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The effects of diet-induced obesity on B cell function

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Summary

B-1 and B-2 B cell subsets carry out a diverse array of functions that range broadly from responding to innate stimuli, antigen presentation, cytokine secretion and antibody production. In this review, we first cover the functional roles of the major murine B cell subsets. We then highlight emerging evidence, primarily in preclinical rodent studies, to show that select B cell subsets are a therapeutic target in obesity and its associated co-morbidities. High fat diets promote accumulation of select murine B cell phenotypes in visceral adipose tissue. As a consequence, B cells exacerbate inflammation and thereby insulin sensitivity through the production of autoantibodies and via cross-talk with select adipose resident macrophages, $CD4^+$ and $CD8^+$ T cells. In contrast, interleukin (IL)-10-secreting regulatory B cells counteract the proinflammatory profile and improve glucose sensitivity. We subsequently review data from rodent studies that show pharmacological supplementation of obesogenic diets with long chain n-3 polyunsaturated fatty acids or specialized pro-resolving lipid mediators synthesized from endogenous n-3 polyunsaturated fatty acids boost B cell activation and antibody production. This may have potential benefits for improving inflammation in addition to combating the increased risk of viral infection that is an associated complication of obesity and type II diabetes. Finally, we propose potential underlying mechanisms throughout the review by which B cell activity could be differentially regulated in response to high fat diets.

Keywords: B cell, diabetes, inflammation, lipid mediators

Introduction

B cells are emerging players in innate and adaptive immune responses associated with metabolic diseases, including obesity, type II diabetes and cardiovascular disease. The objective of this review is to highlight recent studies that demonstrate differential effects of varying obesogenic diets on B cell activation, antigen presentation and antibody production. We first provide a basic review of B cell development and formation of distinct B cell subsets. We then cover data demonstrating that some murine B cell subsets can have a pathological role, while others are anti-inflammatory and have insulin-sensitizing effects in obesity. A central theme that emerges from these studies is that the composition of the high fat diets and downstream lipid mediators derived from specific polyunsaturated fatty acids may be key in regulating B cell activity. Finally, we highlight potential mechanisms by which B cell function is impacted in response to differing dietary fatty acids.

Overview of B cell development and B cell phenotypes

B cells have functional responsibilities in innate and adaptive immunity. The canonical role of B cells is in antibody production, but they also serve as antigen-presenting cells and respond to innate and adaptive stimuli to produce cytokines [1,2]. The major murine B cell subsets, described below, and their primary surface markers and functions are presented in Table 1 in order to familiarize the reader with the current knowledge on murine B cell subsets. We then present in subsequent subsections what is known about the effects of obesity and its complications on the differing B cell subsets.

Table 1. Major murine B cell subsets, their surface marker expression and primary functions.

B cell subset		Phenotype	Characteristics and functional role	Ref.
Developmental subsets				
	Pro	$B220^{+}CD19^{+}$ $CD24^{+}CD43^{+}$ IgM^{-}	B cell precursors in the bone marrow initiating heavy-chain DJ rearrangements	[3,4]
	Pre	$B220^{+}CD19^{+}$ $CD24^{+}CD43^{-}$ IgM^{-}	Express a pre-BCR, a checkpoint in B cell development, in which signalling induces proliferation and recombination of the immunoglobulin light chain	[3,5]
	Immature	$B220^{+}CD19^{+}$ $CD24^{+}CD43^{-}$ IgM^{+}	Express a functional BCR and then exit the bone marrow and home to the secondary lymphoid organs for further development. Immature B cells undergo a negative selection process before maturing to B cells in which BCR cross-linking results in activation	[3,6]
	Transitional 1	$B220^{+}CD19^{+}$ $CD22^{hi}CD23^{-}$ $CD21^{lo}IgM^{hi}IgD^{lo}$	Newly generated non-circulating B cells found in bone marrow and spleen. Survival is dependent upon BCR signals. Give rise to follicular and marginal zone B cells	[7,8]
	Transitional 2	$B220^{+}CD19^{+}$ $CD22^{hi}CD23^{+}$ $CD21^{mid}IgM^{hi}IgD^{+}$	Earliest B cells to express CD23, persisting in all B cell follicles. Attain the ability to recirculate and represent clones that were not eliminated by self-tolerance	[7,8]
Mature subsets				
B-2 lineage	Marginal zone	$B220^{+}IgM^{hi}IgD^{lo}$ $CD21^{hi}CD43^{-}$ $CD23^{-}CD1d^{hi}$	Localized to the marginal sinus where they respond rapidly to blood-borne pathogens. Express high levels of CD1d for lipid antigen presentation. Elevated CD21 levels facilitate transport of immune complexes from the circulation to the splenic follicles. Equipped to elicit T cell-independent immune response	[7–9]
	Follicular	$B220^{hi}CD19^{+}$ $CD23^{hi}CD1d^{mid}$ $CD21^{mid}IgM^{lo}$ IgD^{hi}	Recirculating conventional B cell equipped to elicit T cell-dependent responses to protein antigens	[7–9]
	IL-35 Producing	$IgM^{+}CD138^{hi}$ $CD43^{+}TACI^{+}$ $CXCR4^{+}CD1d^{mid}$ $Tim1^{mid}$	Express anti-inflammatory cytokines, excluding IL-6, and are critical regulators of T cell-mediated immunity	[10]
	Regulatory	$CD5^{+}CD19^{hi}$ $CD1d^{+/hi}CD21^{+}$ $CD23^{+/-}CD43^{+/-}$ $IgM^{hi}IgD^{lo/mid}$	Depend upon CD19 for development. Regulate inflammatory responses with IL-10 production. Variable cell-surface phenotype. May also derive from B-1 lineage cells	[1,2,9,11,12]
B-1 lineage	B-1a	$CD19^{+}IgM^{hi}$ $CD5^{+}CD43^{+}$ $CD23^{-}IgD^{lo}$ $CD1d^{mid}$	Generated before birth and the fetal liver is an efficient source. B-1a cells are poorly reconstituted by adult bone marrow. B-1a cells secrete polyreactive IgM in an antigen-independent manner	[9]
	B-1b	$CD19^{+}IgM^{hi}$ $CD5^{-}CD43^{+}$ $CD23^{-}IgD^{lo}$ $CD1d^{mid}$	B-1b cells produce antibodies after encountering T cell-independent antigens	[13,14]
	Innate response activator	$IgM^{hi}CD23^{lo}$ $CD43^{+}CD93^{+}$	An inflammatory B cell subset derived from B-1a B cells. They control IgM production via autocrine granulocyte/macrophage colony-stimulating factor signalling	[13,14]
Differentiation stages				
	Plasma cells	$CD138^{+}$surface Ig^{neg}	Terminally differentiated, non-dividing B cells that secrete substantial amounts of clonospecific antibodies	[10,15]
	Memory	$B220^{+}$ $CD80^{+/-}PD\text{-}L2^{+/-}$ $CD73^{+/-}$	Quiescent, non-antibody-secreting B cells that have previously encountered antigen. These cells are poised to participate rapidly in secondary antibody responses	[12,16]

BCR = B cell receptor; IgM = immunoglobulin M; IL = interleukin.

