Falk Nimmerjahn *Editor*

Molecular and Cellular Mechanisms of Antibody Activity

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Preface

The humoral immune system, that is, antibodies produced by B cells, is an essential component of our defense against microbial infections. An impaired antibody response against bacterial, viral, or fungal microorganisms results in a heightened level of infections. This book brings together leading experts in the field of immunoglobulin activity and function to provide the reader with up-to-date information on the mechanisms of action of this class of molecules. During the last years, tremendous progress has been made in understanding how the different immunoglobulin isotypes mediate their activity. This book concentrates on IgM, IgA, and the four different IgG subclasses. We will not discuss the activity and function of IgE, which is covered in detail by other textbooks and reviews. The book is meant for readers with a basic understanding of how the immune system works. We will not introduce the molecular mechanism of how B cells develop and become activated and how immunoglobulin class switching is accomplished. Instead, we will focus on how immunoglobulin molecules recruit the humoral and cellular effector functions of the innate immune system. In Chap. 1, Mikael Karlsson from the Karolinska Institute in Stockholm in Sweden, will discuss the role of IgM and IgD in infection and inflammatory diseases. Jenny Woof from the University College of Dundee in the UK will give an in-depth overview in Chap. 2 of how IgA, the immunoglobulin subclass that dominates the inner body surfaces such as the gut, lung, and saliva, is critical to prevent microorganisms from invading the body at these sites. Chapters 3–8 will then switch to the family of immunoglobulin G subclasses, which are indispensable for protective antimicrobial immune responses. Peter Sondermann, head of research at SuppreMol GmbH in Munich, will start with a detailed insight into the IgG structure (Chap. 3), followed by a chapter (Chap. 4) of Jeanette Leussen from the University of Utrecht in the Netherlands and myself on the molecular and cellular mechanisms involved in the activity of IgG which, on the one hand, prevents infections but, on the other hand, is responsible for the destruction of healthy tissues during autoimmune diseases. Besides this pro-inflammatory activity, IgG is used since many years as an anti-inflammatory treatment to suppress autoimmune pathology. The tremendous advances we have made in understanding this "other side" of IgG activity are summarized in Chap. 5 by myself. Shozo Izui from the

University of Geneva in Switzerland will then provide in Chap. 6 a detailed example of how red blood cell or immunoglobulin-specific autoantibodies (so-called rheuma factors) mediate their activity. Michael Karsten and Jörg Köhl from the University of Lübeck in Germany will introduce the intricate interplay between cellular and humoral effector functions triggered by IgG (Chap. 7), followed by a detailed overview of how IgG half-life is controlled by the neonatal FcRn by Kristi Baker, Timo Rath, and Richard Blumberg from Harvard University in Boston (Chap. 8). Besides connecting the adaptive with the innate immune system, antibodies also feedback on B cells to regulate their own production, which will be introduced in Chap. 9 by Birgitta Heyman from Lund University in Sweden. Finally, Christian Kellner and Matthias Peipp from the University of Kiel in Germany will introduce in Chap. 10 how the function of IgG can be enhanced and which novel formats of therapeutic antibodies are currently used and may be used in the near future.

Last but not least, I would like to sincerely thank all the authors for their contributions and efforts for making this book possible.

Erlangen, Germany Falk Nimmerjahn

Contents

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Chapter 1
IgM and IgD in Infection and Inflammatory Diseases

Mikael Karlsson

Abstract The IgM and IgD antibodies were the first to evolve and are also part of the first line of immune defense against invading pathogens. They are multifunctional proteins that both function as receptors mediating activating signaling on the cell surface and when released, they take on a different role mediating many important functions in the immune system. The effectiveness and usefulness of these proteins is proved by the fact that they have been modified by evolution to give rise to all the other subclasses of antibodies in our immune system. In inflammatory diseases IgM and IgD can have both pathogenic and protective roles depending on the type of disease and tissue affected. In this chapter these dual roles of IgM and IgD is discussed as well as their role in B cell development and infectious disease.

