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Current Opinion in Immunology

Control of innate-like B cell location for compartmentalised IgM production

Lucy H Jackson-Jones and Cécile Bénézech

Natural IgM are crucial for early protection against infection and play an important homeostatic function by clearing dead cells. The production of IgM is ensured by a population of B cells with innate-like properties: their response is rapidly activated by innate signals early during the onset of infection. The main reservoir of innate-like B cells (IBCs) are the serous cavities, but their maintenance and activation depends on their relocation to a variety of lymphoid tissues. Recent advances indicate that fat-associated lymphoid clusters (FALCs) and milky spots contribute to local IgM secretion and play a central role in the localisation and regulation of IBC function.

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Introduction

IBCs are characterised by a poly-specific BCR repertoire enriched for receptors that bind microbial and self-antigens and are responsible for the majority of circulating IgM in uninfected animals. These so called 'natural' IgM form pentamers with high neutralisation and complement activation capacity [1]. Self-reactivity and the capacity to be promptly activated following innate stimulation by Toll-like receptor (TLR) agonists and microbial pathogens confers to these B cell subsets an important role in tissue homeostasis and host protection [1]. The main IBC compartment is composed of the B cells of the serous cavities, represented by CD11b expressing B1 cells, divided into two main subsets B1a and B1b based on their expression of CD5, and a minority of serous B2 cells that do not express CD11b.

Paradoxically, serous IBCs cannot secrete IgM [2] and rely on various homing mechanisms to find a lymphoid niche enabling secretion of IgM. Their capacity to migrate to different locations depending on the immune context, ensures production of IgM in the relevant compartment. Indeed, IgM is a large molecule and as such, secretion into the circulation does not guarantee efficacy at sites of infection. In this review, we will discuss the mechanisms controlling the re-location of serous B cells to local lymphoid niches for the secretion of protective IgM and the emerging importance of FALCs and milky spots for IBC immune function.

FALCs and milky spots are essential for the maintenance and function of IBCs in serous cavities

FALCs and milky spots: homeostatic niches for the maintenance of IBCs in serous cavities

The fluid filled phase of the serous cavities plays an important lubricative function for the visceral organs, and is home to various immune cell populations including macrophages [3], T-cells and IBCs [4]. Serous IBCs are as dependent on the existence of a homeostatic niche for their maintenance and activation as conventional B cells. In the serous cavities, this niche is provided by small immune aggregates found in various visceral adipose tissues [5,6]. These aggregates were first identified in the omentum, a large apron-like adipose tissue covering the viscera in humans and called milky spots, because of their visible milky appearance. Existence of similar structures called FALCs was then reported in the mesenteries [7••], the mediastinum and pericardium of mice [8••]. These structures produce the chemotactic B cell factor CXCL13, which is critical for the maintenance of B cells in serous cavities [8••,9–11]. Interestingly, all IBCs express the atypical chemokine receptor D6, which seems to fine-tune CXCL13 responsiveness and control IBC homing and anti-Phosphorylcholine antibody generation [12]. The fact that CXCL13 is required to maintain a normal number of IBCs in serous cavities [9] and that after intra-pleural injection, a fraction of pleural cavity B cells spontaneously home to FALCs [13•], suggests that continuous recirculation to FALCs and milky spots is necessary for IBC homeostasis. To stay in serous cavities, IBCs express very high levels of α4, α6 and β1 integrins as well as CD9 [10], which enable their adherence to the parietal and visceral mesothelium of the serous cavity. Upon TLR stimulation, down-regulation of the surface expression of these molecules induces increased mobility of IBCs and egress from peritoneal cavity toward CXCL13 producing clusters in the omentum, mesenteries and spleen [10].

FALCs and milky spots are a local source of IL-33 and IL-5 for IBC activation in serous cavities

Studies by Moro *et al.* and in our lab identify two key factors secreted by FALCs and milky spots necessary for IBC activation: the cytokine IL-5 produced by type 2 innate lymphoid cells (ILC2) [7••] and the nuclear alarmin IL-33 produced by Gp38^{+}CD31^{-} FALC stromal cells [13•]. IL-5 is a crucial factor for the maintenance and activation of IBC [14], which is produced by FALC ILC2 both at homeostasis to ensure self-renewal [7••] and upon immune challenge to allow proliferation and antibody secretion of serous B1 and B2 cells [13•]. IL-33 is likely to link inflammation, ILC2 activation, IL-5 release and IBC activation. What controls the release of IL-33 by FALC stromal cells is not understood but it is clear that IL-33 function is limited in time and space by its rapid inactivation by oxidation [15] and that FALC provide an IL-33 rich environment bringing together ILC2 and IBCs. Whether this is important for the maintenance of basal ILC2 and IBC numbers remains to be clarified.

