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Natural IgM: Beneficial Autoantibodies for the Control of Inflammatory and Autoimmune Disease

Caroline Grönwall · Gregg J. Silverman

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Abstract Natural IgM are highly represented in the circulation at birth, and these often autoreactive antibodies have been postulated to have innate-like properties and play crucial roles in apoptotic cell clearance, tissue homeostasis, and immune modulation. This review summarizes the known properties of these IgM autoantibodies, and the evidence that these anti-apoptotic cell IgM natural antibodies can regulate inflammatory responses through ancient pathways of the innate immune system that first arose long before the initial emergence of the adaptive immune system. While the regulatory contributions of these natural IgM autoantibodies are certainly not an essential and fundamental component of host defenses, these provide an additional layer to further protect the host. More importantly, these IgM antibody responses are highly inducible and their up-regulation can be a powerful means for the host to survive in a setting of chronic inflammation. The observed beneficial clinical associations for cardiovascular disease and autoimmunity, as well as opportunities for potential therapeutic implications are discussed.

Keywords Immunoglobulin · protective · IgM · apoptotic cells · autoimmunity · inflammation · homeostasis

We are Born with Autoantibodies

In 1908, Ehrlich was awarded the Nobel Prize, in part for his hypothesis that healthy individuals produced antibodies to all potential non-self antigens (even before immune exposure) while autoreactive antibody clones were forbidden from becoming part of the immune system due to their potential to cause tissue injury [1]. Yet, more contemporary investigations have highlighted that certain types of autoantibodies are in fact regular and prominent parts of the physiologic immune system [2]. Indeed, while certain autoimmune diseases are associated with autoreactive antibodies, that arise from traceable breaches-of-tolerance in the mature immune system, it is equally clear that not all human autoantibodies are pathogenic. In fact, some classes of self-reactive IgM antibodies are common in health and are already present at birth [3–6]. These physiologic classes of autoantibodies have been termed natural antibodies (NAbs), as they arise spontaneously without exogenous antigenic or microbial stimuli and in some cases have been shown to also arise in mice raised under germ-free conditions [7]. In the mouse, the natural antibodies have been associated with the B-1 cell subset. This specialized B cell population is responsible for expression of up to 80% of all circulating IgM. B-1 cells are common in the pleural and peritoneal linings, while in relatively low numbers in the spleen and in the circulation, and can be recruited into certain T-cell independent innate-like antibody responses [8–10]. B-1 cell development is reported to involve interactions with certain types of autoantigens, suggesting that this cell population, in contrast to the repertoire of conventional T-dependent B-2 cells in which self-reactivity is edited out, instead undergo a positive clonal selection process to promote certain types of self-reactivity with non-protein antigens [11, 12]. B-1 cells have also been reported to express a recurrent repertoire with overrepresentation of specific types of autoreactive-associated VH gene segments and preferential H-L pairing [13–16]. Furthermore, in the mouse NAbs from B-1 cells are more likely to be encoded by germline configuration variable region rearrangements without evidence of somatic hypermutation [17].

In humans, the presence of B-1 cells has long been a topic of controversy, but recent investigations have identified the human B-1 analogue as a CD43+ CD27+ CD70- B-cell subset

C. Grönwall (✉) · G. J. Silverman
Department of Medicine, New York University School of Medicine, New York, NY 10016, USA
e-mail: caroline.gronwall@nyumc.org

present in the circulation [18–20]. This cell population, which was observed both in human umbilical cord blood as well as in the adult peripheral immune system, was found to spontaneously secrete IgM and have a high representation of cells reactive with non-protein self-antigens, such as phosphorylcholine (PC) and dsDNA [18]. Hence, human B-1 cells are believed to be highly represented during early human immune development, when similar to the mouse there are relative restrictions in diversity with biases towards certain Ig variable gene usage and CDR3 recombination in the fetus and neonate compared to adults [21, 22].

