Title: Immunobiology of the serous cavities

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Abstract

The serous cavities are fluid filled spaces that surround the lung, the heart, and the abdomen. One of their main functions is to provide protection and lubrication for their encapsulated organs. In addition to these physiological roles, the serous cavities are rich immune cell reservoirs. Whilst these cavity-derived immune cells have been studied *ex vivo* for many years, the past decade has led to significant advances in serous cavity biology. Importantly, immune mechanisms that occur uniquely within these fluid environments and communication networks between these cavities and the tissues they contain have been elucidated. In this review, we aim to summarise the current knowledge of cellular and molecular interactions that govern immunology across all serous cavities, comparing animal model and human studies. A deeper understanding of how the serous cavities provide immune protection to the tissues they encompass is likely to reveal therapeutic avenues for manipulation of these cavities to improve disease outcomes.

One-sentence summary: The immunology of the serous cavities is reviewed in the context of local functions and cross-tissue communication

INTRODUCTION

The peritoneal, pleural and pericardial cavities, collectively termed the serous cavities, develop in close association with the organs that they encompass. While the peritoneal cavity has been at the forefront of research for a century (*1*), the functional biology of these tissues is often overlooked. Recent research is revealing the ability of the serous cavities to modulate tissue responses outside of their own boundaries. During infection, these tissues generate immune effector cells, maintain memory populations and collaborate with associated adipose tissue to generate, maintain, and resolve inflammatory responses. Acknowledging this communication between cavity, solid organs, mesothelial lining, and lymphoid tissues is vital for understanding the holistic tissue response to disease.

SEROUS CAVITY ANATOMY AND PHYSIOLOGY

Serous cavity anatomy and function

Anatomically the pleural and pericardial cavities are located within the thorax and the peritoneal cavity sits within the abdomen. These fluid-filled cavities define a space between the visceral mesothelium, which sits on the surface of the internal organs, and the parietal mesothelium lining the interior of the abdominal or thoracic wall (**Figure 1A**) (*2*). The size of the serous cavities differ between different mammalian species, as serosal fluid volume and surface area increase roughly in proportion to body mass (*3*). In contrast, the mesothelium itself is morphologically similar between species, being composed of a monolayer of mesothelial cells (*4*). Connective tissue determines how thick an animal's serosal lining is; small animals such as mice have thin parietal pleurae (~7μm), whereas this is thicker in larger animals like humans (~30-40μm) (*3*, *5*). Notably, elephants do not have a fluid pleural cavity and instead have a dense layer of loosely associated connective tissue between the two pleural membranes (*6*, *7*). The main role of these cavities is to reduce friction between the encapsulated organs and, in the case of the pleural cavity, transmit the forces of respiration from the intercostal muscles to the lung parenchyma. Further detailed anatomy and physiology of the serous cavities have been reviewed previously (*5*, *8–10*). Alongside structural functions, the serous cavities harbour abundant immune cell populations. These cells are poised to combat a variety of challenges including pathogens or contaminants that may have breached the mucosal surfaces of the lung or gut, but also metastatic cancer cells and inherent changes in physiology such as effusion (*11*) and fibrosis. These immune cells can be suspended within the free-flowing fluid, associated with the mesothelial membranes, or organised within fat-associated lymphoid clusters (FALCs) of visceral adipose tissues.

Serous cavity development

In mammals, the mesothelium of the serous cavities originates from the mesoderm and is defined very early in embryonic development via the process of gastrulation. The lateral plate mesoderm splits to

form a cavity, the coelom (**Figure 1B**), which will later separate into the mature peritoneal, pericardial, and pleural cavities (*12*) (**Figure 1 C&D**). From this very early stage of development, the serous cavities are seeded by immune cells. Embryonic primitive haematopoiesis produces the first macrophages from the yolk sac and these cells seed the newly formed cavity (*13–17*). The early incorporation of yolk sac-derived macrophages into the cavity highlights the role of macrophages in shaping and regulating serous cavity function. The cavities only definitively form when their encapsulating organs invaginate into the developing membranes, forming the bi-layered structure that is observed in adults. Concomitantly, the foetal liver becomes seeded with haematopoietic cells (*18*) and will produce both myeloid and lymphoid progenitors. Around this time, B1 cells first appear in the cavity (*19–21*), which function as a reservoir of B cells into adulthood. During this development, some of the mesodermal cells develop epithelial features such as basal-apical polarisation and formation of a basal lamina. These cells go on to become the bordering mesothelial cells (*12*), which form the stromal niche of these cavities.

Serous cavity fluid

In the healthy, unchallenged state, the serous cavities are filled with a small volume of fluid (~100mL in the human peritoneal cavity (*22*, *23*) and around 20mL in the pleural cavity (*24*, *25*), which is generated from the systemic circulation via the mesothelial vasculature (*26*, *27*). Female peritoneal fluid also contains ovarian exudate and menstrual blood released via retrograde menstruation; in contrast, the male reproductive organs are outside the peritoneal cavity (*23*). The fluid itself is in constant flux, and it is estimated that the total volume of the pleural cavity is replaced around every two hours (*24*), and roughly a litre of peritoneal fluid is generated daily. This huge fluid turnover is enabled via specialised structures called stomata, which are small holes interspersed within the mesothelial lining, identified in both animal models (*28–30*) and humans (*31*). Fluid moves from the stomata through the underlying vessels into the regional lymphatics (*32*, *33*). Different organs within the cavities drain via different lymphatics, with several papers detailing the complicated lymphatic anatomy of these tissues (*8*, *33–35*).

