Preface

Among antibodies, the IgM isotype is unique in that it appears first during phylogeny, ontogeny, and the immune response. The importance of both pre-immune "natural" IgM and antigen-induced "immune" IgM antibodies in protection against infection and autoimmunity has been established through studies of mutant mice deficient in IgM secretion (Ehrenstein and Notley 2010) as well as patients with selective IgM immunodeficiency (Louis and Gupta 2014). In this *Current Topics in Microbiology and Immunology* volume entitled "IgM and Its Receptors and Binding Proteins," five groups of investigators will describe their findings in this area of research.

In Chapter "The Appearance and Diversification of Receptors for IgM During Vertebrate Evolution", Dr. Lars Hellman and Dr. Srinivas Akula describe the phylogenetic aspects of three IgM-binding receptors based on currently available genomic sequence databases: (i) polymeric immunoglobulin (Ig) receptor (pIgR) expressed on mucosal epithelial cells, (ii) Fc receptor for IgM (FcμR) on lymphocytes, and (iii) Fc receptor for IgA and IgM (Fcα/μR) on follicular dendritic cells and other cell types. Among these three receptors, the pIgR first appears during vertebrate evolution and is not found in cartilaginous fish, but in bony fish onward. The pIgR has different numbers of extracellular Ig-like domains depending on the taxonomic class: two to six in bony fish, four in amphibians, reptiles, and birds, and five in all mammals. The increase in the Ig-like domain number from four to five in mammals has been implicated to enhance the interaction of the pIgR with polymeric IgA. FcμR is suggested to appear in early reptiles and is found in all three major living (extant) groups of mammals (i.e., egg laying, marsupial, and placental mammals). Fcα/μR has only been found in mammals and is most likely the evolutionary youngest among these three IgM-binding receptors. The domain structure and possible evolutionary relationship between these three receptors and their function in immunity are also discussed.

In Chapter "Authentic IgM Fc Receptor (FcμR)", Dr. Hiromi Kubagawa and his colleagues describe several recent findings about FcμR from their own and other studies. Unlike FcRs for isotype-switched Igs, FcμR is expressed only by adaptive immune lymphocytes; B, T, and, to a lesser extent, NK cells in humans and only B

cells in mice. Conflicting reports on the expression of FcμR by non-B cells in mice are discussed along with possible explanations for such a critical discrepancy. They have shown that the configuration of IgM ligands is important in FcμR binding. FcμR-bearing cells bind pentameric IgM with a high avidity of ~10 nM and much higher (>100-fold) concentrations are required for monomeric IgM to bind FcμR. Intriguingly, their recent assessment indicates that only twofold to threefold concentration differences in FcμR binding are observed between J chain-containing pentameric and J chain-deficient hexameric IgM. This finding is thus distinct from their complement activation activities, where the IgM hexamer is ~50- to 100-fold more efficient than the IgM pentamer. In addition to the above interaction with soluble IgM, FcμR-bearing cells bind the Fc portion of IgM antibody more efficiently when it is attached to a membrane component via its Fab region on the same cell surface (*cis* interaction). This preferential *cis* engagement of FcμR led to their hypothesis that FcμR can modulate the functional activity of lymphocyte surface molecules recognized by either natural or immune IgM antibody. Several key residues in the transmembrane and cytoplasmic tail of human FcμR involved in the receptor function have been defined by mutational analyses. *Fcmr*-deficient (KO) mice have been established by several groups to define its in vivo function. B cells from these mutant mice were found to produce significantly less interleukin 10 (IL-10), an anti-inflammatory cytokine, but comparable amounts of pro-inflammatory IL-6, ex vivo upon stimulation with *Salmonella* bacteria or with ligands for Toll-like receptor 4 (TLR4), TLR7, or TLR9 as compared to those from controls. There are several significant phenotypic differences in the different *Fcmr* KO mice, and possible explanations for this are discussed.

In Chapter "FCRLA—A Resident Endoplasmic Reticulum Protein that Associates with Multiple Immunoglobulin Isotypes in B Lineage Cells", Dr. Peter Burrows, Dr. Teresa Santiago, and Ms. Tessa Blackburn describe their studies of Fc receptor-like molecule A (FCRLA), an FcR-related protein with several unusual features. Apart from its reported expression in melanocytes and melanoma cells, FCRLA is restricted in its expression to B lineage cells, in particular, germinal center (GC) B cells in humans. Biochemical and cell biological features of FCRLA have mainly been studied in human B cells, where it has been shown to be a non-glycosylated resident endoplasmic reticulum (ER) protein. The Ig isotype specificity of FCRLA is much more promiscuous than any of the other FCR molecules described in this volume, in that it associates with every isotype so far examined, IgM, IgG, and IgA. FCRLA retention in the ER is not mediated by any known protein sequence motif, e.g., KDEL at the C-terminus of other ER proteins such as BiP/GRP78, but rather by unknown mechanisms involving the structurally disordered first domain of the protein, perhaps disulfide bond formation via free Cys residues present in this domain. The most unexpected finding of their studies is that FCRLA in the GC-derived human B cell line Ramos associates with the secretory rather than the membrane form of IgM, both of which are synthesized by these cells. This specificity for IgM molecules that differ only in a short segment of the C-terminus alternately encoded by μ membrane or μ secretory exons provides tantalizing clues as to a possible function of FCRLA in preventing secretion of

"decoy" B cell receptor (BCR) molecules by antigen-responsive IgM-bearing B cells, particularly in the GC.