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The development of B cells occurs in the bone marrow from haematopoietic stem cells [7]. Cells destined to become B cells progress to the pro–pre-B cell stage [17]. During the pro-phase of B cell development, B cells must produce a μ heavy chain through the variable (V), diversity (D) and joining (J) gene segment rearrangement [17]. The successfully rearranged μ heavy chain then combines with a non-polymorphic surrogate light chain to form a pre-B cell receptor (BCR) on the B cell surface [18]. Pre-BCR surface expression arrests the heavy chain rearrangement process and proliferation of the pro-B cell is initiated, a process driven by interleukin (IL)-7 [5,18,19]. Inefficiency in rearranging the μ heavy chain would result in elimination of the B cell [17]. The large population of newly generated pre-B cells begins rearranging the light chain through a similar process, only involving the V and J gene segments [17]. Once successful light chain rearrangement has occurred, the immunoglobulin (Ig)M BCR is assembled and expressed on the surface, therefore qualifying the B cell as a naive immature B cell [17]. Antigen-dependent negative selection pressures ensure that conventional immature B cells expressing autoreactive BCRs are silenced appropriately through either receptor editing via additional rearrangements, deletion or anergy [20].

Subsequent to exiting the bone marrow, immature B cells home to the secondary lymphoid tissues for further development. B cells are in the transitional type 1 (T1) B cell phase, characterized by low surface IgD [7]. Type 1 (T1) B cells are present in the spleen and bone marrow and do not possess the ability to recirculate [7]. Up-regulation of IgD surface expression designates the B cell as a transitional T2 B cell that can recirculate [21]. T2 B cells mature into either marginal zone or follicular B cells, a cell fate decision that depends upon BCR signalling strength [7].

Naive follicular B cells are characterized phenotypically by high IgD and low IgM surface expression and are the largest population of B cells [7,9]. Follicular B cells are strategically localized adjacent to the T cell zones in the spleen, ensuring optimal conditions for B and T cell interaction [7]. Follicular B cells are the B cell subset most likely to respond to T-dependent protein antigens [7]. Upon encountering antigen, follicular B cells present antigen to T cells and receive additional activation signals that promote antibody production by short-lived plasmablasts as well as formation of germinal centres. Within these specialized structures, germinal centre B cells undergo rapid expansion, affinity maturation through somatic hypermutation of immunoglobulin variable regions and isotype switching via exchange of immunoglobulin constant regions. Ultimately, this results in the production of high-affinity antibody by long-lived plasma cells and the establishment of a long-lived memory B cell pool poised to rapidly produce high-affinity antibody upon secondary antigen encounter [16].

Marginal zone B cells possess innate-like properties. Marginal zone B cells express high levels of Toll-like receptors (TLR) capable of recognizing microbial ligands, in addition to expressing polyreactive BCRs [22–25]. Marginal zone B cells are at the interface between the circulation and the white pulp of the spleen, allowing them to survey the blood for the presence of blood-borne antigens and shuttle antigens to follicular dendritic cells upon engagement [7,18,26]. One clear distinction between marginal zone B cells and follicular B cells is their self-renewing capability. Marginal zone B cells have an unlimited lifespan compared to the lifespan of follicular B cells, which is as little as a few weeks [27]. Marginal zone B cells typically respond to blood-borne pathogens in a T cell-independent manner, and may do so through engagement of both TLR and BCR [25]. This results in rapid differentiation of marginal zone B cells into antibody-producing plasmablasts, although this process is not effective at inducing conventional memory cells [28].

B-1 cells are innate-like cells enriched in the peritoneal and pleural cavities relative to other B cell populations, although similar numbers (but lower frequencies) are found in the spleen. Additional lymphoid tissues also harbour low frequencies of B-1 cells [9]. B-1 cells derive from a distinct progenitor than B-2 cells and are divided further into B-1a ($CD5^+$) and B-1b ($CD5^-$) cells based on their expression of CD5 and other developmental, functional and phenotypical characteristics [9]. B-1 B cells, similar to marginal zone B cells, primarily express germline-encoded antigen receptors specific for microbial and self-antigens, exhibiting limited diversity [9]. In contrast to the continuous development of B-2 cells *de novo*, B-1 cells undergo limited proliferation to replace dying cells [9]. Antibody production from B-1a cells comprises the natural antibody repertoire, which is generated in the absence of known antigenic exposure [9,29–31]. The natural antibody repertoire may exhibit low affinity and broad cross-reactivity; however, these antibodies directly neutralize and inhibit early pathogen replication [9,32–35]. In contrast, B-1b cells seem to have a more specialized role in rapidly producing antibodies in direct response to T cell-independent antigens, including antigens that lack TLR stimuli. B-1 cells are capable of undergoing class-switch recombination to all isotypes, but prefer switching to IgA in response to signals that are distinct from those that induce IgA switching in B-2 cells [9,36–38].

IL-10-secreting regulatory B cells encompass several relatively newly described IL-10-producing B cell subpopulations, some of which display phenotypical characteristics shared by 'innate-like' B-1 cell and marginal zone B cell populations [1,2,9,11,39]. IL-10-producing B cells are a type of regulatory B cell that suppresses the inflammatory response [1,2,11,40]. The frequency of IL-10-producing B cells is heightened at the climax of inflammation and inhibits progression of T helper type 2 (Th2)-driven diseases, making them critical cells for restraining autoimmunity [1,2,11]. IL-10-producing B cells inhibit Th1/Th17 cells during acute inflammation and induce T regulatory cells [1,2,41]. IL-10-producing B cells also work in parallel to the

newly discovered IL-35-producing B cells [10]. Similar to IL-10-producing B cells, IL-35-producing B cells are negative regulators of immunity, decreasing susceptibility to the development of autoimmune diseases [10].