Natural IgM antibodies have been proposed to have lower affinity and higher polyreactivity than responses from the B-2 subset [23, 24], yet highly specific antibodies can be identified and the polymeric nature of secreted IgM enables high avidity interactions that facilitate stronger binding interactions. While most reports have focused on natural IgM antibodies, NAbs can also be of the IgA isotype and the human IgA pool in the umbilical cord blood of neonates show a similarly restricted repertoire as IgM [25]. Notably, while the womb under normal conditions is sterile and thus free of microbial stimuli, it is not absent of antigens that could potentially influence immune development. Interestingly, microarray analysis of newborns has revealed high serum IgM reactivity towards self-antigens such as ssDNA and LDL, and strikingly conserved recurrent binding patterns between unrelated individuals [5, 26, 27]. Polyreactive B cells are also more prevalent in cord blood of neonates than in adults [28]. Moreover, IgM that specifically recognize oxidation-associated determinants exposed on apoptotic cells are highly represented in human newborns [3, 29], as discussed in more detail below. Significantly, a report using combinatorial cloning methods to isolate autoantibodies from newborns binding oxidation-adducts found that these antibodies were encoded by germline or near germline encoded variable regions [29].

The recurrent autoreactive patterns of IgM NAbs that arise in neonates suggest that these autoantibodies may be part of a previously described programmed developmental expression of an innate-like antibody repertoire [30]. Consequently, the preeminent questions are: what is the evolutionary pressure for the natural selection of these antibodies and what are the functional roles that these serve? While some natural IgM can recognize microbial antigens [31] and may be part of our first line of defense against foreign infectious threats [32], there is also emerging evidence that some autoreactive IgM NAbs may have other essential functions. In the following sections, we aim to summarize the proposed hypothetical roles for natural IgM in homeostasis and immune regulation and their potential impact on human inflammatory disease.

Natural Antibodies Bind to Autoantigens on Dying Cells, Mediate Phagocytosis and Regulate Innate Cells

One of the most fundamental functions of the immune system is the recognition and removal of dead and dying host cells. It has been postulated that during the evolution of the species, with the first appearance of the mesoderm layer, unwanted dead or dying cells could no longer be simply cast off, and there was now a need for a means to specially isolate and/or remove these superfluous cells without disrupting overall tissue architecture. In vertebrates, this important system is tightly controlled by an overlaid series of molecular pathways, which mediate the recognition of dead cells by professional tissue phagocytic cells that can selectively engulf apoptotic cells by a process that has been termed efferocytosis (i.e., for carry out the dead) [33–35]. In a healthy adult, hundreds of billions of cells die every day by apoptosis as part of natural senescence, injury, and cell turn over that is required for the maintenance of tissue homeostasis. Thereby these apoptotic host cells are consequently cleared by innate immune cells without eliciting inflammatory or immune response. Conversely, defects in this process can result in accumulation of dead cells that may progress to secondary necrosis and release of pro-inflammatory molecules as well as autoantigens. In fact, it has been hypothesized that attenuated apoptotic cell clearance may be an initiating force in the pathogenesis of systemic autoimmunity [36].

There are several molecules that have been identified as potential “eat-me” signals, yet increasing evidence points towards a role for natural IgM in enhancing and amplifying the recognition of apoptotic cells. Indeed, there are several known autoantigens, which are recognized by subsets of natural IgM, and have in common that they can be exposed on cells during the tightly regulated process of apoptotic death. The apoptotic cell membrane undergoes many specific changes, including oxidation-associated processes, that can render the otherwise sequestered phosphorylcholine (PC) lipid head group accessible to antibody recognition, and similarly lead to neo-determinants associated with malondialdehyde (MDA) and malondialdehyde acetaldehyde (MAA) adduct modifications. In addition, normally intracellular components, such as dsDNA, Ro and cardiolipin, may be redistributed into apoptotic blebs and available for autoantibody binding [37].

Inhibition studies have suggested that a surprisingly high fraction of all natural IgMs in newborns are reactive with oxidation-associated determinants exposed on apoptotic cells [3], and an independent study similarly showed that antibodies reactive with the oxidative adduct MAA on apoptotic cells are also highly represented in newborns [29]. While these antibody reactivities appear to be highly enriched within the IgM repertoire, purified IgG from healthy adults does not bind to apoptotic cells to the same extent as IgM [38].

