Molecular Biology of B Cells

Second Edition

Edited By

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Dedication

To Michael Neuberger (1953–2013)

We wish to dedicate this volume to the memory of Michael Neuberger, who was a coauthor of the prior volume, wonderful colleague, and truly outstanding B-cell biologist. In his lab at the MRC laboratory of Molecular Biology in Cambridge England he made groundbreaking contributions to elucidate the mechanisms of antibody gene regulation and antibody repertoire diversification. His work was characterized by his careful but very innovative approaches and his remarkable scientific insight.

Neuberger's earlier studies led to his discovery of major enhancer elements downstream of the IgH and Igκ loci, which have been shown to play critical roles in the secondary diversification of antibody genes. The enhancers that Neuberger first found downstream of IgH are now known to be important both for regulation of IgH class switch recombination (CSR), which generates different antibody classes through a DNA breakage and joining mechanism, as well as for IgH variable region somatic hypermutation (SHM) which provides the basis for antibody affinity maturation. In another line of research, Neuberger, together with Greg Winter, was the first to use recombinant DNA techniques to generate human antibodies with desired antigen binding specificities. He also collaborated with Marianne Bruggemann to pioneer the development of human antibody production in transgenic mice. His work in these areas helped lay a foundation for the development therapeutic human antibodies, which now have proven so successful in the clinic.

Neuberger's more recent work on how antibody genes are further diversified by a DNA deamination mechanism has been among his most important and influential. One of the coauthors of this volume, namely Tasuku Honjo discovered the activation-induced cytidine deaminase (AID) and showed that it is required for CSR as well as for SHM. A mystery at the time of the discovery was how the small AID protein could initiate DNA breaks during CSR and mutations during SHM. Neuberger, along with Mathew Scharf and others, proposed that AID could serve this dual role by deaminating deoxycytidines in Ig loci to trigger a cascade of events that lead to DNA double-strand brakes during CSR and mutations during SHM. Neuberger's model was based on his careful, several decade-long studies of the SHM process of antibody genes. Following up on his model, Neuberger performed a beautiful series of genetic studies that provided compelling evidence for his DNA deamination model of AID function in SHM and IgH class switching, a model, which is now widely accepted by nearly all workers in the field and that has formed the basis for their ongoing studies.

Beyond science, Michael was a warm and enthusiastic individual with quite diverse set of interests in history and literature, as well as in various sports. Interacting with him both scientifically and personally was always a great pleasure. It was a privilege to have him as a friend. Michael also was well known as a great mentor and leader. His outstanding scientific contributions and leadership have been acknowledged by many prestigious awards including his recent election as a Foreign Associate of the US National Academy of Sciences which acknowledged both his leadership and discoveries outlined above on antibody diversification.

Preface

B lymphocytes are an essential part of the humoral immune system and produce the specific antibodies generated during infection or vaccination. Soon after their discovery as antitoxins more than a hundred years ago by Emil Behring and Shibasaburo Kitasato it became clear that antibodies are enormously diverse and can be generated against many different structures. The elucidation of the mechanism underlying the generation of diversity (GOD) of the antibody system kept immunologists busy over the last hundred years. With the discovery of the V(D)J recombination mechanism of the immunoglobulin (Ig) genes and the somatic hypermutation (SHM) processes many aspects of this problem were solved. The discovery of the V(D)J recombinase machinery consisting of the lymphocyte lineage-specific proteins recombination activating gene (RAG) 1 and RAG2 which provide the specific endonuclease function and the generally expressed nonhomologous DNA end joining factors that join RAG-generated DNA breaks was a fascinating development as was the discovery of AID and its associated protein machinery mediating class switch recombination (CSR) as well as SHM and gene conversion. The progress in the B-cell field in this area is well documented by the different editions of this book series which started in 1989 under the title "Immunoglobulin genes" and in 2004 became "Molecular Biology of B cells."

This new edition of the "Molecular Biology of B cells" brings the reader up to date with these Ig diversifying processes. However, this book has now a much broader scope as it covers many different aspects of B cell Biology. B cells are a well-characterized and easily assessable cellular system that can be used to answer many issues of general cell biology. Furthermore due to the availability of several different B cell-specific Cre deleter mice the B cell system is also useful for general gene function studies. These are reasons why many scientists worldwide start to work on B cells although they are not regarded as classical 'B cell immunologists' and for these this book is particularly useful. In fact B cells have served as excellent model systems to study many common biological questions including transcriptional regulation of differentiation, signal transduction, and tumorigenesis. Furthermore, the mechanism of GOD has been considered to be unique to lymphocytes especially B cells as the expression of AID is specific to B cells. Subsequently, however, the DNA repair phases of GOD are shown to be common between B cells and other types of cells, indicating that GOD employs factors that normally are entrusted with preserving genome stability. More recently, IgA synthesis has been shown to influence the whole body metabolic regulation through symbiotic interaction with the gut microbiota. These striking developments convince us that molecular biology of B cells does not only mean molecular biology 'for' B cells but also molecular biology 'through' B cells to understand the whole biology.

The chapters of this new edition of "Molecular Biology of the B cells" have been written by an international faculty of experts in their fields and the readers can expect to get a comprehensive overview about the current status and the future development of the B-cell field. In particular the reader will learn how a B-cell-specific transcriptional network drives differentiation of hematopoietic stem cells (HSC) through B lymphopoiesis and how during their development B cells repeatedly switch between molecular programs promoting proliferation and those involved in differentiation. B-cell research in the age of genomics also means that we now know many more details about the gene expression program of different B-cell developmental stages. This is due to the joint efforts of many scientists, for example those working in the ImmGen Consortium. We also learned much more about the signaling mechanisms controlling the development and activation of B cells. For example, it was found that tumor necrosis factor (TNF) superfamily members such as lymphotoxin and BAFF play an important role in the homeostasis and survival of B cells in the periphery.

New topics that were not at all covered in the last edition of this book are, for example, the role of evolutionarily conserved microRNAs during B-cell development, function, and transformation and the role of IL-10- and IL-35-producing regulatory B cells. Furthermore, jawless vertebrates (lampreys and hagfish) were recently shown to have B cells employing the leucine-rich repeat (LRR)-based variable lymphocyte receptors (VLR), a type of antigen receptor completely different from their mammalian counterpart.

Apart from being a useful tool for basic cell biological and signaling studies B cells are also playing an increasingly important role in the clinic. Genetic defects of the B-cell system are the cause of important human immunodeficiency

diseases. A dysregulation of this system causes autoimmunity or tumor diseases, topics which are both well covered in this new edition. Furthermore, not only the B cells but also their product, namely antibodies made a remarkable career in the recent years. As the reader will learn by reading this book, antibodies are highly versatile tools that are not only used in clinical diagnostics but also play an important role as therapeutic agents. Thus most drug companies have antibody departments and factories that produce antibodies and bring them into the clinic for the treatment of various diseases.

In spite of the importance of B cells in basic research and the clinic, there are still many questions that B biology needs to address in the future. We still have to learn more about how the B cell system distinguishes between self and foreign antigens, in particular after the finding that many newly generated B cells have a certain level of autoreactivity. What is the role of B cells in specialized compartments such as mucosal tissues? The maintenance of B-cell memory and antibody production over a long period of time is also a topic of active research where major breakthroughs are to be expected.

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May, 2014.

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