Obesity entails infiltration of T cells into the adipose tissue

Obesity is associated with a wide range of complications that exact a high economic burden [42–44]. The most commonly studied complications of obesity include type II diabetes, hypertension, cancer, stroke and cardiovascular disease [43,45,46]. Obesity is characterized by chronic inflammation and lipid overload. Macrophages are well known to infiltrate adipose tissue and undergo a phenotypical switch from an anti-inflammatory M2 to a proinflammatory M1 phenotype that promotes insulin resistance [47]. Recently, the involvement of T lymphocytes in regulating adipose tissue inflammation has emerged primarily from rodent experiments. Nishimura *et al.* demonstrated that $CD8^+$ T cells infiltrated adipose tissue of mice consuming high fat diets prior to accumulation of M1 macrophages. Depletion of $CD8^+$ T cells with antibody improved the inflammatory profile and insulin/glucose sensitivity, suggesting that cytotoxic T cells are potential therapeutic targets in obesity and insulin resistance [48].

$CD4^+$ T cells also have a role in the pathogenesis of inflammation and insulin resistance in mouse models. Generally, helper $CD4^+$ T and regulatory forkhead box protein 3 $(FoxP3)^+$ T cells (T_{regs}) are less abundant in the adipose tissue. Classically defined Th1 cells appear to support a proinflammatory environment in contrast to Th2 cytokines, which have a beneficial role in improving inflammation and whole-body metabolism [49,50]. T_{regs} are critical for maintaining adipose tissue inflammation, whereas proinflammatory Th17 cells have also been identified in the adipose tissue of obese mice, which may be under the regulation of dendritic cells [51–53]. For example, Bertola *et al.* demonstrated that mouse $CD11c^+F4/80^{low}$ and human $CD11c^+CD1c^+$ dendritic cells accumulated in obese adipose tissue, which correlated with an increase in the frequency or differentiation of Th17 cells [54]. Overall, a variety of T cell subsets, in addition to other cell types such as invariant natural killer T cells and eosinophils, infiltrate the adipose tissue to regulate insulin and glucose sensitivity in obesity [55–57].

Select B cells can promote chronic inflammation through contact with T cells

Generally, there is no clear consensus on how obesity impacts B cell development in the bone marrow. For instance, Adler *et al.* showed that high fat diets suppress B cell lymphopoiesis [58]. This was in contrast to a previous study by Trottier *et al.*, which demonstrated that a high fat diet increased the frequency of B cells in addition to other cell types in the bone marrow [59]. Therefore, more work is clearly needed in this area to resolve some of the discrepant literature.

More recently, the involvement of B cells in adipose tissue inflammation associated with obesity has emerged. Winer *et al.* demonstrated that obesogenic diets promoted the infiltration of class-switched mature B cells into visceral adipose tissue. This was accompanied by an increase in serum and adipose-specific IgG2c, which is proinflammatory. Experiments with several mouse strains provided convincing evidence for the role of B cells in exacerbating chronic inflammation. For instance, B^{null} mice, which have a μ heavy chain knock-out, had improved insulin sensitivity despite consumption of a high fat diet. To further demonstrate cause and effect, B cells were transferred into B^{null} mice, which led to increased fasting insulin levels and diminished glucose clearance [60]. In contrast, B cell depletion with a monoclonal anti-CD20 antibody improved glucose tolerance and fasting insulin accompanied a reduction in the adipose inflammatory profile. Thus, the data suggested that depletion of B cells might be a potential therapeutic target in obesity. However, it is important to note that complete depletion of B cells and T cells, as demonstrated with severe combined immunodeficiency (SCID) mice consuming high fat diets, diminished glucose homeostasis compared to controls [61].

Mechanistically, *ex-vivo* measurements by Winer *et al.* showed that by suppressing B cell infiltration into adipose tissue, M1 macrophage activation, M1 polarization and expression of $CD8^+$ T activation markers were lowered. Furthermore, studies using major histocompatibility complex (MHC) I^{null} and MHC II^{null} mice revealed, respectively, that the activation of $CD8^+$ and $CD4^+$ T cells in the adipose tissue was probably driven by B cell antigen presentation to T cells. A recent report confirmed the role of MHC II in activating T cells in adipose tissue in response to leptin, and thereby accelerating the conversion of M2 to M1 macrophages [62]. In this study, adipocytes effectively presented ovalbumin to $CD4^+$ T cells, establishing adipose tissue-specific MHC II antigen presentation as one mechanism by which $CD4^+$ T cells are activated. Moreover, supporting microarray analysis revealed that obese women have increased MHC II expression in subcutaneous fat [62]. Nevertheless, the underlying antigen(s) presented by MHC class I and II molecules are unknown. This is a major obstacle to uncover in order to target B cells or B cell specific MHC I or II molecules to diminish adipose tissue inflammation.

The Nikolajcyk laboratory has also established that B cells have an inflammatory role in obesity and type II diabetes, which was mediated by T cells [63]. The authors reported that obesity enhanced proinflammatory cytokine secretion from B cells and verified the notion that B^{null} mice have improved glucose/insulin sensitivity, adipose tissue

inflammation, diminished adipose tissue hypertrophy and no effect on circulating adiponectin. Furthermore, B^{null} mice were found to have a higher proportion of T_{regs} and lower expression of Th17 cells. The results from the murine studies were then confirmed with human B cells. Co-culture experiments revealed that human B cells from type II diabetic patients had enhanced Th17 function driven specifically by B cells and not other cell types. A more recent study showed that murine periodontitis, a secondary inflammation associated with obesity and type II diabetes, was B cell-dependent [64]. These results open the door to the possibility that secondary inflammation in response to obesity may be B cell-driven and, again, B cells are potential therapeutic targets for improving aspects of diet-induced obesity.

The results from the aforementioned murine experiments provide strong support of observations made in human studies to show that type II diabetes, a common complication of obesity, results in increased proinflammatory cytokine secretion from B cells [65]. In particular, diabetic patients have elevated secretion of IL-8 accompanied by a lack of secretion of IL-10 in response to TLR agonists. IL-10 is noteworthy, given its anti-inflammatory role in insulin sensitivity [66,67].