When a natural IgM autoantibody targets apoptotic cells through (for example) PC epitopes, this leads to recruitment of early complement recognition factors, Mannose Binding Lectin (MBL) and C1q, which then significantly increases efferocytosis by innate immune cells of dying cells also at early stages of apoptosis [39, 40]. Pentameric IgM binding to surface antigens changes the conformation of the IgM, exposing residues which enhance C1q binding to the antibody-antigen co-complex [41]. Similarly, the structurally related MBL binds to high mannose glycoconjugates on some pentameric IgM [42]. Importantly, studies in serum-free medium showed that IgM-mediated apoptotic cell phagocytosis did not require downstream complement activation or C3 breakdown components [39, 40]. Hence, the postulated role for pentameric IgM NAbs is to facilitate the formation of an apoptotic-cell-synapse between the phagocyte and the dead cell. This synapse is likely to involve many different components including integrins, complement receptors, apoptotic cell receptors and additional soluble factors. Many receptors and soluble molecules have been identified as contributing to apoptotic cell engulfment (reviewed in [34, 35]). Considering the fundamental importance of this system there may be a high level of functional redundancy among the different innate factors to enhance the efficiency of apoptotic clearance. Nevertheless, genetically manipulated mice that are deficient in either secreted IgM (i.e., sIgM −/−) or MBL or C1q, all display marked impairment in their capacity for apoptotic cell clearance with spontaneous accumulations of apoptotic cells [43–46]. This further highlights the now well-accepted importance of the contributions of these components to efferocytosis related pathways.

Importantly IgM NAbs are postulated to have anti-inflammatory influences that are intertwined with roles in apoptotic cell phagocytosis. Apoptotic cell clearance is associated not only with removal of cell corpses and but also with protection from the release of potentially harmful factors, such HMGB-1 and heat shock proteins (HSP). In general, the engulfment of an apoptotic cell can induce an immunologically quiescent anti-inflammatory state of the post-efferocytosis innate immune cell, with inhibition of the expression of pro-inflammatory cytokines, and at times also with the release of immunosuppressive cytokines, such as TGF-β [47–49]. In murine models, in vivo treatment with apoptotic cells can inhibit inflammatory responses [39, 50, 51]. However, recent studies that compared IgM deficient with wild-type mice showed that the anti-inflammatory effects of apoptotic cells in a model of inflammatory arthritis was dependent on the presence of circulating natural IgM [39, 52]. Hence, IgM seems to enhance these potential anti-inflammatory properties of apoptotic cell membranes [39].

In vitro studies have demonstrated that anti-apoptotic cell natural IgM specific for the PC determinant inhibits TLR-mediated cytokine expression and MAPK activation in innate immune cells [39]. Importantly, IgM can induce specific anti-inflammatory signaling pathways that were shown to be dependent on the induction of the immunosuppressive phosphatase Mitogen Activated Protein Kinase (MAPK) phosphatase 1 (also termed MKP-1 or DUSP-1) in bone marrow-derived dendritic cells [53]. IgM can block both TLR stimulation by agonists and the pro-inflammatory influences of lupus-associated RNA or DNA IgG immune complexes [39, 53, 54]. In addition, not only purified monoclonal IgM anti-apoptotic cell antibodies, but also polyclonal IgM in serum from neonatal mice, or adult mice injected with apoptotic cells to boost the IgM anti-apoptotic cells pool, have the capacity to induce the same anti-inflammatory signaling [53]. Notably, MKP-1 induction and inhibition of MAPK phosphorylation by serum IgM can be significantly inhibited by either soluble PC or MDA antigens, suggesting that these apoptotic cell-associated determinants are dominant epitopes for IgM antibodies in the circulation in mice that have immunomodulating properties [53]. In these studies, neither serum polyclonal IgG nor serum without immunoglobulin (from B-cell deficient mice) have the same anti-inflammatory properties [53].