In Chapter "Specific IgM and Regulation of Antibody Responses", Dr. Birgitta Heyman and Dr. Anna Sörman describe the IgM antibody-mediated enhancement of humoral immune responses. In 1968, Claudia Henry and Niels Jerne reported the seminal finding that passive administration of 19S (IgM) or 7S (IgG) antibodies against sheep red blood cells (SRBC) prior to immunization of the mice with the SRBC antigen resulted in opposing immunoregulatory effects. IgM anti-SRBC antibody enhanced the subsequent immune responses to SRBC, whereas IgG anti-SRBC antibody suppressed the response (Henry and Jerne 1968). IgM-mediated feedback enhancement led to the foundation of the Ph.D. thesis studies of Dr. Heyman in the laboratory of Dr. Hans Wigzell in the 1980s. Since then, she and her colleagues have explored the molecular mechanism behind this phenomenon. Enhancement by IgM antibody is preferentially observed when mice are immunized with relatively large antigens such as erythrocytes, malaria parasites, or keyhole limpet hemocyanin. The timing is important, in that IgM antibody must be administered in close temporal relation to the antigen challenge. Moreover, antigens must be given in suboptimal doses. Complement activation, but not its lytic activity, is required for this IgM-mediated enhancement, since it is not observed in mice lacking complement receptors 1 and 2 (CR1/2), but is unaffected in mice lacking C5, a factor required for the lytic pathway. Passively administered IgM anti-SRBC antibody binds to SRBC and activates complement leading to deposition of C3d on the SRBC antigen. This IgM/SRBC/C3d complex binds to CR1/2-bearing marginal zone B cells which transport it to CR1/2-bearing follicular dendritic cells. In parallel, IgM/SRBC/C3d may cross-link CR1/2 and the BCR on B cells, thereby facilitating B cell responses. This chapter covers the nearly 35-year studies on IgM-mediated enhancement of humoral immune responses conducted by Dr. Heyman and her colleagues.

In Chapter "Role of Natural IgM Autoantibodies (IgM-NAA) and IgM Anti-Leucocyte Antibodies (IgM-ALA) in Regulating Inflammation", Dr. Peter Lobo describes the many important roles of IgM natural antibodies in regulation of inflammation. As opposed to immune IgM, the natural IgM antibodies arise spontaneously without deliberate immunization, can be produced under germfree conditions and in the absence of a thymus, and are present at high levels in human umbilical cord blood, meaning they were generated before exposure to foreign antigens. B1 and marginal zone B cells are major sources of these antibodies, which are often polyreactive and bind autoantigens as well as pathogens with low affinity but with functional consequences. They can bind neo self-antigens to prevent autoimmune disorders and inhibit the growth of microorganisms until other arms of the innate and adaptive immune system mount a protective response. These IgM antibodies can also bind to apoptotic cells to enhance their removal, least they induce an inflammatory response or autoantibody production, and can bind to live leukocytes to regulate their function. Using mice unable to produce secreted IgM, he also shows that regulatory B and T cells require IgM to control the inflammatory response. The repertoire of leukocyte-binding IgM differs in healthy and diseased

humans, which may partially explain differences in the inflammatory response after infection, ischemic injury, or organ transplantation. In this regard, natural IgM antibodies are shown to have tremendous therapeutic potential, since infusion of polyclonal IgM or DCs pre-treated ex vivo with IgM can prevent or treat over exuberant inflammatory responses in vivo.

Berlin, Germany — Hiromi Kubagawa
Birmingham, USA — Peter D. Burrows

References

Ehrenstein MR, Notley CA (2010) The importance of natural IgM: scavenger, protector and regulator. Nat Rev Immunol 10:778–786

Henry C, Jerne NK (1968) Competition of 19S and 7S antigen receptors in the regulation of the primary immune response. J Exp Med 128:133–152

Louis AG, Gupta S (2014) Primary selective IgM deficiency: an ignored immunodeficiency. Clin Rev Allergy Immunol 46:104–111

http://www.springer.com/978-3-319-64524-7

IgM and Its Receptors and Binding Proteins
Kubagawa, H.; Burrows, P.D. (Eds.)
2017, IX, 117 p. 30 illus., 15 illus. in color., Hardcover
ISBN: 978-3-319-64524-7