knowledge. With the rapid advancement in immunology, this book, I believe, will help us to broaden our understanding of immunology and the pathogenesis of various immune-related diseases.

Beijing, China — Youhui Zhang

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This book is designated as the comprehensive collection of research work related to non B immunoglobulins, which were initially discovered over 30 years ago. Much about the origin, structure, physicochemical characteristics as well as functions of non B-Ig has been unveiled. I am grateful to Prof. Youhui Zhang (Institute of Oncology, Chinese Academy of Medical Sciences) for his encouragement and comments since he served as a reviewer of my Ph.D. thesis; the completion of the non B-Ig-related research would not have been possible without his unwavering support. I am grateful to Prof. Peter J Delves (University College London) for his patience, commentary, and discussions as the manuscripts took shape. His professional experience is invaluable to the entire project. I would also like to extend my gratitude to all the authors of this book, including young clinicians and immunologists. Their significant contributions to the writing of the book, despite their demanding clinical and research commitments, have been crucial, especially as the whole project took longer than anticipated. They also provided professional suggestions for clarity and accuracy.

Many individuals have supported our research in various ways over the past 20 years. The realisation of this book was made possible only when all initial hypotheses were validated. I am grateful to Prof. Guizhen Yang (Norman Bethune Health Science Centre of Jilin University, my Ph.D. supervisor) and Prof. Peixian Tang (Academy of Military Medical Sciences, my post-doctoral supervisor) for their steadfast support. My gratitude also goes to Prof. Lieping Chen (Yale University) for his support, particularly his assistance in revising my manuscripts, which were first published in Cancer Res, 2003. I must also express my sincere appreciation to Prof. Wei He, Prof. Xuetao Cao, and Prof. Bo Huang (Institute of Basic Medicine, Chinese Academy of Medical Sciences), Prof. Zhigang Tian (Institute of Immunology, University of Science and Technology of China), Prof. Xiyun Yan (Institute of Biophysics, Chinese Academy of Sciences) for their affirmation and robust support of this study; Prof. Ning Fu (Southern Medical University) for her selfless help and encouragement over the past 20 years; Prof. Yang Ke, Weigang Fang, Dalong Ma, Yuxin Yin, Xian Wang, You Wan, Baoxue Yang, and Wei Kong (all of Peking University) for their long-term support. My gratitude is extended to my collaborator Prof. C. Cameron Yin (the University of Texas MD Anderson Cancer Centre, USA), Prof. Youli Zu (Weill Medical College, Cornell University, USA), Prof. Yupei Zhao (Union Hospital, Chinese Academy of Medical Sciences), Prof. Tao Xu (Peking University

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About the Editor

Dr. Xiaoyan Qiu Prof. Xiaoyan Qiu is the director of the Department of Immunology at the School of Basic Medical Sciences, Peking University, and also the director of the Key Laboratory of Medical Immunology, Ministry of Health, China. Her research focuses on non-B cell-derived immunoglobulins and cancer immunotherapy. In 1989, she was the first to discover that immunoglobulins can be produced by non-B cells, including normal cells, and are highly expressed in malignant tumor cells. These non-B-Igs play important roles in physiological and pathological conditions, such as antibody functions, immune regulation, maintenance of cellular growth and survival, as well as mediation of inflammation and tumor occurrence. She has published more than 80 articles in international peer-reviewed journals, such as Cancer Research, Leukemia, and Cellular & Molecular Immunology. Her discovery on non-B Igs has breakthrough implications for basic and clinical immunology.

Dr. Jing Huang is an Associate Professor of Immunology at Peking University. Dr. Jing obtained her Ph.D. degree in Immunology at Peking University in 2008. From 2013 to 2014, she was a visiting scholar in the Department of Cancer Immunology & AIDS at Dana-Farber Cancer Institute. Her research interests include cancer immunology and immunotherapy. In recent years, her research has focused on emphasizing non-B cell-derived immunoglobulins that regulate tumor immunity. Dr. Jing has published more than 30 peer-reviewed papers in international journals including Cancer Research, Cellular & Molecular Immunology, and Brain Behavior and Immunity. She also serves as a reviewer for several peer-reviewed immunology and cancer journals.