Over exuberant inflammation contributes to tissue damage in a number of diseases, and no doubt can represent a threat to the species. These anti-apoptotic cell IgM natural antibodies can regulate inflammatory responses through effects on ancient pathways of the innate immune system that first arose long before the initial emergence of B cells and the adaptive immune system. Indeed, orthologs of TLR were first characterized in insects [55], and the MAPK signaling system represents one of the earliest evolutionarily conserved pathways of immunity, being present in plants and animals [56]. Likewise, MKP-1 orthologs have been described in protozoa [57]. While the regulatory contributions of these natural IgM autoantibodies are certainly not an essential and fundamental component of host defenses, these provide an additional layer to further protect the host. More importantly, these IgM antibody responses are highly inducible and their up-regulation can be a powerful means for the host to survive in a setting of chronic inflammation that can not otherwise be well controlled (discussed further below).

In Vivo Anti-Inflammatory Effects of Natural IgM

A large number of reports from in vivo murine studies point to the importance of IgM for protection against autoimmunity and cardiovascular disease. In fact, mice without the ability to produce secreted IgM have a predisposition for development of pathogenic IgG autoantibodies and lupus-like autoimmunity [58, 59]. Furthermore, mice without IgM also suffer from over exuberant inflammation in models of ischemic reperfusion injury and cardiac allograft rejection [60] and the lack of sIgM further accelerates atherosclerosis in hyperlipidemic

LDL receptor-deficient mice [61]. Other investigations show that natural IgM, enriched in anti-PC activity, secreted by the B1 cell subset can arrest the progression of atherosclerotic lesions in hypercholesterolemic ApoE-deficient mice [62]. Similarly, treatment with polyclonal natural IgM reduces atherosclerosis and lowers the levels of potentially pathogenic CD4+ T-cells in these mice [63]. These studies confirm earlier evidence that induction of IgM anti-PC antibodies by a vaccination approach halted the progression of atherosclerosis in LDL-receptor deficient mice [64]. In addition, treatment with monoclonal IgM anti-PC suppresses inflammatory arthritis in both the anti-collagen induced (CIA) model and the anti-collagen antibody passive transfer mouse model [39]. Furthermore, monoclonal IgM antibodies against dsDNA, which may also recognize apoptotic cells, can ameliorate the lupus-like disease and glomerulonephritis in MRL/lpr mice [65] and delay the onset of disease in (NZBxNZW) F1 mice [66]. Autoreactive polyclonal IgM can also decrease the progression of autoimmunity in FcγRIIB/TLR9 double knockout mice, by mechanisms that may include the inhibition of Th17 cells [67]. In summary, these murine studies strongly imply that IgM NAbs can have immunoregulatory and protective properties in inflammatory disease.

Natural Antibodies and Interactions with Microbes

Some IgM and IgA natural antibodies recognizing autoantigens can also bind to homologous molecules produced by different microbes. The prototypical murine natural antibody T15 clone that uses canonical antibody rearrangements formed by primary sequence dependent rearrangements, which has also been isolated by a number of independent research groups (e.g. S107 and EO6), binds equally well to PC determinants in oxidized lipid layers on apoptotic cells and dominant epitopes in cell wall polysaccharide of pneumococci [68]. Additionally, in both mice and humans IgM anti-PC can be induced by pneumococcal vaccination [64, 69].

Natural IgM antibody binding to I/i carbohydrates blood group antigens can also be increased during clinical infection by *Mycoplasma pneumonia* or Epstein-Barr Virus [70–72]. A recent study also suggested that anti-MDA IgM can cross-react with epitopes associated with the bacterial pathogen, *Porphyromonas gingivalis*, which is a primary cause of periodontal disease [73]. Consequently, constant interactions of the host immune system with microbes, representing both commensals and pathogens, may change the IgM antibody repertoire. Therefore, the adult autoreactive IgM, although these may initially arise as natural antibodies, certain specificities may later increase when these B-cell clones become further expanded during bacterial or viral infections.

The natural antibody repertoire may become strongly influenced by continuous interactions with the microbiome, which is the community of microbial commensals that resides on and within all of us. Starting early in life the constant dynamic equilibrium between host immune system and microbial antigens molds both our innate and adaptive immunity. In the complex cross-talk with the gut microbiome, B-1 cells, which are known to be an important source of intestinal IgA, may be a major factor in the control of the relative representation of microbial species, and likewise the microbial milieu may affect the clonal distribution within the B-1 repertoire and its secreted antibody products [74–77].