The molecular composition of the serous cavity fluids is highly complex and remarkably dynamic. As a baseline, albumin, transferrin and hemopexin are found at high levels within the cavities, reflecting its generation from plasma ultrafiltrate (*11*, *36*). However, the specific composition is determined by local demands and conditions. For example, the metabolic profile of peritoneal fluid has been shown to direct the mitochondrial activity of tissue-resident macrophages, with glutamate and other amino acids being locally enriched compared to serum (*37*). Additionally, hyaluronan and phospholipids such as phosphatidyl choline are present at high levels (*5*), which likely act together for tissue lubrication (*38*). Multiple studies report dramatic changes in serous cavity cytokine profiles following disease and there are indications that the fluid composition differs between neighbouring cavities, particularly with respect to lipid composition. Given the role of lipids in modulating immune responses (*39–41*) and the

presence of both bioactive lipid and other immune regulatory metabolites within serous fluid, a better understanding of how fluid varies between different cavities and under distinct conditions is needed.

Fat-associated lymphoid clusters

In addition to fluid-phase immune cells and the mesothelium, it has been recognised for over a hundred years (*42*) that other distinct structures within the serous cavities have immune functions (*42–45*). Fat-associated lymphoid clusters (FALCs) are small immune cell clusters present within immune-adipose tissues (primarily the pericardium, mediastinum, omentum and mesenteries) of the serous cavities. FALCs are key co-ordinators of cavity immune responses, acting as hubs for immune cell activation within visceral adipose tissues (*46*). The term 'FALCs' was coined in 2010 when they were identified in the mesenteric adipose of the peritoneal cavity and is now used widely to describe these structures in all three cavities (*47*). However, FALCs that occur within the omentum of the peritoneal cavity were originally identified as *taches laiteuses* or milky spots by *Ranvier* in 1874 (*44*, *48*). Additionally, in 1928 (*43*), immune cell clusters known as Kampmeier's foci were described in the human mediastinum, between the left and right pleural cavity. Our understanding of the importance of mediastinal and pericardial FALCs in local disease processes has expanded recently (*49–52*). FALCs are rich in both B1 and B2 B cells, macrophages and group 2 innate lymphoid cells (ILCs) and are key portals for the entrance and egress of leukocytes within the serous cavities (*47*). Notably, stomata (described above) are present in adipose tissues that contain FALCs, and as such facilitate the filtration of serous fluid including antigen through these cellular clusters (**Figure 2**) (*53*). Importantly, during infection and inflammation, stromal-immune cell crosstalk facilitates *de novo* FALC formation and expansion which supports B cell activation, including the formation of germinal centres (*47*, *54*, *55*).

KEY IMMUNE CELL POPULATIONS WITHIN THE CAVITIES

The fluid phase of the serous cavities contains a remarkable range and number of immune cells, which move freely within the cavity (*56*, *57*). While almost all immune cell types can be found within serous cavities, the proportions differ in humans and mice. While in both species the dominant cell types are monocyte/macrophages and lymphocytes, the macrophage subtypes differ (*58*) and the murine lymphocyte pool is predominantly B cells in mice while T cells in humans (*58*, *59*). The specific populations of cells present also depends on prior exposure to infectious and inflammatory stimuli as well as the age and sex of the organism (*60*).

Lymphocytes

The murine serous cavities possess large populations of B1 B cells (*21*) in addition to a smaller B2 population. B1 cells develop during foetal haematopoiesis and are characterised by expression of CD11b in addition to CD19, which is also expressed by T-dependent B2 B cells (*61*). B1 B cells produce natural IgM, which is polyreactive and recognises self-antigens such as phospholipids (*62*). A large

proportion of the abundant natural IgM antibodies in the serous fluid recognise phosphorylcholine, which is the headgroup of neutral phospholipids exposed on dead or dying cells, contributing to their steady-state clearance (*63*). Peritoneal B1 cells contribute 80-90% of the natural IgM in the serum, however they do not secrete IgM while in the fluid phase but relocate to tissue niches such as FALCs (*64*) to produce antibody. B1 and B2 cell entry into the peritoneal cavity is dependent on CXCR5 via its ligand CXCL13, which is abundantly produced by omental FALCs. The omentum acts as an entry point for B2 cells within the peritoneal cavity, with a 40% reduction in entry following surgical removal of this tissue; however, B2 cells can still exit the peritoneal cavity of omentectomised mice (*65*). While the existence of human B1 cells is not unequivocally confirmed (*66*), a small subset of circulating $CD20^{+}CD27^{+}CD38^{lo/int}CD43^{+}$ cells that spontaneously secrete antibodies has been proposed (*67*, *68*), but further work is required to define human B1 cells within serous fluid (*69*).

T lymphocytes are key effectors of the adaptive immune response within the serous cavities and increase during infection. Conventional T cells can enter the peritoneal cavity via high endothelial venules (HEV) within omental FALCs (*70*), and FALCs facilitate T cell-dependent responses to foreign antigens in the cavity (*55*). Studies detailing entry and egress of lymphocytes within the pericardial and pleural cavities are sparse in comparison to those detailing peritoneal immune composition. Further knowledge of immune cell positioning and movement between organs, adipose tissue and serous fluid in these cavities is needed, as well as comparisons across cavities.

Innate lymphocyte populations are also present in the cavities with their contributions highly varied, and far more still to learn. For example, γδ T cells, important for immune surveillance at barrier sites, have been shown to have detrimental and protective roles during cancer in the peritoneal (*71*), and pleural (*72*) cavities, respectively. ILCs contribute to the initiation of immune responses as well as lymphoid tissue formation, tissue repair and homeostasis (*73*). Group 1 (*74*) and group 2 ILCs are documented within the serous cavities, with the latter originally identified within mesenteric FALCs (*47*) and considered as key cells involved in both pericarditis and pleural infection.