IL-10-secreting regulatory B cells (B_{regs}) have an anti-inflammatory role in murine obesity

A potential beneficial role for B cells has also emerged in obesity. Nishimura *et al.* recently identified a distinct set of IL-10 secreting B_{regs}, which had a positive influence on adipose inflammation [68]. IL-10-secreting B cells from subcutaneous and epididymal adipose tissue were phenotyped via flow cytometry as $CD1d^{low}CD5^{-/low}CD11b^{low}CD21/CD35^{low}CD23^{-/low}CD25^{+}CD69^{+}CD72^{high}CD185^{-}CD196^{+}IgM^{+}IgD^{+}$. This population of B cells was phenotypically distinct from other IL-10-secreting B cells such as splenic B-10 cells, which are $CD1d^{high}CD5^{+}$. Several lines of evidence were provided to demonstrate that IL-10-secreting B cells in adipose tissue had a regulatory role. First, IL-10 selectively deleted from B cells increased the infiltration of $CD8^{+}$ T and M1 macrophages in adipose tissue of obese mice. Furthermore, lean mice that had deleted B_{regs} showed insulin resistance and limited fasting glucose clearance. Secondly, transplantation of B_{regs}, but not splenic B cells, from lean mice into obese B cell knock-out mice lowered interferon (IFN)-γ secretion from $CD8^{+}$ T cells and diminished tumour necrosis factor (TNF)-α secretion from macrophages. Similar results were also observed when B cells from lean mice were transferred adoptively into obese animals. The results from the murine study were correlated with human adipose tissue markers. Supporting gene expression profiles from isolated stromal vascular fractions from humans revealed that phenotypical markers for B cells and IL-10 had an inverse correlation with body mass index. One potential underlying mechanism may be that IL-10 secretion from B cells is regulated by IL-35 [69].

An intriguing aspect of the research by Nishimura *et al.* was the identification of several adipose-specific environmental factors that could support B_{reg} activity. *In vitro* treatment of adipose B_{regs} with the saturated fatty acid palmitate (C16:0) increased survival of the B_{reg} population. The rationale for studying palmitate was to model fatty acids that are released from adipose tissue in response to lipolysis and can serve as ligands for TLR-4 [70]. This was consistent with previous work to show that saturated and polyunsaturated fatty acids have differential effects on B cell and macrophage activation through TLRs [70–72]. However, it was not clear how saturated fatty acids would provide support for enhanced survival of the B_{reg} population.

Previous studies show that palmitate induces lipoapoptosis in several metabolic tissues, which has led to the hypothesis that saturated fatty acids can lead to lipotoxicity in several cell types, including macrophages [73–75]. For instance, Wen *et al.* demonstrated that palmitate treatment of bone marrow-derived macrophages selectively activated the NLRP3-ASC inflammasome, which is responsible for the activation of caspase-1 and secretion of IL-1β and IL-18 [76]. IL-1β, in turn, dysregulated insulin signalling *in vitro*, suggesting a potential mechanism by which palmitate in high fat diets may diminish insulin signalling *in vivo* [76]. This line of evidence is supported by data showing that obese individuals have higher levels of circulating saturated fatty acids [77]. Thus, future mechanistic studies need to resolve how palmitate would enhance IL-10 secretion from B cells in the context of the fatty acid exerting lipotoxic effects. Perhaps there are differences in the metabolic response to palmitate between select B cell subsets and macrophages. While one study showed that palmitate treatment induced lipoapoptosis of murine $B220^{+}$ splenic B cells, more studies are needed in this area [71].

The studies with palmitate also raise the question of what role each dietary fatty acid has on B cell activity. The diets used in many of the studies on B cells described above rely on high fat diets (60% of total kcal) that are predominately enriched in saturated and monounsaturated fatty acids. It is entirely possible that select fatty acids are promoting B cell dysfunction through the accumulation of select lipids as triglycerides, which can promote lipotoxicity. This notion is supported by a study showing that dendritic cells accumulate triglycerides in mouse models and in human cancer tissue samples [78]. Perhaps B cells can also accumulate triglycerides, which leads to changes in B cell activity.

The role of B cells in co-morbidities associated with obesity

Obesity is associated with a wide range of co-morbidities. Many of these have a B cell component that contributes

towards the pathology. For example, obesity can increase the risk for coronary atherosclerosis [79]. As reviewed elsewhere, atherosclerotic lesions in humans and mice contain B cells and B-1a cells are atheroprotective through the production of natural IgM antibodies [80–82]. Depletion of murine B cells with anti-CD20 antibody also leads to an improvement in atherosclerosis [83]. These results, similar to the studies described above for B cells in adipose tissue, reveal a delicate balance of B cells subsets that exert positive and negative effects.

One complication that is poorly studied is the impact of positive energy balance on host defence, and particularly humoral immunity [84]. Epidemiological studies have established that obese individuals are more likely to develop post-surgical infections [85,86]. Studies in rodents and humans also show that an increase in body mass index is correlated with increased susceptibility to bacterial and viral infections such as *Staphyloccocus pneumonia*, *Mycobacterium tuberclosis*, *H. pylori*, *Candida albicans*, encephalomyocarditis and influenza virus [84]. Furthermore, increased body mass index, although very poorly studied, is correlated with a poor vaccination response. For instance, Weber *et al.* showed that body mass index was a strong predictor of the inability to develop antibody to hepatitis B vaccine [87].

Targeting B cells in obesity may have potential benefits for improving adipose tissue-specific inflammation; however, this could compromise the immune response to infection. Very few laboratories have addressed how B cell activity is influenced by obesity. Milner *et al.* recently demonstrated that obese mice, relative to lean controls, delayed the primary antibody response to a sublethal challenge with influenza PR8 infection [88]. Obese mice displayed a lower rate of production of haemagglutination inhibition (HAI) antibodies, and HAI antibodies were undetectable in obese mice by 35 days postinfection. Furthermore, during a secondary heterologous challenge with H1N1, there was a nearly 50% reduction in the frequency of obese mice that had detectable H1N1 HAI antibodies in serum. In addition, only 5% of obese mice had HAI antibodies to PR8 upon the secondary infection with H1N1 relative to 75% of the lean controls with detectable HAI antibodies to PR8 [88]. These findings were consistent with human studies to show that obese individuals have a steep decline in antibody production to influenza vaccination compared to lean controls [89]. While the mechanisms by which obesity suppresses antibody production are pleiotropic, the cellular mechanisms at the level of the B cell are unknown. For instance, it is unclear if obesity is suppressing the frequency of antibody-producing cells that respond to infection and/or if the decrease in antibody production is driven by dysregulation at the molecular level.