Protective Natural IgM in Clinical Surveys

Diseases of autoimmunity and chronic inflammation are multifactorial conditions, with complex intertwined genetic and environmental risk factors contributing to pathogenesis. Hence, the potential defects responsible for the often associated dysregulation of apoptotic cell clearance are not easy to dissect. Although uncommon, hereditary homozygous C1q deficiency has near complete penetrance for the development at an early age of severe systemic autoimmune disease, and it is the single strongest reported genetic deficiency state that can predispose to systemic lupus erythematosus (SLE) [78]. It has been postulated that this effect may be related to the ability of C1q to bind apoptotic cells and mediate their clearance. Although selective IgM deficiency is a rare clinical condition, it has been associated with the development of systemic autoimmunity [79, 80]. A recent study has also suggested that IgM deficiency is more common among SLE patients than controls [81] and patients with SLE generally have lower total IgM levels [82]. Interestingly, there are also reports of increased number of apoptotic cells in the circulation of SLE patients [83]. Yet it remains difficult to discern whether these variations reflect a cause or effect relationship between clinical autoimmunity and this immunodeficiency state. It is uncertain if lower IgM levels predisposes to autoimmunity or if the chronic inflammation and increased apoptotic cell burden instead leads to consumption of certain types of natural IgM antibodies. Furthermore, even if higher levels of certain IgM antibodies to apoptotic cells have been associated with protection from different disease manifestation, they may still be overall higher levels of these beneficial autoantibodies in many patients with autoimmunity compared to healthy controls [84].

We hypothesize that some specificities within circulating IgM may become increased as part of a positive feedback system that reflects a compensatory drive to resolve inflammation and improve apoptotic cell clearance. Indeed, experimental infusions of apoptotic cells have been shown to raise levels of anti-PC and anti-MDA IgM [40]. It is feasible that

during clinical progression the chronic inflammation and higher oxidative injury and accumulation of dying cells leads to induction of higher levels of anti-apoptotic cell antibodies. The milieu of this type of chronic disease state may also be very different from what happens in response to acute vascular injury. Padilla et al. have shown that following arterial infusions of TNFα into the limbs of patients with sarcomas, the circulating levels of natural IgM anti-PC decreased by up to 60% over 48 h, presumably due to in vivo consumption [85]. Hence, while apoptotic cell immune exposure can greatly elevate IgM anti-PC levels, intravascular injury can also consume these antibodies. Other types of therapeutic interventions may also affect levels of this special type of IgM antibodies. In a small cohort of rheumatoid arthritis patients, treatment with the anti-CD20 antibody, rituximab, was associated with decreases in natural IgM anti-PC levels, but future studies are needed to further clarify the topic [86].

The majority of recently reported clinical surveys of natural antibodies have focused on the study of IgM antibodies that recognize PC-containing antigens. PC is indeed an intriguing molecule that is not only present on apoptotic cells but is also an immunodominant epitope on pneumococcal cell wall bacterial polysaccharide, as well in pro-atherogenic oxidized LDL (oxLDL) [3, 68, 87], and there is now strong evidence for the direct protective properties of anti-PC IgM in murine models of both autoimmunity and atherosclerosis [39, 40, 64]. The potential protective mechanisms for anti-PC antibodies in cardiovascular disease have been posited to derive from their contributions to apoptotic cell clearance [39, 40] and for the regulation of innate immune cells [39, 53, 54]. In addition, these antibodies may also directly block oxidized lipids in PC-containing pro-inflammatory molecules, such as platelet activating factor (PAF), or the inhibition of oxLDL uptake by macrophages otherwise involved in the formation of atherosclerotic plaques [88, 89]. Anti-PC antibodies are present in all healthy individuals and levels can be further elevated by microbial stimuli associated with pulmonary infection and periodontal disease [90, 91].