Dr. Xiaojun Xu graduated from University College London (UCL) with a Ph.D. degree. He then worked at King's College School of Medicine and Dentistry (London) and Royal London Hospital before joining the Department of Immunology at Peking University as an associate professor in 2003. Dr. Xu has been engaged in teaching immunology for a long time and has a deep understanding of immunology theory. His research interests include autoimmune diseases, primary immunodeficiency diseases, and immunotherapy.

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Part I

Non B Cell-Derived Immunoglobulins: From Gene to Structure and Function

1 Non B Cell-Derived Immunoglobulin, A Brighter Horizon for the Future

Ming Chu, Ning Fu, Liang Zhang, Meng Yu, Youhui Zhang, and Xiaoyan Qiu

Abstract

The canonical theory of immunology stating that "Immunoglobulin (Ig) is produced by B lymphocytes and exerts antibody activity" has been established since the 1970s. However, the discovery of non B cell-derived Igs (non B-Igs), which can exert multiple biological activities in addition to their antibody activities, necessitates a reevaluation of the classic concept of Ig. This has been documented with a number of characteristics related to their structure, modification, genetic regulation as well as the functions associated with clinical conditions, particularly multiple cancers. The discovery of non B-Ig provides us with a new perspective to better understand not only basic immunology, but also various Ig-related clinical manifestations including autoimmune diseases, chronic inflammation, and anaphylaxis. Notably, non B-Ig can directly promote the occurrence of malignant tumours.

Keywords

Non B cell-derived immunoglobulins (non B-Igs)

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1.1 The Historical Background and Limitations of the Classic Theory About the Formation, Structure, and Function of Ig

1.1.1 The Broadly Accepted Classic Concept That Ig Only Exhibits Antibody Activity Needs to Be Reevaluated from a Fresh Perspective

The discovery of Ig began with the identification of the antibody. In 1890, von Behring and Kitasato first identified an "antitoxin" produced as a result of injecting diphtheria toxin into animals (Fig. 1.1) (von Behring et al. 1991). Over

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the subsequent decade, antibactericidal substances were frequently reported in animal serums. Preiffer and Bordet noted the lysis of *Vibrio cholerae* in the intestines of immunised guinea pigs and dubbed the substance responsible as bacteriolysin (Pfeiffer 1895). Gruber and colleagues found that serums from animals immunised with bacteria could induce bacterial agglutination, and the substance causing this agglutination was termed agglutinin (Scheibner et al. 1977). Subsequently, antitoxin, bacteriolysin, and agglutinin were collectively referred to as "antibody (Ab)", and the substance that could induce the production of Ab became known as an antigen (Ag).

From these early observations, the concept of antigen and antibody became firmly established. However, the nature of the antibody was unclear until 1937 when Tiselius and, separately, Kabat and coworkers used serum electrophoresis to discover that the level of gammaglobulin in serum increased significantly following Ag immunisation (Fig. 1.1). Furthermore, the gammaglobulin demonstrated clear antibody activity, leading to the proposal that gamma globulin was indeed the antibody (Tiselius 1937). In 1968, a special committee of the World Health Organisation (WHO), and in 1972, the International Society for Immunology, defined proteins with either antibody activity or antibody structure as immunoglobulin (Ig) (Fig. 1.1). Although a few exceptions, such as Ig produced by multiple myeloma, have been found to have an antibody structure but not the immune defence activity, Ig has not been identified to have other activities. Thus, the concept of "Ig function equates to antibody" has been generally accepted. Yet, it has never been explained why vertebrates produce large amounts of Ig at nearly constant levels daily without antigen stimulation conditions, and whether the Ig might serve some non-antibody function, apart from immune defence. Recently, we have found that Igs, including IgM, IgG, and IgA, are abundantly present in T cell-deficient nude mice. However, the nude mice are unable to produce specific IgG or IgA antibodies against specific antigens when immunised with thymus-dependent (TD) antigens. Further analysis showed that IgG in the circulation of nude mice often combined with other molecules, such as apolipoprotein and cytokines. This discovery suggests that Ig not only exhibits antibody activity according to the classical concept but also performs various biological activities that have yet to be identified.