Chronic inflammation and humoral immunity are influenced by long chain polyunsaturated fatty acids and specialized pro-resolving lipid mediators

The composition of dietary fat influences the immune response, but is not well studied in relation to B cells [90]. The studies described above relied on high fat diets that are not highly enriched in n-3 polyunsaturated fatty acids (PUFAs). A few emerging studies show diets containing n-3 PUFAs, derived from marine oils, can also impact B cell activation and antibody production. Generally, n-3 PUFAs have beneficial effects for treating elevated triglycerides, a common symptom associated with obesity and type II diabetes [91]. Furthermore, during the past decade studies have revealed that n-3 PUFAs suppress chronic inflammation associated with obesity in preclinical models [92,93].

n-3 PUFAs may boost murine humoral responses from B-1 and B-2 cells, depending on the model system. Teague *et al.* demonstrated that administration of n-3 PUFAs from fish oil, modelling human pharmacological intake, to C57BL/6 mice modestly enhanced IgM levels in lean mice and rescued the decrement in antibody production in obesity in response to *in vivo* stimulation with a hapten-conjugated lipopolysaccharide (LPS) [94]. The enhancement in antibody production correlated with an increase in the frequency of select B cell subsets. Similarly, n-3 PUFAs as ethyl esters modestly increased natural IgM and fecal IgA in diet-induced obesity, again correlating with an increased frequency of B-2 cell subsets [95]. These findings were consistent with work to show that n-3 PUFAs enhanced LPS-driven cytokine secretion from $B220^{+}$ splenic B cells in lean and obese C57BL/6 and colitis-prone $SMAD3^{-/-}$ mice [71,96,97]. In addition, a recent murine study demonstrated that n-3 PUFAs enhanced the frequency of B-1 cells and increased antigen-specific IgM levels in a mouse model of peritonitis but had no influence on the B-2 response [71,96–98]. Altogether, dietary n-3 PUFAs may have the potential to enhance B cell-mediated immunity in diet-induced obesity. However, it remains unclear if this would ultimately have a beneficial effect, notably on B cells in the adipose tissue that are regulating insulin and glucose sensitivity. As described above, the role of dietary fat composition may be an important variable in regulating B cell activity at a mechanistic level.

Specialized pro-resolving lipid mediators (SPM) also have a role in suppressing adipose tissue inflammation and potentially boosting humoral immunity. SPMs are synthesized endogenously from n-3 and n-6 PUFAs and aid in the resolution phase of inflammation [99–101]. SPMs are broadly categorized as resolvins, protectins, lipoxins and maresins that target G-protein-coupled receptors in a stereospecific manner to limit inflammatory responses [101]. Recent reports suggest that SPMs aid in resolving adipose tissue inflammation. For instance, adipose tissue samples collected from obese humans reveal a reduction in

select SPMs [102]. Supporting animal studies show that administration of select SPMs can improve adipose tissue inflammation and insulin sensitivity [103,104]. SPMs also have potential benefits for boosting the immune response to infection. Protectin D1, which is produced from the oxygenation of the n-3 PUFA docosahexaenoic acid, suppressed influenza replication and improved survival in response to severe influenza infection [105]. This efficacy of protectin D1 was of significance, given that many pharmacological interventions fail in severe influenza infection. This raises the possibility of developing SPMs for clinical intervention, particularly in the obese population, which has compromised immunity.

Far less is known about the role of SPMs on B cell activity. The SPMs resolvin D1 (RvD1) and 17(*R*)-hydroxy docosahexaenoic acid (17-HDHA), derived from docosahexaenoic acid and found in the murine spleen, increased antigen-specific IgM production from human $CD19^+$ B cells when stimulated with cytosine–phosphate–guanosine (CpG) oligonucleotide (ODN) 2395 and anti-IgM in cell culture [106]. 17-HDHA also increased IgM and IgG levels after 7 days of incubation in culture in a dose-dependent manner [106]. B cell proliferation assays revealed that 17-HDHA did not influence the number of B cells; however, it increased the number of B cells secreting IgM and IgG [106]. In another study, LXA4, a lipoxin derived from arachidonic acid with known anti-inflammatory properties, was shown to suppress IgM and IgG production of primary human $CD19^+$ $CD27^+$ memory B cells in response to stimulation with CpG ODN 2395 [107]. Furthermore, *in vivo* studies with mice showed that ovalbumin-specific IgM and IgG production was also suppressed in response to LXA4. Taken together, these studies reveal SPMs can have immunomodulatory effects on B cells, and consistent with studies on inflammation, not all SPMs are equal. Clearly more studies are needed in this area at the functional and mechanistic levels, particularly in the context of obesity.

Summary

The role of B cells in regulating inflammatory and humoral immune responses in the context of obesity is in its infancy. Some B cell subsets can exacerbate adipose tissue inflammation through interactions with other adipose resident immune cells, particularly $CD4^+$ T cells. Other B cell subsets such as IL-10 secreting B_{regs} have anti-inflammatory and insulin-sensitizing effects in obesity. Furthermore, manipulating the composition of high fat diets with select long chain polyunsaturated fatty acids or their derived lipid mediators could improve tissue inflammation and B cell activity. More studies are clearly needed in this area, given the potential to target B cells through dietary and pharmacological intervention for improving the obese phenotype and treating its associated co-morbidities.

Disclosure

The authors have no conflicts of interest.

References

1 Mauri C, Bosma A. Immune regulatory function of B cells. Ann Rev Immunol 2012; **30**:221–41.
2 Candando KM, Lykken JM, Tedder TF. B10 cell regulation of health and disease. Immunol Rev 2014; **259**:259–72.
3 Nagasawa T. Microenvironmental niches in the bone marrow required for B-cell development. Nat Rev Immunol 2006; **6**:107–16.
4 Allman D, Li J, Hardy RR. Commitment to the B lymphoid lineage occurs before DH–JH recombination. J Exp Med 1999; **189**:735–40.
5 Herzog S, Reth M, Jumaa H. Regulation of B-cell proliferation and differentiation by pre-B-cell receptor signalling. Nat Rev Immunol 2009; **9**:195–205.
6 King LB, Monroe JG. Immunobiology of the immature B cell: plasticity in the B-cell antigen receptor-induced response fine tunes negative selection. Immunol Rev 2000; **176**:86–104.
7 Pillai S, Cariappa A. The follicular versus marginal zone B lymphocyte cell fate decision. Nat Rev Immunol 2009; **9**:767–77.
8 Pillai S, Cariappa A, Moran ST. Marginal zone B cells. Annu Rev Immunol 2005; **23**:161–96.
9 Baumgarth N. The double life of a B-1 cell: self-reactivity selects for protective effector functions. Nat Rev Immunol 2011; **11**:34–46.
10 Shen P, Roch T, Lampropoulou V *et al.* IL-35-producing B cells are critical regulators of immunity during autoimmune and infectious diseases. Nature 2014; **507**:366–70.
11 Mizoguchi A, Mizoguchi E, Takedatsu H, Blumberg RS, Bhan AK. Chronic intestinal inflammatory condition generates IL-10-producing regulatory B cell subset characterized by CD1d upregulation. Immunity 2002; **16**:219–30.
12 Zuccarino-Catania GV, Sadanand S, Weisel FJ *et al.* CD80 and PD-L2 define functionally distinct memory B cell subsets that are independent of antibody isotype. Nat Immunol 2014; **15**:631–7.
13 Weber GF, Chousterman BG, Hilgendorf I *et al.* Pleural innate response activator B cells protect against pneumonia via a GM-CSF–IgM axis. J Exp Med 2014; **211**:1243–56.
14 Rauch PJ, Chudnovskiy A, Robbins CS *et al.* Innate response activator B cells protect against microbial sepsis. Science 2012; **335**:597–601.
15 Shapiro-Shelef M, Calame K. Regulation of plasma-cell development. Nat Rev Immunol 2005; **5**:230–42.
16 Shlomchik MJ, Weisel F. Germinal center selection and the development of memory B and plasma cells. Immunol Rev 2012; **247**:52–63.
17 Zuidscherwoude M, de Winde CM, Cambi A, van Spriel AB. Microdomains in the membrane landscape shape antigen-presenting cell function. J Leukoc Biol 2014; **95**:251–63.
18 Clark MR, Mandal M, Ochiai K, Singh H. Orchestrating B cell lymphopoiesis through interplay of IL-7 receptor and pre-B cell receptor signalling. Nat Rev Immunol 2014; **14**:69–80.
19 Clark MR, Cooper AB, Wang LD, Aifantis I. The pre-B cell receptor in B cell development: recent advances, persistent questions and conserved mechanisms. Curr Top Microbiol Immunol 2005; **290**:87–103.