Myeloid cells

Granulocytes

The serous cavities have minimal numbers of fluid phase neutrophils in the steady state but often contain low numbers of eosinophils. This is particularly evident in the peritoneal cavity (*75*) where eosinophils also reside within adipose depots including those that house FALCs. Eosinophils are linked to type 2 cytokines, most notably interleukin (IL)-5, which is required for their differentiation within the bone marrow and later activation within tissue sites. Additionally, in the naive murine peritoneum, mast cells represent <5% of cellular exudate but may have critical roles as initiators of immune responses on challenge (*76*). Indeed, mast cells communicate widely with other immune and stromal cells and

contribute to the development of pleural effusion (*77*). Well-documented in the peritoneal and pleural cavities, mast cells have also been identified in the paracardial adipose of humans and the epicardium of mice but have not yet been documented within pericardial fluid (*78*).

Macrophages

Serous cavity macrophages are one of the most well-studied macrophage populations, in part because of the relative ease of obtaining large numbers from the peritoneal cavity. Peritoneal macrophages were initially discovered by Zanvil Cohn (*79*), building on the identification of phagocytes by Eli Metchnikoff at the start of the 20th century, and many advances in macrophage biology have come from the study of peritoneal cells. In the absence of perturbation, mononuclear phagocytes account for around a third of the cells in the fluid of the serous cavities. These are divided into two main populations originally defined by their size and hence called small and large peritoneal macrophages (SPM/LPM) for studies undertaken in the peritoneal cavity (*80*). More recently, these cells have been referred to as "cavity macrophages" (SCM/LCM) to more broadly encompass the different serous cavities in which they are present (*58*, *81*) (**Figure 3**).

SCM are typically F4/80^{Lo} and MHCII^{Hi}, contrasting with LCM which are F4/80^{Hi} and MHCII^{Lo}. These markers reliably distinguish the two main serous cavity murine macrophage populations, even in the single-cell era. SCM are recently derived from circulating monocytes (*82–85*) and depend upon the transcription factor IRF4 (*82*). They are a heterogenous population, containing both monocyte-like and DC-like cells (*86*, *87*). In contrast to SCM, LCM are self-renewing tissue-resident cells involved in tissue maintenance, controlling apoptotic cell clearance and regulating the cavity fluid environment (*88–90*). Their tissue-resident identity is imprinted by the transcription factor GATA6 (*91*, *92*). Expression of GATA6 is induced by retinoic acid produced by Wilm's Tumour 1 (WT1)$^{+}$ stromal cells (mesothelial and fibroblasts) (*93*), though other pathways are likely involved.

LCM are initially embryonically yolk sac-derived (*93*, *94*), but over time are replaced by circulating monocytes that infiltrate into the cavities and initially take on a SCM phenotype. These SCM can further differentiate into LCM analogous to the embryonically derived cells (*82*, *86*). Monocyte infiltration into tissues is a defining feature of classical inflammation and inflammatory monocytes arriving within the serous cavities can differentiate to become SCMs. In contrast, during a type 2 immune response, the large increase in macrophage cell number in the serous cavities is predominantly due to proliferative expansion of the LCM population in response to IL-4 receptor alpha (IL-4Rα) signalling (*95*). These IL-4Rα-activated macrophages produce type 2 effector molecules such as Resistin-like molecule alpha (RELMα) and Ym1 (*96*, *97*). Recent work has shown that in these settings, IL-4Rα signalling can also drive incoming monocytes into the LCM pool via an intermediate converting cavity macrophage (CCM)

population characterised by expression of markers such as lymphatic vessel endothelial hyaluronan receptor-1 (LYVE1) and folate receptor beta (FRβ) (*81*, *98*) (**Figure 3**).

Strikingly, the rate at which bone-marrow derived cells replenish the peritoneal cavity differs between sexes, with a low rate of replenishment in females compared to males (*60*). Whether there are functional differences between these embryonic and monocyte-derived cells is under active investigation. Elegant studies have already highlighted an enhanced capability of macrophages from female mice, which retain more embryonic-derived cells, to control *Streptococcus pneumoniae* (*60*), suggesting that differences in ontogeny impact the interaction between ageing and disease pathogenesis.

Whilst $GATA6^+$ LCM have been found in the peritoneal (*58*, *99*) and pericardial (*100*) space of humans, these cells are a far smaller population than observed in mice. Instead, in the human peritoneal cavity, the majority of the LCM population more closely resembles a converting phenotype (*81*) between SCM and LCM that has been described in mice (*58*). Macrophage phenotypes in the human pleural cavity, including the presence of $GATA6^+$ cells, remains unconfirmed but likely mimic the LCM populations observed in the pericardial and peritoneal spaces.

In addition to these fluid phase macrophages, which are readily accessible via lavage of the cavities, specialised populations are intimately associated with the serosal membranes (*101–103*) (**Figure 3**). Intra-vital microscopy initially revealed the presence of $CD169^+$ sessile macrophages embedded within the peritoneum. These resident cells dynamically cloak sterile microlesions (ablation of single cells) to limit the neutrophil swarming that occurs in response to a larger injury (*101*) (**Figure 3**). Assessment of further serosal linings including the intestinal serosa, diaphragm, epicardium, parietal and visceral pleurae confirmed their presence at these sites as well as in the connective tissues (epimysium/endomysium) surrounding muscle (*101*). Further work has defined two subsets of these tissue-resident macrophages within mesothelial linings. In particular, careful work on the mesenteric mesothelium identified $LYVE1^{hi}$ $CX_3CR1^{lo/-}$ and $LYVE1^{lo/-}CX_3CR1^+$ populations. $LYVE1^{hi}$ cells were found to be embryonically derived and account for approximately 60% of the total macrophage population within the mesenteries (*103*). $LYVE1^{hi}$ macrophages also exist within the parietal peritoneum and have a transcriptional profile enriched in modulation of extracellular matrix. In contrast to fluid phase macrophages, mesothelial $LYVE1^{hi}$ cells are independent of GATA6 and IRF4 but still require colony stimulating factor 1 (CSF1) produced by $WT1^+$ stromal cells (*103*). Comparable populations of $LYVE1^{hi}$ macrophages also exist in the omentum, where they have been shown to drive tumour progression (*102*) (**Figure 3**).