Keywords IgM • IgD • Inflammatory diseases • Immune system • Adaptive immune system • Immunoglobulin domain • Innate immunity

1.1 Evolution of IgM and IgD

1.1.1 Evolution of the Antibody Isotypes IgM and IgD

Even though the principal building blocks of the immune system are well defined, much is still not known about when and how the adaptive immune system evolved to work in cooperation with innate immunity (Pancer and Cooper 2006). The development of antibodies was preceded by the evolution of the immunoglobulin (Ig) domain which is used not only in antibodies but also in, among others, the TCR and

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MHC proteins. The Ig domain is also found in *Drosophila,* for example, in the Dscam proteins that aid in opsonization of bacteria and immune defense. Just as in the mammal antibody coding locus, the so-called Ig locus, the *Dscam* gene is composed of a number of alternative exons that can be put together to create molecular diversity (Ghosh et al. 2011). This recent discovery shows that diversification using Ig domains is used also in invertebrates and that these rely on more than innate immunity and pattern recognition for their immune defense. Furthermore, similar molecules have evolved separately in lamprey and hagfish (agnathans) using leucine-rich repeats to make up variable lymphocyte receptors (Alder et al. 2005). Importantly, this shows a strong selective pressure to evolve this type of diversification. The IgM subclass was the earliest antibody to evolve followed later by IgD (Hadge 1985). IgM is present in jawed vertebrates (gnathostomes) that existed already during the Devon period over 400 million years ago. The IgD subclass is first found in bony fish (teleosts) which is the only organism expressing it besides mammals. However, somatic hypermutation (SHM), a way to further diversify the immune repertoire, has so far only been found in vertebrates (Stavnezer and Amemiya 2004). This mutagenic process can be found in fish and coincides with occurrence of the activation-induced deaminase (AID), essential for this reaction (Muramatsu et al. 2000). AID is also crucial for class-switch recombination (CSR), to other isotypes than IgM and IgD, a process that did not occur until much later in evolution. It has been suggested that this is more due to evolutionary changes in the Ig locus rather than alterations of the AID enzyme itself. Amphibians are the most primitive vertebrates known to use DNA recombination to switch antibody classes. This remarkable diversification process has been kept in every group of animals that developed thereafter, suggesting a strong evolutionary advantage of having CSR.

1.1.2 Evolution of Natural Antibodies and the Germline Repertoire

Natural antibodies are defined as inherited and germline-encoded antibodies produced by naïve mature B cells that have gone through selection but that have not yet encountered external antigenic stimuli (Hooijkaas et al. 1984). The existence of these antibodies stems from studies of antibodies found in germ-free mice as well as in human cord blood (Chou et al. 2009). Some of the natural antibodies including IgM (nIgM) are part of the pool of antibodies that are described as polyreactive, meaning that they individually react to a number of unrelated antigens, including lipopolysaccharide (LPS) and self-antigens, such as dsDNA and insulin (Satoh et al. 1983; Dighiero et al. 1983). This type of "promiscuity," binding both self and non-self, exists both in the IgM and IgG compartments, despite that switching to IgG developed much later than IgM. Much of the studies of the natural IgG repertoire have been done on intravenous immunoglobulin (IVIG) preparations used for therapy, which is purified IgG antibodies pooled from thousands of individuals (Nimmerjahn and Ravetch 2008). These IgGs are composed essentially by the same

repertoire of specificities as the primordial IgM (Marchalonis et al. 2006). One underlying reason for this is that evolution of the VH and VL as well as joining (J) segments is highly conserved, and as an example, the VH regions in shark show 50 % identity to the human VH germline prototype gene. Still, even though the basic gene segments are conserved over millions of years, how they are used to create antibodies shows great individual diversity within vertebrates (Marchalonis et al. 2006). The extremes are the individual IgM gene cassettes in sharks and the translocation processes and VDJ recombination that occur in mammals. Furthermore, diversification in chickens depends almost completely on gene conversion, showing yet another way to create diversity within the immune system (Ratcliffe 2006).