20 Nemazee D. Receptor editing in lymphocyte development and central tolerance. Nat Rev Immunol 2006; **6**:728–40.

21 Allman D, Lindsley RC, DeMuth W, Rudd K, Shinton SA, Hardy RR. Resolution of three nonproliferative immature splenic B cell subsets reveals multiple selection points during peripheral B cell maturation. J Immunol 2001; **167**:6834–40.

22 Treml LS, Carlesso G, Hoek KL *et al.* TLR stimulation modifies BLyS receptor expression in follicular and marginal zone B cells. J Immunol 2007; **178**:7531–9.

23 He B, Santamaria R, Xu W *et al.* The transmembrane activator TACI triggers immunoglobulin class switching by activating B cells through the adaptor MyD88. Nat Immunol 2010; **11**:836–45.

24 Janeway CA Jr, Medzhitov R. Innate immune recognition. Ann Rev Immunol 2002; **20**:197–216.

25 Cerutti A, Cols M, Puga I. Marginal zone B cells: virtues of innate-like antibody-producing lymphocytes. Nat Rev Immunol 2013; **13**:118–32.

26 Cinamon G, Zachariah MA, Lam OM, Foss FW, Cyster JG. Follicular shuttling of marginal zone B cells facilitates antigen transport. Nat Immunol 2008; **9**:54–62.

27 Hao Z, Rajewsky K. Homeostasis of peripheral B cells in the absence of B cell influx from the bone marrow. J Exp Med 2001; **194**:1151–64.

28 Martin F, Oliver AM, Kearney JF. Marginal zone and B1 B cells unite in the early response against T-independent blood-borne particulate antigens. Immunity 2001; **14**:617–29.

29 Bos NA, Kimura H, Meeuwsen CG *et al.* Serum immunoglobulin levels and naturally occurring antibodies against carbohydrate antigens in germ-free BALB/c mice fed chemically defined ultrafiltered diet. Eur J Immunol 1989; **19**:2335–9.

30 Haury M, Sundblad A, Grandien A, Barreau C, Coutinho A, Nobrega A. The repertoire of serum IgM in normal mice is largely independent of external antigenic contact. Eur J Immunol 1997; **27**:1557–63.

31 Hooijkaas H, Benner R, Pleasants JR, Wostmann BS. Isotypes and specificities of immunoglobulins produced by germ-free mice fed chemically defined ultrafiltered 'antigen-free' diet. Eur J Immunol 1984; **14**:1127–30.

32 Baumgarth N, Herman OC, Jager GC, Brown LE, Herzenberg LA, Chen J. B-1 and B-2 cell-derived immunoglobulin M antibodies are nonredundant components of the protective response to influenza virus infection. J Exp Med 2000; **192**:271–80.

33 Boes M, Prodeus AP, Schmidt T, Carroll MC, Chen J. A critical role of natural immunoglobulin M in immediate defense against systemic bacterial infection. J Exp Med 1998; **188**:2381–6.

34 Ochsenbein AF, Fehr T, Lutz C *et al.* Control of early viral and bacterial distribution and disease by natural antibodies. Science 1999; **286**:2156–9.

35 Zhou ZH, Zhang Y, Hu YF, Wahl LM, Cisar JO, Notkins AL. The broad antibacterial activity of the natural antibody repertoire is due to polyreactive antibodies. Cell Host Microbe 2007; **1**:51–61.

36 Kaminski DA, Stavnezer J. Enhanced IgA class switching in marginal zone and B1 B cells relative to follicular/B2 B cells. J Immunol 2006; **177**:6025–9.

37 Tarlinton DM, McLean M, Nossal GJ. B1 and B2 cells differ in their potential to switch immunoglobulin isotype. Eur J Immunol 1995; **25**:3388–93.

38 Roy B, Brennecke AM, Agarwal S, Krey M, Duber S, Weiss S. An intrinsic propensity of murine peritoneal B1b cells to switch to IgA in presence of TGF-beta and retinoic acid. PLOS ONE 2013; **8**:e82121.

39 Yanaba K, Bouaziz JD, Haas KM, Poe JC, Fujimoto M, Tedder TF. A regulatory B cell subset with a unique CD1dhiCD5+ phenotype controls T cell-dependent inflammatory responses. Immunity 2008; **28**:639–50.

40 Fillatreau S, Sweenie CH, McGeachy MJ, Gray D, Anderton SM. B cells regulate autoimmunity by provision of IL-10. Nat Immunol 2002; **3**:944–50.

41 Carter NA, Vasconcellos R, Rosser EC *et al.* Mice lacking endogenous IL-10-producing regulatory B cells develop exacerbated disease and present with an increased frequency of Th1/Th17 but a decrease in regulatory T cells. J Immunol 2011; **186**:5569–79.

42 Finkelstein EA, Trogdon JG, Cohen JW, Dietz W. Annual medical spending attributable to obesity: payer- and service-specific estimates. Health Aff 2009; **28**:w822–w831.

43 Prospective studies C. Body-mass index and cause-specific mortality in 900 000 adults: collaborative analyses of 57 prospective studies. Lancet 2009; **373**:1083–96.

44 Malik VS, Willett WC, Hu FB. Global obesity: trends, risk factors and policy implications. Nat Rev Endocrinol 2013; **9**:13–27.