FALCs and milky spots allow production of IgM for protection of serous cavities

Activation of IBCs in the omentum, mediastinum and pericardium leads to secretion of poly-reactive IgM in the peritoneal, pleural/pericardial cavities, which does not diffuse away from the cavity of origin and protects the serous cavity locally. This is exemplified in the model of filarial infection *Litomosoides sigmodontis* which resides between the pleural membranes of its murine host. The presence of this worm activates FALCs within the pericardium and mediastinum to secrete large amounts of IgM that can be detected within the pleural (site of infection) but not the peritoneal (separate compartment) lavage fluid [13•]. Importantly this locally produced antibody is not detectable in the lavage fluid of naïve animals, nor is it detectable in the serum during the innate phase of this infection [13•]. The inability to detect such a response in the serum highlights a deficit in many of the studies to date that attempt to address the contribution of serous B-cells to innate antibody production but fail to look locally within the serous cavities. Secreted IgM is unquestionably important for protection following infection within the peritoneal cavity as shown by studies in mice that lack secreted IgM. Worm survival is enhanced in animals infected with the filarial nematode *Brugia malayi* in the absence of secreted IgM [16]. Survival of animals that lack secreted IgM is reduced in a model of peritonitis induced by cecal ligation and puncture, in which intestinal contents (bacteria) are released into the peritoneal cavity [17]. Using splenectomised mice, a recent study confirmed the importance of the omentum as a site of IgM production for protection from intraperitoneal bacterial infection [18]. Within the peritoneal cavity, natural IgM works in concert with macrophages and complement to neutralise pathogens (worms and bacteria alike), limiting their systemic spread.

Serous B-cell relocation: getting secretion of IgM in the right compartment

The spleen and bone marrow (BM): secretion of natural IgM into the blood

B1 cells produce 80–90% of the total serum IgM pool in uninfected mice [19], which is crucial for limiting the early spread of infection and for protection against a number of pathogens [1]. The spleen and BM, while only hosting a small proportion of B1 cells compared to the serous cavities, are the main producers of basal serum IgM [20–26]. A recent study revealed the existence of two main subsets of IgM secreting B1 cells in the spleen and BM: one dependent on B lymphocyte-induced maturation protein 1 (Blimp-1) and terminal differentiation into CD138^{+} plasma cells and one independent of Blimp-1 [24]. When migrating to the spleen, peritoneal B1a cells gain the expression of CD6, which is required for self-renewal of this population in the spleen [27]. Studies in splenectomised and asplenic mice confirm the importance of the spleen for supporting the production of serum IgM and for maintaining the B1a cell pool in the peritoneal cavity [28,29]. However, it is unclear whether peritoneal B1 cells are dependent on a splenic precursor for their maintenance or are indirectly affected by reduced serum IgM levels in splenectomised mice. Conversely, upon infection, peritoneal cavity B1 cells migrate to the spleen in response to TLR activation, which allows increased secretion of poly-reactive IgM into the circulation at early stages of infection [10,26] to limit the spread of blood-borne pathogens [30] and the risk of sepsis during peritonitis [17].