1.1.2 Several Influential Hypotheses Had Emerged Regarding the Mechanism of Antibody Production

In the annals of history, several significant doctrines about the source of antibodies have emerged. Before the 1960s, immunologists were primarily focused on the biochemical process of

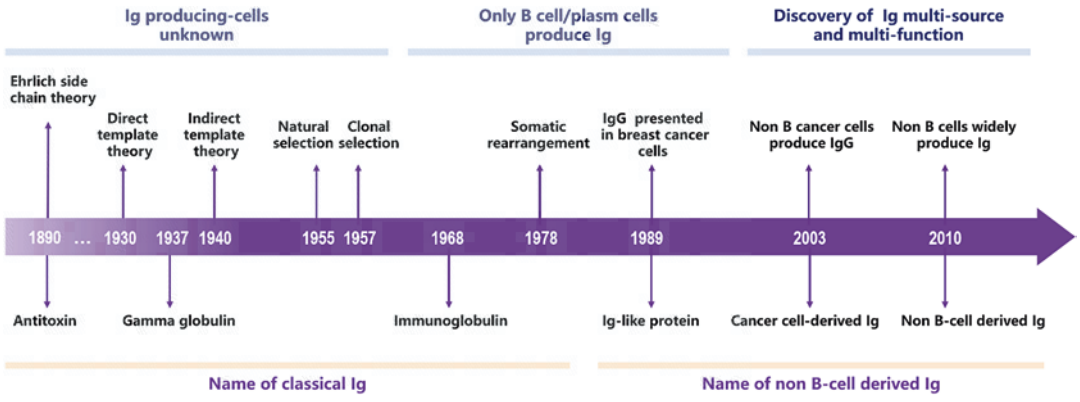

Fig. 1.1 A historical briefing of immunoglobulin

antibody production, rather than the actual cell types producing the antibodies. In 1897, Paul Ehrlich proposed the "side chain theory", suggesting that antitoxin molecules on the cell surface (i.e., cell receptor) recognised the toxin entering the body. After the invasion of the toxin into cells, the cells stimulated by the toxin produced more anti-toxin molecules from the cell surface and released them into the bloodstream (Ehrlich 1900). However, due to the inability to explain the issue of antibody diversity, this hypothesis had not been widely accepted. In 1930, Haurowitz put forward the "direct template hypothesis" that antigen molecules serve as templates that determine the structure of antibodies (Breinl et al. 1930). Nevertheless, the "direct template hypothesis" couldn't account for immune memory. Accordingly, Pauling and colleagues modified the "direct template hypothesis" and proposed an indirect template hypothesis, wherein rather than being guided directly by the antigen to synthesise antibodies, the antibody-producing cells produced a corresponding structure using the antigen as a template, and integrated the corresponding structure into their genomes and transmitted the genetic information to their daughter cells (Pauling 1940). In 1955, Jerne proposed the "natural selection hypothesis", which posited that under normal conditions, the body synthesised various specific antibodies in advance, known as natural antibodies (Fig. 1.1). Upon the entry of an antigen into the body, it selectively binds to the corresponding antibodies, which then stimulates the antibody-producing cells to produce more such antibodies (Jerne 1955). In 1957, Mac Farlane Burnet further proposed the "clonal selection hypothesis", wherein the body produced a variety of clones of immune cells, each expressing a specific receptor generated by genetic somatic mutation (Fig. 1.1). When a particular receptor was selected and bound by its specific Ag, the process induced clonal proliferation and antibody production (Mackay 2008). Following the formation of specific cell clones, some would divide to form memory cells. In addition, the immune cells recognising antigens during the embryonic phase would either be inhibited or undergo apoptosis, thus establishing immunological tolerance to the corresponding antigens. This theory explained most immunological phenomena exquisitely.