Stromal cells

Stromal cells are key regulators of immune cell function within the serous cavities. Like immune cells they possess pattern recognition receptors, antigen presentation molecules and the capacity to secrete and respond to cytokines and chemokines. The two major populations of stromal cells found in the serous cavities are fibroblasts (including populations such as fibroblast reticular cells (FRCs)) and mesothelial cells. The cavities themselves are lined by a single-cell mesothelial layer. which can sense and respond to their environment, secreting a plethora of immune modulatory molecules (*4*). Mesothelial cytokine secretion is highly polarised, for example, stimulation with bacterial extracts initiates release of IL-8 at the apical surface, resulting in directed secretion into the serous cavities (*104*). Stromal cells are key regulators of macrophage phenotype, in particular, the production of retinoic acid by $WT1^+$ cells within the cavities specifies GATA6 expression within LCM (*93*). In addition to retinoic acid, mesothelial cells also produce colony stimulating factor 1 (CSF1), which can drive peritoneal macrophage proliferation *in vitro* (*105*) and support mesothelial-associated macrophages (*103*) (**Figure 2**). Fluid phase macrophage specification is also influenced by Mesothelin (*Msln)* and Mucin16 (*Muc16*) with secretion of these factors from mesothelial cells modifying the acquisition of GATA6 by monocyte-derived macrophages as they enter the cavities with age or following inflammation (*106*) (**Figure 2**).

FALC stromal cells are enriched in immune regulatory molecules and orchestrate immune responses within the cavities (*107*). FALC mesothelial cover cells act as co-ordinators of fluid to tissue immune activation, recruiting immune cells from the within serous fluid, to the cluster. Whereas FRCs are key for recruiting immune cells to the peritoneal cavity and positioning them within FALCs. A $Ccl19^+$ FRC population is responsible for recruitment of inflammatory monocytes into FALCs, via MyD88-dependent secretion of CCL2 (*108*). A second FRC subset defined by expression of $Ccl11^+$ is present within naive omentum (*107*) and expresses high levels of *Aldh1a2* and aldehyde dehydrogenase activity (*70*), providing a non-mesothelial source of retinoic acid within the peritoneal cavity (*93*). Selective loss of $Ccl11^+Aldh1a2^+$ FRC from the omentum results in a significant reduction in the number of T and B2 cells, but strikingly not B1 cells within FALCs (*70*), highlighting the critical role of FRCs in instructing cell location. Over time, this results in a progressive loss of lymphocytes in the peritoneal fluid (*70*), consistent with the lymphocyte niche being populated from the circulation via the omentum (*54*). Notably, while the absence of $Aldh1a2^+$ *FRC* led to fewer T, B1 and B2 B cells entering the peritoneal cavity, there was no impact on peritoneal LCM (*70*). The authors suggest this may be due to reduced endothelial CXCL12 expression in the absence of retinoic acid from FRCs (*70*), which would limit lymphocyte recruitment via omental HEVs (*70*) (**Figure 2**). In contrast, LCM are described to respond to retinoic acid derived from $WT1^+$ stromal cells that include both mesothelial cells and fibroblasts (*93*). Taken together, these studies suggest that mesothelial-derived retinoic acid may be of greater importance than fibroblasts for specifying LCM.

Although an in depth single-cell RNA sequencing analysis of the murine pleura has not been performed, a comprehensive characterisation of the human parietal pleurae from patients experiencing pneumothorax exists (mesothelialcellatlas.com) (*109*). This valuable data can be utilised to compare and contrast the immune-stromal network of humans with the well-characterised serous mesothelial populations of the mouse (*70*, *107*, *110*).

Taken together, this brief overview of key players within the serous environment highlights the complex network of cells that must act in collaboration to protect the local organs and the cavity itself. In the steady state, the serous cavities are a sterile environment, however this may not be the case during cavity breach such as following injury or infectious peritonitis (*107*, *111*), pericarditis (*112*) or pleural infection (*113*). In the following sections we highlight key features of the complex interplay between the fluid and tissue response by exploring settings in which disruption of the cavity homeostasis leads to a disease state.

BEYOND THE STEADY STATE

Peritonitis-immune regulation in a fluid environment

Inflammation of the peritoneal lining or cavity that occurs following injury or infection is termed peritonitis. Given the proximity to the intestines, which sit just below the mesothelial lining of the peritoneal cavity, it is not surprising that a major insult to peritoneal homeostasis is bacterial leakage from the intestine. In most cases, peritoneal bacteria resulting from barrier breakdown are cleared by the combined effort of recruited neutrophils and monocytes, resident LCM and omental filtration. However, when this fails, bacterial peritonitis is associated with high mortality and progression to sepsis. A key example is the bursting of the appendix and the release of a large bolus of bacteria into the peritoneal cavity. To mimic this, the caecal ligation and puncture (CLP) model was used to investigate the role of the omentum in regulation of immune cell recruitment to the peritoneal cavity (*111*). In the context of CLP (or i.p. delivery of *Escherichia coli (E.coli)*), neutrophils enter the peritoneal cavity via the HEVs of omental FALCs, and this contributes to protection from sepsis (*111*). As *E. coli* are a frequent cause of peritonitis, intraperitoneal delivery of this bacterial species is also used to model peritonitis in mice. Injection of *E.coli* converts the peritoneal fluid phase response to a solid phase response with formation of macrophage clots that trap bacteria (*56*), as well as resulting in rapid adhesion of aggregates to the mesothelium via fibrin-dependent aggregation of LCM (*114*) (**Figure 3**). Together, these macrophage-mediated pathways can effectively control peritoneal infection.