45 Manson JE, Colditz GA, Stampfer MJ *et al.* A prospective study of obesity and risk of coronary heart disease in women. N Eng J Med 1990; **322**:882–9.

46 Calle EE, Rodriguez C, Walker-Thurmond K, Thun MJ. Overweight, obesity, and mortality from cancer in a prospectively studied cohort of U.S. adults. N Engl J Med 2003; **348**:1625–38.

47 Lumeng CN, Bodzin JL, Saltiel AR. Obesity induces a phenotypic switch in adipose tissue macrophage polarization. J Clin Invest 2007; **117**:175–84.

48 Nishimura S, Manabe I, Nagasaki M *et al.* CD8+ effector T cells contribute to macrophage recruitment and adipose tissue inflammation in obesity. Nat Med 2009; **15**:914–20.

49 Winer S, Chan Y, Paltser G *et al.* Normalization of obesity-associated insulin resistance through immunotherapy. Nat Med 2009; **15**:921–9.

50 Feuerer M, Herrero L, Cipolletta D *et al.* Lean, but not obese, fat is enriched for a unique population of regulatory T cells that affect metabolic parameters. Nat Med 2009; **15**:930–9.

51 Winer S, Paltser G, Chan Y *et al.* Obesity predisposes to Th17 bias. Eur J Immunol 2009; **39**:2629–35.

52 Chen Y, Tian J, Tian X *et al.* Adipose tissue dendritic cells enhances inflammation by prompting the generation of Th17 cells. PLOS ONE 2014; **9**:e92450.

53 Zhong J, Rao X, Braunstein Z *et al.* T-cell costimulation protects obesity-induced adipose inflammation and insulin resistance. Diabetes 2014; **63**:1289–302.

54 Bertola A, Ciucci T, Rousseau D *et al.* Identification of adipose tissue dendritic cells correlated with obesity-associated insulin-resistance and inducing Th17 responses in mice and patients. Diabetes 2012; **61**:2238–47.

55 Schipper HS, Rakhshandehroo M, van de Graaf SFJ *et al.* Natural killer T cells in adipose tissue prevent insulin resistance. J Clin Invest 2012; **122**:3343–54.

56 Lynch L, Nowak M, Varghese B *et al.* Adipose tissue invariant NKT cells protect against diet-induced obesity and metabolic disorder through regulatory cytokine production. Immunity 2012; **37**:574–87.

57 Wu D, Molofsky AB, Liang H-E *et al*. Eosinophils sustain adipose alternatively activated macrophages associated with glucose homeostasis. Science 2011; **332**:243–7.

58 Adler BJ, Green DE, Pagnotti GM, Chan ME, Rubin CT. High fat diet rapidly suppresses B lymphopoiesis by disrupting the supportive capacity of the bone marrow niche. PLOS ONE 2014; **9**:e90639.

59 Trottier MD, Naaz A, Li Y, Fraker PJ. Enhancement of hematopoiesis and lymphopoiesis in diet-induced obese mice. Proc Natl Acad Sci USA 2012; **109**:7622–9.

60 Winer D, Winer S, Shen L *et al*. B cells promote insulin resistance through modulation of T cells and production of pathogenic IgG antibodies. Nat Med 2011; **17**:610–17.

61 Ballak DB, Stienstra R, Hijmans A, Joosten LAB, Netea MG, Tack CJ. Combined B- and T-cell deficiency does not protect against obesity-induced glucose intolerance and inflammation. Cytokine 2013; **62**:96–103.

62 Deng T, Lyon Christopher J, Minze Laurie J *et al*. Class II major histocompatibility complex plays an essential role in obesity-induced adipose inflammation. Cell Metab 2013; **17**:411–22.

63 DeFuria J, Belkina AC, Jagannathan-Bogdan M *et al*. B cells promote inflammation in obesity and type 2 diabetes through regulation of T-cell function and an inflammatory cytokine profile. Proc Natl Acad Sci USA 2013; **110**:5133–8.

64 Zhu M, Belkina AC, DeFuria J *et al*. B cells promote obesity-associated periodontitis and oral pathogen-associated inflammation. J Leukoc Biol 2014; **96**:349–57.

65 Jagannathan M, McDonnell M, Liang Y *et al*. Toll-like receptors regulate B cell cytokine production in patients with diabetes. Diabetologia 2010; **53**:1461–71.

66 van Exel E, Gussekloo J, de Craen AJM, Frölich M, Bootsma-van der Wiel A, Westendorp RGJ. Low production capacity of interleukin-10 associates with the metabolic syndrome and type 2 diabetes: the leiden 85-plus study. Diabetes 2002; **51**:1088–92.

67 Kim H-J, Higashimori T, Park S-Y *et al*. Differential effects of interleukin-6 and -10 on skeletal muscle and liver insulin action *in vivo*. Diabetes 2004; **53**:1060–7.

68 Nishimura S, Manabe I, Takaki S *et al*. Adipose natural regulatory B cells negatively control adipose tissue inflammation. Cell Metab 2013; **18**:759–66.

69 Wang R-X, Yu C-R, Dambuza IM *et al*. Interleukin-35 induces regulatory B cells that suppress autoimmune disease. Nat Med 2014; **20**:633–41.

70 Huang S, Rutkowsky JM, Snodgrass RG *et al*. Saturated fatty acids activate TLR-mediated proinflammatory signaling pathways. J Lipid Res 2012; **53**:2002–13.

71 Rockett BD, Salameh M, Carraway K, Morrison K, Shaikh SR. n-3 PUFA improves fatty acid composition, prevents palmitate-induced apoptosis, and differentially modifies B cell cytokine secretion in vitro and ex vivo. J Lipid Res 2010; **51**:1284–97.

72 Wong SW, Kwon M-J, Choi AMK, Kim H-P, Nakahira K, Hwang DH. Fatty acids modulate Toll-like receptor 4 activation through regulation of receptor dimerization and recruitment into lipid rafts in a reactive oxygen species-dependent manner. J Biol Chem 2009; **284**:27384–92.

73 Schaffer JE. Lipotoxicity: when tissues overeat. Curr Opin Lipidol 2003; **14**:281–7.

74 Listenberger LL, Han X, Lewis SE *et al*. Triglyceride accumulation protects against fatty acid-induced lipotoxicity. Proc Natl Acad Sci USA 2003; **100**:3077–82.

75 Schilling JD, Machkovech HM, He L, Diwan A, Schaffer JE. TLR4 activation under lipotoxic conditions leads to synergistic macrophage cell death through a TRIF-dependent pathway. J Immunol 2013; **190**:1285–96.

76 Wen H, Gris D, Lei Y *et al*. Fatty acid-induced NLRP3-ASC inflammasome activation interferes with insulin signaling. Nat Immunol 2011; **12**:408–15.