Studies of healthy twins have suggested that levels of anti-PC antibodies may in part be regulated by inheritable factors [92, 93]. In contrast, in studies of lupus disease discordant twins, the healthy twin was more likely to have higher levels of IgM anti-PC than the twin with SLE, which implicates that the levels of these antibodies are also affected by environmental factors and disease [6]. As a potential biomarker, higher levels of IgM anti-PC in patients with SLE have been associated with lower disease activity by the SLEDAI index and with lower organ damage by the SLICC scale, further reinforcing the potential anti-inflammatory and disease modifying properties of these natural antibodies [84, 89]. Moreover, cross-sectional studies have shown that higher concentrations of circulating IgM anti-PC in lupus are associated with a lower probability of a cardiovascular event, such as a myocardial infarction or stroke [84, 89] and lower prevalence of atherosclerotic plaques in the carotids [94]. In non-autoimmune patients, prospective screening has demonstrated that levels IgM anti-PC may provide a biomarker for prediction of pre-clinical cardiovascular disease associated with atherosclerotic plaque burden as measured by ultrasound intima-media thickness [95, 96]. Retrospective studies have also suggested that lower baseline levels of IgM anti-PC may be predictive for stroke [97, 98], myocardial infarction [99] or overall atherosclerotic cardiovascular disease incidence [100].

Lower levels of IgM anti-PC may also be associated with higher mortality in acute coronary syndromes [101] and in patients undergoing haemodialysis [102], as well as vein graft stenosis and failure in patients undergoing vein bypass for atherosclerotic peripheral vascular disease [103]. In addition, although the significance is less clear, patients with dementia have significantly lower levels of anti-PC antibodies than controls [104].

Oxidized LDL is a large complex that contains prominent PC and MDA determinants as well as other neo-epitopes. Nevertheless, clinical surveys of IgM anti-oxLDL have generally revealed close parallel associations with levels of antibodies to PC-containing antigens. Indeed, the levels of anti-oxLDL antibodies are lower in patients with a greater overall burden of pre-clinical atherosclerosis as measured by carotid intima-media thickness [105, 106] and patients with more severe multi-vessel coronary artery disease [107].

Natural IgG Antibodies

The term "natural antibody" is not easily applied to antibodies of the IgG isotype, and as it may not be possible to separate spontaneously secreting B-cell clones from clones stimulated by microbial encounters or following the activation of memory B cells. Nevertheless, it is interesting that healthy individuals have a substantial number of auto- and poly-reactive IgG positive memory B-cells in the circulation [108].

While anti-PC and anti-MDA antibodies are both present within the IgM antibodies found in healthy adults, and IgG anti-PC antibodies are prevalent in health, we have found that IgG anti-MDA is normally not highly expressed, except in patients with inflammatory disease [84]. Human anti-PC IgG are predominantly IgG2 while anti-MDA in contrast are generally of the IgG1 or IgG3 subclasses that have greater potential to trigger the complement cascade and engage activating Fc receptors [84]. It is interesting to speculate that these antibodies may be produced by distinct B-cell subsets. T-cell independent responses to non-protein antigens are generally regarded to generate human IgG2 antibodies [109]. Consequently, it has been assumed that if human

B-1 cells or MZ B cells class-switch that they will express IgG2. However, a recent report found that the anti-carbohydrate antibodies in pooled IgG in intravenous immunoglobulin (IVIG) preparations are not restricted to IgG2 but can be associated with other subclasses as well [110]. IgG of different subclasses may convey functional differences, and it may therefore be relevant that a recent clinical survey found correlative evidence that IgG1 anti-PC levels are more strongly associated with protective properties in atherosclerosis than IgG2 [95]. This topic remains controversial, in part because it will require characterization of the fine specificity and functional properties of monoclonal anti-PC antibodies in the context of different subclasses.

The properties of an IgG antibody may also be affected by their patterns of Fc N-glycosylation, in part because these can affect interactions with Fc receptors [111]. Ravetch and colleagues have also highlighted the immunosuppressive role of sialylated IgG that can interact with the anti-inflammatory receptor DC-SIGN on macrophages [112]. The physiological regulation of differentially glycosylated IgG has not been well explored, yet a recent report reveals that T-cell independent responses induce higher levels of sialylated IgG antibodies that may explain anti-inflammatory effects [113]. Future studies are needed to elucidate the relevance of these findings for natural antibodies.