Zymosan-A is a fungal cell wall mixture isolated from *Saccharomyces cerevisiae* frequently utilised experimentally to induce peritonitis. Instillation of between 10µg-1mg of zymosan *i.p.* results in rapid neutrophil recruitment to the peritoneal cavity, and loss of the resident LCM population. Replenishment by monocytes and SCM occurs over the following 3-7 days, with resolution of inflammation, as

evidenced by reduction of neutrophil and eosinophil numbers back to baseline by day 7-14 (*115*). Studies of zymosan-induced peritonitis revealed that release of CXCL1 by murine mesothelial cells within the omentum co-ordinates accumulation of peritoneal neutrophils on top of FALCs. The build-up of neutrophils is dependent upon release of extracellular traps and if NETosis is blocked, zymosan spreads to the spleen (*107*). Thus, trapping of peritoneal particles by the omentum, serves as a mechanism to clear contaminants from the cavity. This process converts the immune action of early inflammation from the fluid to the solid/tissue-associated phase (*107*), akin to the process described above for containment of *E. coli* (*56*, *114*).

These findings from diverse systems suggest that conversion of the fluid immune response to solid phase is a central feature of serous cavity immunity. Indeed, this process can now explain the commonly observed peritoneal 'macrophage disappearance reaction' which can occur via the clotting of resident tissue macrophages (*56*, *116*) (**Figure 3**). Inhibition of coagulation via the delivery of heparin, or deletion of the clotting factor V within resident LCM reverses the macrophage disappearance reaction induced by high dose Zymosan (*56*). LCM also 'disappear' from the fluid phase during experimental inflammation by recruitment to the omentum (*91*). Intra-peritoneal infection with the single celled protozoan parasite *Toxoplasma gondii* drives LCM recruitment to the omentum where, in contrast to conventional expectation, infected LCM rather than dendritic cells prime naive $CD8^+$ T cells (*117*) This experimental system illustrates the importance of the tissue environment, even within the 'fluid' cavities, in regulating immune response.

In another example of how tissue environment regulates immunity in a fluid environment, the functional phenotype of monocyte-derived cells in the peritoneal cavity is dictated by available resources (*118*). The capacity of a SCM to acquire a resident-like phenotype, such as acquisition of the transcription factor GATA6, is dependent upon competition for factors including retinoic acid (**Figure 2**). Following mild inflammation induced by low-dose zymosan, the LCM population remains within the peritoneal cavity, and infiltrating SCM persist but cannot acquire residency (*118*). Following high doses of zymosan, when LCM are ablated, retinoic acid availability increases and incoming monocytes can acquire residency (*118*). Inflammatory loss of LCM from the peritoneal cavity also results in loss of $CD11b^+$ B1 B cells following resolution of inflammation (*118*). This is because, in addition to FALC stromal cells, LCM produce CXCL13, which is responsible for the sustained recruitment of B1 cells to the peritoneal cavity (*49*, *53*, *118*) (**Figure 2**).

The examples above highlight that even within a fluid environment, 'niches' can form, either through resource availability, conversion from fluid phase to solid phase, or migration to local organised immune or adipose structures. Perhaps more remarkable is the evidence that macrophages and B cells can migrate from serous fluid to enter the liver (*119*), heart (*51*, *100*, *120*), intestine (*121*), lung (*122*) and lung tumour metastases (*123*). How deep into organs serous immune cells can infiltrate is a current

topic of debate with different reports presenting data suggesting serous cavity macrophages infiltrate deep within organs (*100*, *119*, *121*) or, alternatively, only accumulate on the surface (*124*). Improved understanding of how and why serous immune cells, and macrophages in particular, migrate into organs may enable their future repurposing for therapeutic use. More generally, understanding communication between the cavities and the organs they encompass and how these cavities communicate with each other is direct relevance to many diseases, as highlighted with examples below.

Pleuritis and pericarditis: Cross-Communication between organs and cavities

The lungs are considered the main route by which infectious agents can enter the pleural cavity and oropharyngeal flora are also understood to contribute to pleural infection, particularly in the context of hospital acquired infections due to the higher risk of aspiration (*113*). *Mycobacterium tuberculosis* is the causative agent of tuberculosis (TB), and the pleural space is a key site of extra-pulmonary manifestations of this devastating disease. Pleural TB is a topic that has been comprehensively reviewed by others (*125*) and is characterised by the presence of neutrophils and monocytes and subsequently lymphocytes within pleural effusion. TB pleuritis is characterised by homing of memory T helper 1 (Th1) cells to the pleural space, often 6-12 weeks after pulmonary TB (*126*). Local increases in interferon (IFN)-γ are found within pleural fluid during TB pleuritis, which indicates a localised inflammatory response separate from the systemic circulation (*125*). To our knowledge, the contribution of FALCs to development of or protection from TB-pleuritis is unknown.

These findings raise important questions about cross-talk between the lung and the pleural cavity. For example, whether FALCs contribute to protection from sepsis originating from lung and/or heart by filtering the serous fluid has not been unequivocally demonstrated, in contrast to the peritoneal cavity where the omentum undertakes this function (*107*). Nonetheless, there is ample evidence for communication between these body systems. In pre-clinical models, particulate material delivered into the pleural space can be found within the FALCs of the pericardium and mediastinum, and labelled immune cells delivered directly into the pleural space can relocate to the lung (*122*), pericardium and mediastinum (*50*). The relevance to human disease of communication with and between these cavities is highlighted by findings that pericardial adipose tissue is activated by myocardial infarction (*51*), and respiratory viruses are a known trigger for myocardial infarction (*127*).

Alternaria alternata is a common household mold that can drive allergic responses in atopic individuals and provides an excellent model for IL-33-dependent allergic airway inflammation. IL-33 is expressed by FALC stromal cells, including mesothelial cells, cover cells and fibroblasts (*107*), and can be released into the pleural space following intra-nasal instillation of *Alternaria* (*50*). Localised IgM antibody production in response to intra-nasal *Alternaria* occurs within the pleural cavity via IL-33-dependent activation of mediastinal and pericardial FALC-resident ILC2, which produce IL-5 to

activate FALC B1 and B2 B cells (*50*). IL-5 is also a key cytokine required for eosinophil differentiation within the bone marrow and later activation within tissue sites (*128*). IL-33 can also activate eosinophils, either directly or via ILC2s (*129*, *130*).