1.2 Structure and Expression of IgM and IgD

1.2.1 Molecular Genetics, Selection, and Survival

The production of the IgM heavy chain (μHC) is the first antibody subclass specific gene expression to occur in the developing B cell in the bone marrow (BM) (Martensson et al. 2007; Raff et al. 1976; Burrows et al. 1979). The assembly is ordered; first upregulation of RAG genes leads to D to J gene segment ligation already in lymphoid progenitor cells, with the ability to produce both B and T cells (Schatz and Swanson 2011). The subsequent V to DJ and μ-constant region rearrangement requires additional expression of the transcription factor Pax5 which is essential in the initial developmental stages for B cell linage commitment in the bone marrow (Medvedovic et al. 2011). Furthermore, Pax5 is needed throughout B cell development, to maintain cell identity, and is later also involved in regulating activation of mature B cells (Medvedovic et al. 2011). After being expressed, μHC is involved in B cell selection in the bone marrow, where it first is part of the preBCR, together with the surrogate light chain and associated with Igα– and Igβ-chains on the cell surface. The Igα and Igβ contain the signaling motifs (ITAM) of the BCR, whereas the μHC adds little to the signaling (Martensson et al. 2007; Reth 1989). In the next step of development, the μHC is paired with λ or κ light chains and participates in receptor-editing processes where up to 50 % of the B cells escape negative selection by rearranging their IgM-BCR (Gay et al. 1993). These steps and the distinct development stages in the BM assure a functional BCR and set a first threshold for autoreactivity (Luning Prak et al. 2011). The δ heavy chain (δHC) is expressed when the naïve B cell has gone through selection and leaves the bone marrow. These naïve mature B cells express both IgM and IgD on the surface with identical VDJ, making up their BCRs (Fig. 1.1). This is achieved by a process where the δHC is transcribed on the same mRNA unit as μHC (Gritzmacher 1989). The relative surface expression of IgM- and IgD-BCRs is then regulated by alternative transcriptional termination and splicing, and not by DNA recombination. When IgM and IgD are part of the BCR, the accompanying Igα and Igβ chains mediate the

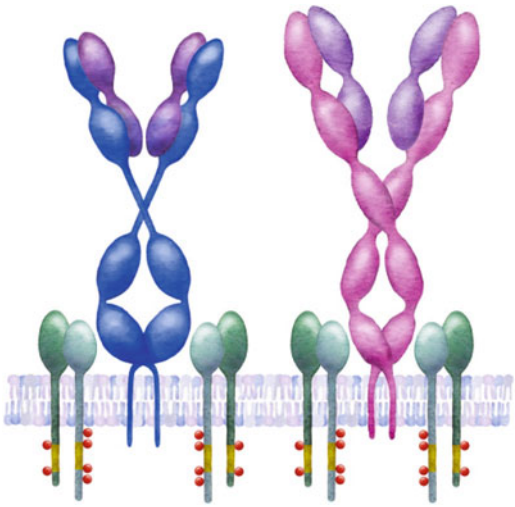

Fig. 1.1 IgD and IgM as B cell receptors. IgD (*left*) and IgM (*right*) are first expressed as B cell receptors when the B cell leave the bone marrow. They are anchored in the plasma membrane through a transmembrane region and associate with two Iga and Igb chains that provide ITAM-containing signaling motifs that mediate activation when the B cell meets its antigen

signaling from the receptor following interaction with its cognate antigen. These side chains are also responsible for internalization of the BCR for antigen uptake to present peptides on MHC II (Jang et al. 2010). After activation, the B cells will have the ability to permanently switch and become producers of soluble IgM and IgD molecules as well as other subclasses. Importantly, in the periphery constant signaling from the BCR is needed for B cell survival. If the BCR is experimentally deleted, B cells die within 5 days. Rescue from death can be achieved by inducing tonic PI3 kinase signaling through activation of the FOXO1 transcription factor (Srinivasan et al. 2009). The source for the tonic signaling in non-manipulated cells is not fully understood, but could be mediated via weak BCRs binding to self-ligands or even independently of BCR phosphorylation. In the final stage of B cell development, the fully activated cells terminally differentiate into plasma cells. This is accompanied by loss of expression of the BCR as well as Pax5 and upregulation of, among others, Pax5-suppressed genes such as *Blimp-1*, *Xbp1,* and J chain, all essential for plasma cell differentiation as well as assembly of soluble IgM (Kallies and Nutt 2007).

1.2.2 Subpopulations of Naïve B Cells Expressing IgM and IgD B Cell Receptors

Naïve B cells leaving the BM, at this time expressing BCR receptors made up with IgM and IgD, continue to develop in the periphery and go through a number of transitional (T) stages called T1, T2, and T3 to end up in the naïve mature B cell repertoire (Allman et al. 2001; Sims et al. 2005). Interestingly, at the T1 stage about 40 % of the B cells have reactivity to self-antigens. This drops to around 20 % as the cell develops further, showing that an additional peripheral selection step