77 Cascio G, Schiera G, Di Liegro I. Dietary fatty acids in metabolic syndrome, diabetes and cardiovascular diseases. Curr Diabetes Rev 2012; **8**:2–17.

78 Herber DL, Cao W, Nefedova Y *et al*. Lipid accumulation and dendritic cell dysfunction in cancer. Nat Med 2010; **16**:880–6.

79 McGill HC, McMahan CA, Herderick EE *et al*. Obesity accelerates the progression of coronary atherosclerosis in young men. Circulation 2002; **105**:2712–18.

80 Tsiantoulas D, Diehl CJ, Witztum JL, Binder CJ. B cells and humoral immunity in atherosclerosis. Circ Res 2014; **114**:1743–56.

81 Mohanta SK, Yin C, Peng L *et al*. Artery tertiary lymphoid organs contribute to innate and adaptive immune responses in advanced mouse atherosclerosis. Circ Res 2014; **114**:1772–87.

82 Kyaw T, Tipping P, Bobik A, Toh B-H. Protective role of natural IgM-producing B1a cells in atherosclerosis. Trends Cardiovasc Med 2012; **22**:48–53.

83 Ait-Oufella H, Herbin O, Bouaziz JD *et al*. B cell depletion reduces the development of atherosclerosis in mice. J Exp Med 2010; **207**:1579–87.

84 Karlsson EA, Beck MA. The burden of obesity on infectious disease. Exp Biol Med 2010; **235**:1412–24.

85 Anaya DA, Dellinger EP. The obese surgical patient: a susceptible host for infection. Surg Infect (Larchmt) 2006; **7**:473–80.

86 Choban PS, Flancbaum L. The impact of obesity on surgical outcomes: a review. J Am Coll Surg 1997; **185**:593–603.

87 Weber DJ, Rutala WA, Samsa GP, Santimaw JE, Lemon SM. Obesity as a predictor of poor antibody response to hepatitis b plasma vaccine. JAMA 1985; **254**:3187–9.

88 Milner JJ, Sheridan PA, Karlsson EA, Schultz-Cherry S, Shi Q, Beck MA. Diet-induced obese mice exhibit altered heterologous immunity during a secondary 2009 pandemic H1N1 infection. J Immunol 2013; **191**:2474–85.

89 Sheridan PA, Paich HA, Handy J *et al*. Obesity is associated with impaired immune response to influenza vaccination in humans. Int J Obes (Lond) 2012; **36**:1072–7.

90 Wallace FA, Miles EA, Evans C, Stock TE, Yaqoob P, Calder PC. Dietary fatty acids influence the production of Th1- but not Th2-type cytokines. J Leukoc Biol 2001; **69**:449–57.

91 Davidson MH, Stein EA, Bays HE *et al*. Efficacy and tolerability of adding prescription omega-3 fatty acids 4 g/d to Simvastatin 40 mg/d in hypertriglyceridemic patients: an 8-week, randomized, double-blind, placebo-controlled study. Clin Ther 2007; **29**:1354–67.

92 Kim J, Li Y, Watkins BA. Fat to treat fat: emerging relationship between dietary PUFA, endocannabinoids, and obesity. Prostaglandins Other Lipid Mediat 2013; **104–105**:32–41.

93 Kalupahana NS, Claycombe KJ, Moustaid-Moussa N. (n-3) Fatty acids alleviate adipose tissue inflammation and insulin resistance: mechanistic insights. Adv Nutr 2011; **2**:304–16.

94 Teague H, Fhaner CJ, Harris M, Duriancik DM, Reid GE, Shaikh SR. n-3 PUFAs enhance the frequency of murine B-cell subsets and restore the impairment of antibody production to a T-independent antigen in obesity. J Lipid Res 2013; **54**:3130–8.
95 Teague H, Harris M, Fenton J, Lallemand P, Shewchuk B, Shaikh SR. Eicosapentaenoic and docosahexaenoic acid ethyl esters differentially enhance B-cell activity in murine obesity. J Lipid Res 2014; **55**:1420–33.
96 Gurzell EA, Teague H, Harris M, Clinthorne J, Shaikh SR, Fenton JI. DHA-enriched fish oil targets B cell lipid microdomains and enhances *ex vivo* and *in vivo* B cell function. J Leukoc Biol 2013; **93**:463–70.
97 Rockett BD, Teague H, Harris M *et al*. Fish oil increases raft size and membrane order of B cells accompanied by differential effects on function. J Lipid Res 2012; **53**:674–85.
98 Tomasdottir V, Thorleifsdottir S, Vikingsson A, Hardardottir I, Freysdottir J. Dietary omega-3 fatty acids enhance the B1 but not the B2 cell immune response in mice with antigen-induced peritonitis. J Nutr Biochem 2014; **25**:111–17.
99 Bannenberg G, Serhan CN. Specialized pro-resolving lipid mediators in the inflammatory response: an update. Biochim Biophys Acta 2010; **1801**:1260–73.
100 Spite M, Clària J, Serhan Charles N. Resolvins, specialized proresolving lipid mediators, and their potential roles in metabolic diseases. Cell Metab 2014; **19**:21–36.
101 Serhan CN. Pro-resolving lipid mediators are leads for resolution physiology. Nature 2014; **510**:92–101.
102 Clària J, Dalli J, Yacoubian S, Gao F, Serhan CN. Resolvin D1 and resolvin D2 govern local inflammatory tone in obese fat. J Immunol 2012; **189**:2597–605.
103 González-Périz A, Horrillo R, Ferré N *et al*. Obesity-induced insulin resistance and hepatic steatosis are alleviated by ω-3 fatty acids: a role for resolvins and protectins. FASEB J 2009; **23**:1946–57.
104 Neuhofer A, Zeyda M, Mascher D *et al*. Impaired local production of proresolving lipid mediators in obesity and 17-HDHA as a potential treatment for obesity-associated inflammation. Diabetes 2013; **62**:1945–56.
105 Morita M, Kuba K, Ichikawa A *et al*. The lipid mediator protectin D1 inhibits influenza virus replication and improves severe influenza. Cell 2013; **153**:112–25.
106 Ramon S, Gao F, Serhan CN, Phipps RP. Specialized proresolving mediators enhance human B cell differentiation to antibody-secreting cells. J Immunol 2012; **189**:1036–42.
107 Ramon S, Bancos S, Serhan CN, Phipps RP. Lipoxin A4 modulates adaptive immunity by decreasing memory B-cell responses via an ALX/FPR2-dependent mechanism. Eur J Immunol 2014; **44**:357–69.