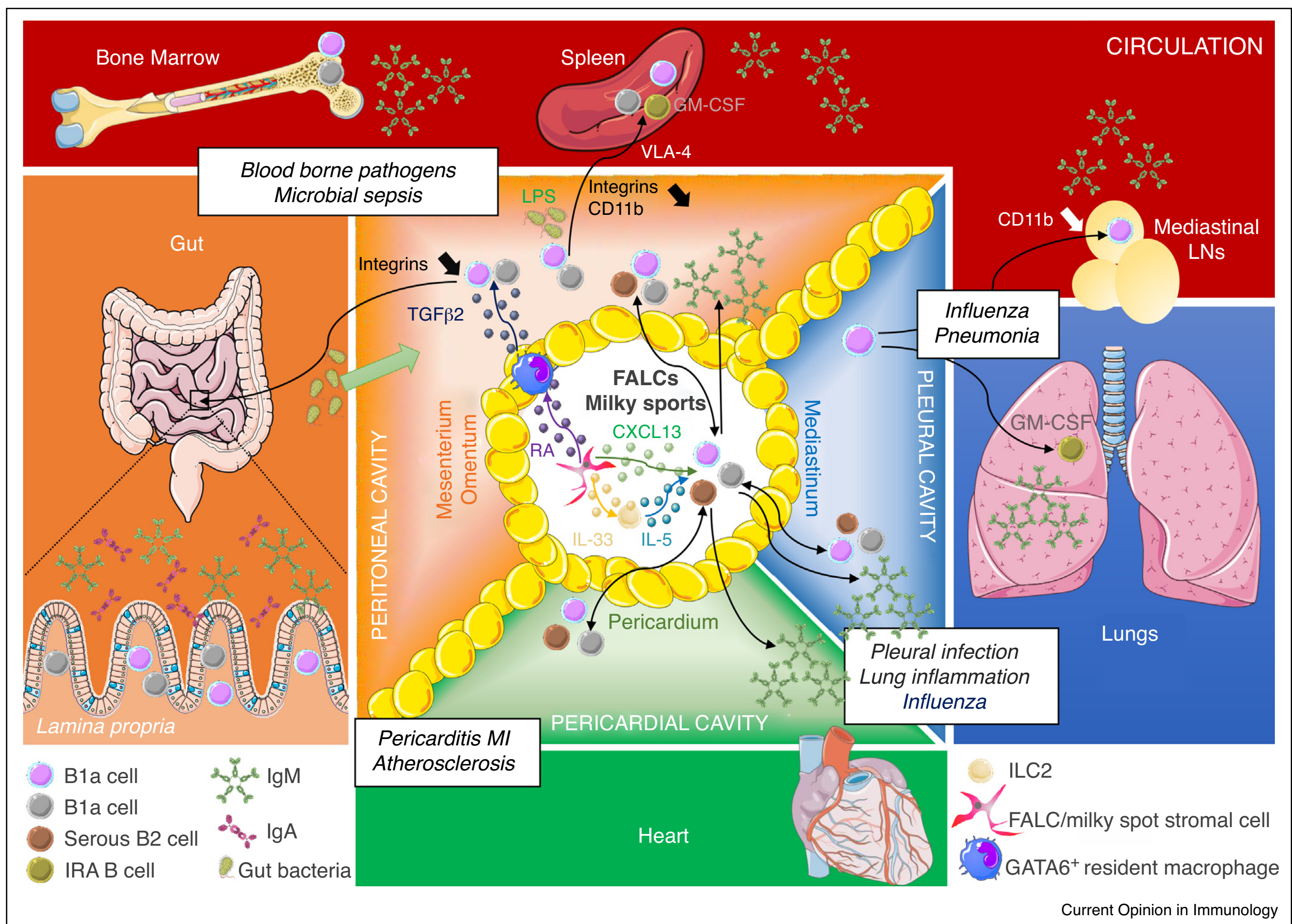
During bacterial infection and in response to TLR4 activation by LPS, peritoneal B1a cells can also give rise to a distinct IBC subset, called Innate Response Activator (IRA) B cells. IRA B cells migrate to the splenic red pulp using VLA-4, where they produce granulocyte/macrophage colony stimulating factor (GM-CSF) which by binding the common γ-chain of the GM-CSF receptor, common to GM-CSF, IL-3 and IL-5 receptors, increases the secretion of IgM in an autocrine loop, limiting bacterial dissemination and preventing sepsis [31]. Considering that the secretion of IgM by IBCs in FALCs was highly dependent on IL-5 [13•] raises the question of whether IL-5 is required for IRA B cell activation or whether the autocrine GM-CSF loop is a way to licence IgM secretion by B1 cells independently of IL-5 producing cells. The requirement for either IL-5 or GM-CSF may be entirely dependent upon the context of the inflammatory stimulus with type 2 inflammation resulting in IL-5 secretion as compared to a type-1 inflammatory situation (such as sepsis) requiring GM-CSF. In support of this concept, blockade of GM-CSF does not limit the

activation of B1 cells in the FALCs of *Alternaria alternata* exposed mice (Benezech lab, unpublished data).

The gut: secretion of IgM and IgA at the lamina propria
Naïve B-cells do not generally gain entry to the small intestine, however, peritoneal B1 cells and transferred B-cells that have trafficked through the peritoneal cavity have the capacity to migrate into this site to become IgM and IgA secreting plasma cells [10,32,33]. The production of mucosal antibodies in the intestine by IBCs is dependent on the presence of commensal bacteria [34].

Retinoic acid (RA) is a key factor for the gut homing of IgA producing B cells [35]. In the peritoneal cavity, RA is mainly produced by the omentum and is essential for GATA6 induction in peritoneal macrophages and their localisation and functional polarisation in the peritoneal cavity [36••]. In particular, GATA6 controls the secretion of TGF-β2 by peritoneal macrophages which is required for IgA secretion by IBCs at the lamina propria [36••]. RA can also directly potentiate peritoneal B1b cells IgA class-switching [37] and is directly important for the maintenance and function of B1 cells [32,38] through the control of the expression of the nuclear factor of activated T cells c1 (NFATc1) in B1 cells [32]. This suggests that RA production by omental cells is a central regulatory mechanism of IBC function in the peritoneal cavity and at the gut barrier (Figure 1).