ILC2s are also implicated in IL-33-mediated pathologies within the pericardium and are present in pericardial fluid from patients with pericarditis (*52*). Eosinophilic pericarditis can be induced via repeated intraperitoneal injection of IL-33 in murine models (*52*). Repeated IL-33 injection induces cardiac fibroblast amplification of IL-33 release and ST2-dependent accumulation of IL-5^{+}IL-13^{+} ILC2 within the heart. Co-culture of ILC2s and cardiac fibroblasts in the presence of IL-33 induces CCL11 (Eotaxin) release from fibroblasts, suggesting a mechanism for the increased eosinophilia in this model. Intra-pleurally injected eosinophils migrate into the heart of eosinophil-deficient mice during pericarditis (*52*), highlighting the inter-niche movement of immune cells from serous fluid to organs housed within the cavities.

Fibrosis

In the context of prolonged or repetitive inflammation, the mesothelium can become fibrotic. Pleural fibrosis is characterised by remodelling of the extracellular matrix of the pleural mesothelial membrane, with more severe cases affecting the visceral pleura (*131*). Instillation of bleomycin into mouse airways is used as a model of pulmonary damage and fibrosis, and although this model has caveats when it comes to translation to human disease (*132*), studies of bleomycin in mice have provided data that correlate with human Idiopathic Pulmonary Fibrosis (IPF). Bleomycin treatment of mice causes upregulation of WT1 and migration of mesothelial cells into the lung parenchyma (*133*, *134*), increased expression of WT1 within the lung parenchyma is also seen in IPF patients, suggesting a correlation between mesothelial cells and fibrosis (*133*). This migration recapitulates processes seen in development of the lungs and the pleural cavity, where mesothelial cells can undergo mesothelial-to-mesenchymal transition and migrate into the lung parenchyma where they are vital for establishing smooth muscle and fibroblast progenitors (*135*). Altogether, this data fits with an idea that has been termed the ‘inside out model of pulmonary fibrosis’ (*133*).

Fibrotic serous cavity adhesions are a common consequence of abdominal surgery but also a feature of endometriosis (discussed below). Focal thermal laser injury that results in damage to the peritoneum causes GATA6^{+} cavity macrophage aggregation, resulting in rapid repair and sealing of the peritoneal injury (*57*). Although a beneficial response to prevent immediate threat to the host, such tethering of foreign material can contribute to formation of adhesions between the serosal surface and organs. Macrophage aggregation via class A scavenger receptors, including macrophage scavenger receptor 1 (MSR1) and macrophage receptor with collagenous structure (MARCO) also contribute to adhesion

formation (*57*) (**Figure 3)**. Mesothelial cells ordinarily secrete plasmin and plasminogen activators that degrade fibrin, limiting fibrin deposition on serosal surfaces (*136*). However, when the balance of fibrin production and degradation becomes unbalanced in favour of fibrin deposition, adhesions occur. Recruited monocytes reduce peritoneal adhesion formation in a murine surgical model, and this may be due to monocytes actively degrading immature adhesions through fibrinolytic activity or via disruption of super-aggregates of tissue-resident F4/80^{high} macrophages (*137*, *138*). Neutrophils can also actively control ECM deposition possibly via active movement of matrix components from the mesothelial lining (*139*).

IPF and surgical adhesions are both very serious and unfortunately very common intractable clinical consequences of maladapted wound repair. These studies highlight the need to understand the complex interaction between stromal and immune cells within the serous cavities and how these contribute to both beneficial and harmful responses.

Insights from tissue-dwelling metazoan parasites

Multi-cellular metazoan parasites, or helminths, that live within the tissues represent a very common evolutionary event with virtually all mammals infected by a variety of species. These parasites often survive for decades in the mammalian host and as such they provide fascinating tools to study immune responses. Whilst few species reside directly within the serous cavities (see *Mansonella* below), others can escape their natural niche and infect the cavities. A notable example is the *Uncinaria* species of hookworm that infects fur seals. These worms reside in the gastrointestinal tract but can migrate from the gut to the peritoneal cavity, where they cause fibrinohaemorrhagic peritonitis (*140*). This is associated with times of reduced food intake for the seals, which may be responsible for driving the parasites out of the intestines in search of nutrients. Table 1 provides a list of human-infecting metazoan parasites that reside in or impact the serous cavities.

The filarial nematodes *Mansonella ozzardi* and *Mansonella perstans*, estimated to infect > 100 million people in Africa alone, represent one of the most neglected tropical diseases (*141*, *142*). These vector-borne parasites reside within the serous cavities where they mature and produce blood-circulating microfilaria. The rodent nematode, *Litomosoides sigmodontis*, a model for human filarial infection, resides in the pleural cavity (*97*). Infection with *L. sigmodontis* drives pleural oedema and huge increases in eosinophils and IL-4Rα-activated macrophages in the cavity. Using this model, the capacity of IL-4 to drive local macrophage proliferation was discovered (*95*) as well as a new understanding of monocyte to LCM dynamics described above (*81*). These LCMs that expand during infection in response to Th2 cells are important for the killing of parasites as well as inhibition of inflammatory cell recruitment to the cavity (*81*, *143*).

Many parasite infections that do not directly reside within the serous cavities still drive serous cavity immune responses. For example, during infection with *Fasciola hepatica*, there is a strong recruitment of eosinophils to both the liver and peritoneal cavity. These recruited eosinophils are important for controlling tissue damage during infection, though the importance of peritoneal vs liver eosinophils was not assessed (*144*). Similarly, infection with the gastrointestinal parasite *H. polygyrus* increases effector Th2 cells (*145*) and IL-4Rα-activated macrophages (*146*) within the peritoneal cavity. In addition to mounting direct responses during infection, the serous cavities have been shown to harbour memory immune cell populations, both within the mesenteric adipose (*110*) and the peritoneal fluid (*147*). After infection with *H. polygyrus,* the gut, draining lymph nodes, and peritoneal cavity all harbour memory Th2 cells(*147*).