1.1.3 B Cells and Plasma Cells Have Been Found to Secrete Antibodies

In the 1960s, immunologists began to identify Ig-producing cells. As the function of Ig was first discovered through its antibody activity, immunologists principally focused on immune cells, but not on other types of cells, in their search for Ig-producing cells. Gowans discovered that a graft versus host reaction occurred following the transplantation of small lymphocytes (Gowans 1962). Additionally, after irradiation, there was a significant reduction in both the number of small lymphocytes and antibody production. These results implied that antibody-producing cells were part of the small lymphocyte population. Subsequent findings using immunofluorescence staining with anti-isotype serum showed that Ig could be located on the membrane of bone marrow-derived lymphocytes (B cells), but not the thymus-derived lymphocytes (T cells). Following on from this, Miller and his colleagues found that bone marrow-derived B cells could differentiate into plasma cells to produce secreted antibody (Miller 1961). As a result, the concept of antibodies/Ig being generated by B cells/plasma cells became widely accepted. Logically, the "immunocompetent cells" in Burnet's "clonal selection theory" were replaced by "B cells". However, whether non B cells could also produce Ig was largely overlooked.

1.1.4 The Concept That "Only B Cells/Plasma Cells Can Produce Ig" Was Further Reinforced by a Misinterpretation of the Findings by Susumu Tonegawa

For a long period, immunochemists recognised that Ig demonstrates an incalculable diversity within an individual, with the diversity primarily located in the first functional domain at its N-terminus (known as the variable region). The mechanism behind this Ig diversity remained a mystery. Australian immunologist Frank Macfarlane Burnet once proposed that the genes encoding the Ig variable region consisted of different gene fragments, with their diversity stemming from the random rearrangement of these gene fragments. In 1978, Suzumu Tonegawa confirmed Burnet's hypothesis for the first time (Fig. 1.1). Tonegawa discovered that Ig genes encoding the Ig variable region did indeed include numerous variable (V), diversity (D), and joining (J) fragments within the genome, which could be randomly rearranged to form diverse VHDJH (for Ig heavy chain) or VLJL (for light chain) genes. For this significant discovery, Tonegawa Susumu was awarded the Nobel Prize in Physiology or Medicine in 1987 (Brack et al. 1978; Tonegawa et al. 1977, 1978; Tonegawa 1976). In his study, Tonegawa utilised a mouse myeloma cell known to produce Ig as a model and used the mRNA of the Igκ produced by the myeloma cell itself as a probe. He demonstrated through a Southern blot that there was Ig gene rearrangement in the genome of the myeloma cell, while no band of Ig gene rearrangement was observed in the mouse embryonic tissue, liver tissue or spermatid used as a negative control. This result is consistent with the notion of "B cells/plasma cells generate Ig" mentioned above, which further reinforced the concept of "only B cells/plasma cells generate Ig"—a concept that has been documented in immunological textbooks to this day. It is important to note that this is entirely a historical misunderstanding, limited by the insufficient understanding of scientists at the time regarding Ig diversity and Ig gene rearrangement mechanisms. It has since been revealed that different cell types can exhibit different VHDJH or VLJL rearrangement patterns. It should be highlighted that the probe used to analyse the VLJL rearrangement on the genome in the mouse myeloma cells by Tonegawa was the Igκ chain mRNA from the myeloma cells themselves, not from other tissues. As a result, it is reasonable that only the myeloma cells themselves, but not the mouse embryos, liver tissues, and spermatogenic cells, showed the Igκ rearranged band. In fact, Zheng et al. confirmed that epithelial cancer cells and normal tissue cells can also express Ig, and both VHDJH and VLJL expressed by non B cells displayed unique rearrangement characteristics (Huang et al. 2008; Zheng et al. 2009). This implies that the classical concept "only B lineage can produce Ig" needs to be corrected.

1.2 The Discovery and Identification of Non B Cell-Derived Igs

A growing body of evidence demonstrates that, in addition to B cells' capability of producing Ig (B-Ig), non B cells broadly produce Ig (non B-Ig). Moreover, non B-Ig presents features distinct from traditional B-Ig in variable region sequence, physicochemical properties, and function.

1.2.1 Non B Cell-Derived Ig Was Initially Discovered in Epithelial Tumour Cells

In 1989, Qiu first discovered that IgG staining was clearly present in breast cancer cells, but not in epithelial cells of normal breast and benign breast tumour tissues (such as fibroadenoma) (Fig. 1.1). Subsequently, Qiu and colleagues found that IgG is also present in a range of other malignant tumour cells. Importantly, Ig gene rearrangement, a specific event once thought to solely occur in B cells, was also found in these