Figure 1



Mechanisms governing homing of IBC from the serous cavities to other compartments. FALCs and milky spots play a central role in the maintenance and activation of innate-like B cells (IBC) in the serous cavity by secreting the B cell homeostatic chemokine CXCL13, the cytokine IL-33 and retinoic acid (RA). IL-33 acts on type 2 innate lymphoid cells (ILC2) that in turn secrete IL-5 necessary for IBC maintenance and activation. In the milky spots of the omentum, RA is necessary for the secretion of TGFβ2 by GATA6^{+} peritoneal macrophages, which leads to peritoneal IBC homing to the gut and secretion of IgM and IgA at the lamina propria. Upon gut and/or peritoneal infection, IBCs migrate to the omentum and the spleen for secretion of IgM in the peritoneal cavity and blood. Microbial sepsis lead to the differentiation of peritoneal B1a cells into protective GM-CSF^{+} IgM secreting IRA B cells in the spleen. Upon influenza infection, pleural IBCs migrate to the mediastinal lymph nodes (LNs) and mediastinal and pericardial FALCs. During pneumonia, pleural B1a cells differentiate into protective GM-CSF^{+} IgM secreting IRA B cells in the lungs. Upon pleural infection and lung inflammation, pleural IBCs migrate to FALCs of the mediastinum and pericardium to produce IgM in the pleural/pericardial cavities. Downregulation of integrins enables exit of IBCs from the serous cavities.

The airways: secretion of IgM in the mediastinal lymph nodes and lung

IBCs and natural IgM are important for protection against viral and bacterial infection of the airways. In general, the contribution of pleural IBCs has been less studied than peritoneal IBCs and the mechanisms leading to secretion of natural IgM or IBC derived IgA in the airways and lung tissue are less clear. However, two distinct mechanisms have emerged, involving accumulation of B1a cells in the draining lymph nodes or relocation to the lung parenchyma.

Following respiratory tract infection with influenza virus, pleural B1a cells migrate to the draining lymph nodes and contribute to the secretion of protective poly-reactive neutralising IgM against the virus, limiting viral load in the respiratory tract [39,40,41•]. Accumulation of B1a cells in regional lymph nodes is induced by type I IFNR signalling which activates CD11b to form a high affinity state and mediates the transfer of B1a cells across the blood/lymphatic endothelium [41•]. Interestingly, after migration to the lymph nodes [41•] and spleen [26], the expression of CD11b is downregulated. It is therefore possible that CD11b expression by IBCs in serous cavities is a pre-requisite for their relocation from serous cavities into secondary lymphoid organs. Work in our lab indicates that upon influenza infection, IBCs also home to mediastinal and pericardial FALCs where they proliferate and secrete IgM (Benezech lab, unpublished). The relative importance of FALCs and regional LNs for IBC function in influenza will need to be clarified.

During pneumonia, pleural B1a cells give rise to IRA-B cells that migrate to the lung parenchyma and secrete poly-reactive IgM via autocrine GM-CSF signalling [42•]. Whether IRA-B cell function during pneumonia is independent of mediastinal and pericardial FALCs or require these structures for their migration or to complete their activation is not known.

Future perspectives

Although it has become apparent that the peritoneal and pleural cavities provide an important layer of immune surveillance supporting immunity at the gut and lung mucosa, the immune function of the pericardial cavity remains elusive. The omentum is emerging as an important platform linking peritoneal cavity and gut immunity but there is still evident deficit of experimental studies investigating IBCs of both the pleural and pericardial cavities. The exact contribution of mediastinal and pericardial FALCs to lung immunity needs to be further explored. There are obvious reasons why the pericardial cavity has been less studied — the murine pericardial cavity is small and experimentally inaccessible. The presence of FALCs in the peri-aortic area of atherosclerotic animals and the importance of IL-5 secreting ILC2 for protection has also been recently reported [43]. B1 cells and natural IgM (recognising oxidation specific epitopes) are known to be protective [44] and clinical studies show that lower levels of IgM correlate with increased risk of cardiovascular disease [45,46]. It is therefore important that we start investigating the role of pericardial and peri-aortic FALCs in cardiovascular disease.

Conflict of interest

No conflict of interest.

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