The consequences of an intestinal Th2 response extending into the cavities is not clear but may help strengthen the intestinal wall to reduce the risk of penetration by the worm (*110*). The danger however would be increased susceptibility to bacterial infection if rupture did occur; however, two studies do not support this possibility. The type 2 immune response following gastrointestinal nematode infection was found to enhance survival in a Klebsiella peritonitis model with mast cells contributing to protection (*148*). In another study, the expanded IL-4Rα activated LCM present after *H. polygyrus* infection did not enhance susceptibility to *Salmonella enterica ser. Typhimurium* (*146*). Instead, nematode-expanded LCMs upregulate canonical type 1 markers such as nitric oxide synthase 2 (NOS2). However, while the LCMs generated by nematode infection demonstrate the capacity to become anti-microbial, the dominant effector response that controls bacterial infection is an influx of monocytes that displace these LCMs (*146*). These findings further reveal the enormous complexity of the immune responses within the cavity, which have evolved to protect against an immensely diverse range of threats.

Modification of self: Cancer in the cavities

Mesothelioma

The immune system's role in protection not only from external threats but from inappropriate modification of self, as seen in cancer, is well-established (*149*). In the serous cavities, mesothelioma is the one of the most devastating malignancies and yet least studied in terms of the role of the immune system. This cancer is linked to inhalational asbestos exposure and though it predominantly impacts the pleural mesothelium, peritoneal mesothelioma does occur. Following inhalation, asbestos fibres migrate into the pleural cavity where macrophages attempt to phagocytose them. Short fibres are efficiently cleared; however, longer fibres are too big to be phagocytosed resulting in macrophages becoming 'frustrated' (*150*). These frustrated cells release reactive oxygen and nitrogen species (ROS/NOS) into

their local environment, which is then thought to cause DNA damage in mesothelial cells that over time accumulate mutations. These mutations occur in addition to the direct damage caused by asbestos fibres becoming lodged in the mesothelium (*151*). Importantly, long bio-persistent fibres other than asbestos can also cause mesothelioma in pre-clinical models (*152*). Given the known capacity of FALCs to clear contaminants from the serous cavities, it is perhaps surprising that the role of FALCs in development of malignant pleural mesothelioma has not been investigated. However, there is normally a decades long delay between fibre exposure and development of mesothelioma, which has made assessment of the immune processes leading to tumour development difficult to dissect in patient cohorts. Murine models of disease are beginning to facilitate assessment of the immune trajectory of mesothelioma development following asbestos exposure (*153*, *154*) but more work is needed in this area.

Metastatic niches within the cavities

Our knowledge of tumorigenesis within the pleural cavity is well-developed with studies showing how malignant pleural effusions (MPE) develop both within mouse models and patient cohorts (*155*). Mouse models of MPE frequently utilise delivery of cancer cell lines directly into the pleural space with resultant tumour formation on the mesothelial surfaces, including the diaphragm, parietal and visceral pleura. Monocytes recruited via CCL2 have been shown to create a pre-metastatic tissue niche for the establishment of a secondary tumour in models of pulmonary metastasis of breast cancer cells (*156*, *157*).

Studies within the pleural space have extended these findings to show that KRAS-expressing tumour cells promote the development of MPE via the secretion of CCL2 to recruit myeloid cells from bone marrow which travel via the spleen to enter the pleural cavity (*158*). Furthermore, deletion of *Gata6* and ablation of LCM reduces metastasis, decreases tumour burden and extends survival in a B16F10 melanoma model (*123*) . The role of mediastinal FALCs in metastasis to the pleural cavity is under-investigated despite this cavity being a key site to which cancers of the breast and lung metastasise (*159*). The role of FALCs in peritoneal metastasis has been more comprehensively investigated, in particular the frequent metastasis of ovarian cancers to the omentum (*102*, *160*).

Similar to the mechanisms by which contaminants such as intestinal bacterial are trapped, omental neutrophils can capture extravasating tumour cells to initiate development of an ovarian cancer premetastatic niche within the omentum (*160*). Depletion of neutrophils, or deficiency of PAD4, a key enzyme required for NET formation, reduces colonisation of the omentum by ID8 murine ovarian cancer cells. Additionally, increased presence of neutrophils within the omentum correlates with patients having high-grade serous carcinoma (*160*).

Serous Macrophages in Cancer

Macrophages within peritoneal fluid and omentum are also a key link that can capture cancerous cells and facilitate tumour development within FALCs, supporting the metastatic spread of ovarian cancer (*102*, *161*). Macrophage inflammatory protein beta (MIP1β) secretion by macrophages acting on mesothelial cells facilitates tumour cell adhesion in high-grade serous ovarian cancer (*162*). The origin of peritoneal macrophages determines their ability to migrate to and repopulate the omental macrophage niche (*163*), and their capacity to do so changes dependent upon whether they have been derived during inflammation. Inflammation-elicited but not established resident macrophages can migrate to the omentum and acquire the $CD102^{+}$ omental macrophage phenotype (*163*).

Mice with macrophages lacking the retinoic acid receptors RXRα and RXRβ have reduced LCM and expanded SCM populations. This has implications for ovarian cancer progression, as RXRαβ-deficient mice have reduced peritoneal LCM infiltration of early ovarian tumours, which reduces tumour progression (*164*). Depletion of embryonically derived $CD163^{+}Tim4^{+}$ tissue-resident macrophages using diphtheria toxin reduces the volume of ascites, number of tumour cells within peritoneal fluid, and the development of invasive disease in a mouse model of metastatic ovarian cancer (*102*). Peritoneal LCM isolated from mice with ID8-derived ovarian carcinoma promote tumour growth via the production of the metabolite itaconate (*165*). Additionally, monocytes isolated from ascites of patients with ovarian carcinoma also express IRG1, the enzyme responsible for itaconate production (*165*). Taken together, these studies support a pro-tumour role for fluid phase peritoneal LCM in the development of ovarian carcinoma and highlight an additional context in which fluid phase cells regulate solid tissue function.