The immunogenetic relationships between germline-encoded protective natural IgM and pathogenic mutated IgG in autoimmune pathogenesis are also poorly understood. It has been proposed that heritable differences in the autoreactive natural antibody repertoire at birth could contribute to predisposition to autoimmunity later in life [114]. For example, first-degree relatives of patients with SLE have similar levels of IgM anti-Ro antibodies [115]. In fact, there is evidence that disease-associated regulatory abnormalities can cause some IgM natural antibody-expressing B-cells to be recruited into T-cell dependent germinal center responses later in life, possibly changing their binding specificity through somatic hypermutation and class-switch to IgG. Many rearrangements of the human VH4-34 germline gene encode for IgM natural autoantibodies that can bind I/i carbohydrates on erythrocytes and may facilitate clearance of senescent red cells [116]. In healthy individuals, these B cells appear to secrete only low levels IgM antibodies and VH4-34-encoded IgG are rare or undetectable. However, a major subset of SLE patients have high levels of mutated circulating VH4-34 IgG antibodies, which may contribute to pathogenesis due to acquired native DNA binding activity and recognition of antigens on late apoptotic cells [117–119]. Significantly, the presence of a higher proportion of IgM VH4-34 compared to IgG VH4-34 antibodies is associated with less severe lupus disease activity [120].

Natural Antibodies and New Therapeutic Approaches

Therapeutic treatment with intravenous infusions of polyclonal IgG (IVIG) has been shown to provide benefits for patients with a number of autoimmune and systemic inflammatory diseases (reviewed in [121]), although there is considerable debate regarding the exact underlying immunoregulatory mechanism(s). IVIG contains pooled IgG from a large number of healthy individuals and should consequently contain a significant fraction of natural IgG antibodies [122], with potentially only trace amounts of polyclonal natural IgM and IgA. These IgGs will be of a variety of fine binding specificities, and anti-oxLDL antibodies that cross-react with the PC epitope can be detected [123]. In health, homeostatic pathways are responsible for maintaining a delicate equilibrium between pro-inflammatory and immunomodulating factors, and with the onset of overt autoimmune disease this balance can become disturbed. We therefore postulate that therapeutic supplementation by passive antibody transfer of regulatory natural antibodies may favorably shift this balance to resolve an otherwise self-perpetuating inflammatory state.

The cross-reactivity of natural antibodies between self-antigens and microbial antigens also means that anti-PC antibodies can be enhanced by vaccination. Indeed, potentially protective cross-reactive anti-oxLDL levels are significantly higher after pneumococcal vaccination [69].

Preparations of pooled natural IgM may also provide an attractive therapeutic alternative in the future, and it has been hypothesized that IVIgM could have much more potent anti-inflammatory properties than conventional IVIG. Experimental animal models using pooled normal IgM from 2500 individuals or IgM enriched IVIG have shown promising results in some inflammatory diseases [124–127]. Furthermore, preparations of clinical grade IgM and IgA enriched IVIG have been developed for the treatment of sepsis [128, 129] but have not yet been clinically tested for human autoimmune disease.

Conclusions

In summary, human self-reactive natural IgM antibodies are common in health and disease and can play fundamental roles in tissue homeostasis and the maintenance of immune equilibrium. Accumulating evidence suggests that natural IgM may have protective properties in cardiovascular disease and autoimmunity. Increasing our knowledge about the natural antibody system and early immune development may lead to a better understanding of autoimmune pathogenesis and how antibodies contribute to protection from microbial pathogens, as well as maintenance of homeostasis to protect from harmful autoreactivity. The utility of measuring levels of natural antibodies as potential biomarkers has been shown in a large number of studies and may have a potential for future clinical

test. While there may be some technical challenges in producing polymeric IgM, new expression systems are available and monoclonal natural IgM for the treatment of MS is already in development [130]. Therapeutic applications that could harness the potency of immunoregulatory NAbs as polyclonal IVIgM [121], or the development of specific monoclonal therapeutic IgM that specifically recognize neo-determinants on apoptotic cells.

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