Ectopic self: Endometriosis

Endometriosis is a chronic, debilitating, inflammatory condition impacting ~190 million women worldwide, and is characterised by the presence of endometrial-like tissue (uterine lining) at sites outside the uterus, most commonly the peritoneal cavity (*166*). These lesions form on the mesothelial linings and are comprised of a mix of progenitor, glandular epithelial and stromal cells. The presence of endometriotic lesions within the peritoneal cavity is understood to occur primarily via retrograde menstruation (*167*), whereby endometrial tissues pass out of the fallopian tubes and into the peritoneal cavity, acting as the 'seed' that can then embed within the soil of an activated mesothelium (*168*). Additionally, endometrial cells have been proposed to metastasise to the peritoneal cavity via vascular and lymphatic spread (*166*). Additional sequalae of endometriosis include the formation of adhesions within the peritoneal cavity. Surgical intervention to diagnose and remove these lesions is the main therapy for patients with complex disease. Other treatments focus on reducing circulating levels of oestrogen (*168*, *169*), a known risk factor for disease development.

Extra-uterine endometrial tissue that has passed into the peritoneal space can contain endometrial resident immune cells as well as recruiting innate and adaptive cells from the circulation into the peritoneal cavity and into lesions themselves (*168*). Macrophages are key to the development of endometriosis and, in the context of experimentally induced endometriosis, fewer lesions form following depletion of the peritoneal macrophage population that is replenished by monocyte-derived cells (*170*). This finding is consistent with the experimental model of surgical adhesions discussed above (*137*) and suggests in both contexts fluid phase monocytes are protective. Monocyte-derived cells were subsequently revealed by single-cell RNA sequencing to become pro-disease once recruited into the lesions (*171*), suggesting that tissue-derived factors within the lesion modulate macrophage phenotype. The immune environment of endometriosis patients has been characterised as Th2-skewed (*172*), as well as having a significant population of Th17 cells within the peritoneum (*173*). These responses have parallels with those mounted against helminths, perhaps suggesting the presence of mis-placed multi-cellular endometrial tissue activates similar immune processes to those that have evolved to combat migrating multi-cellular worms.

CONCLUSIONS

Taken together, the data from multiple studies show that serous cavity cells respond not only to challenges within the cavity but also are important in adjacent associated organs. Overall, the serous cavities provide a comprehensive and diverse arsenal of immune effector cells that provide protection against a wide array of exogenous micro, macro, and self insults that arrive within these sites and act as a defence behind the mucosal frontline. Unravelling the complex communication occurring between the serous cavities and the organs which they encase remains a major challenge in immunology.

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Figure Legends

Figure 1. Development dictates formation of serous cavities and associated immune adipose tissues. A. The pericardial, pleural and peritoneal cavities. The parietal mesothelium lines the cavity wall and reflects back over the organs within each cavity, where it becomes known as the visceral mesothelium; each cavity contains a small volume of lubricating serous fluid **B**. Each serous cavity contains fat-associated lymphoid clusters (FALCs) within specialized adipose depots. Serous fluid circulates due to gravity and internal pressure changes within the cavities **C.** Developing embryo showing relationship between embryonic coelom which forms the serous cavities, the yolk sac which is the site of primitive hematopoiesis, the developing gut and the heart. **D.** Cross section through the peritoneal cavity and its association with abdominal organs including kidney, uterus and gut; the mesentery is indicated. **E.** Cross-section through thorax, detailing location of the pericardial cavity associated with the heart and the two pleural cavities enclosing the lungs, in mice the pericardial and pleural cavities are interconnected by pores; the mediastinum is indicated.

Figure 2. Stromal – immune interactions define cellular position and phenotype within the serous cavities. Mesothelial-derived retinoic acid (RA), mesothelin (Msln) and Mucin16 (Muc16) released from mesothelial cells enhance fluid phase macrophage acquisition of GATA6. Mesothelial-derived colony stimulating factor (CSF) 1 directs mesothelial macrophage phenotype. Serous fluid flows through stomata within the mesothelium located over FALCs, facilitating contaminant and immune cell egress out of the cavity. Immune cells can also enter the cavities via high endothelial venules (HEV) within FALCs. FALC fibroblast reticular cells (FRC) position monocytes via secretion of CCL2 and modify peritoneal B and T cells via RA secretion. IL-33 secretion from stromal cells activates ILC2s within FALCs, initiating IL-5 secretion. CXCL13 secretion from LCM and FALC cover cells positions B cells within the peritoneal fluid.

Figure 3. Multiple macrophage populations contribute to functional immune protection within the serous cavities. CCR2+ monocytes, F4/80^{lo} small cavity macrophages (SCM), FRβ+ converting cavity macrophage (CCM) and F4/80^{hi} large cavity macrophages (LCM) occupy the fluid phase serosal niche with additional populations of CD169+ , Lyve1^{hi} and Lyve1^{lo} macrophages associating with serosal linings and FALCs. Micro-insults perturbing the serous cavities can initiate conversion of a fluid to solid phase response via the clotting, scaffolding, tethering and aggregation of LCM. In addition, CD169^{+} macrophages can dynamically cloak sterile micro-lesions, limiting neutrophil recruitment from the circulation.

Table 1. Non-classical multi-cellular metazoan parasites that modify immunobiology within the serous cavities

Parasite	Cavities Involved	Route to Cavity / Evidence	Symptoms	Prevailing Immune Response	References
***Mansonella* spp.**	Peritoneal, pleural, pericardial	Recovered from connective tissue in serous cavities during surgery or autopsy	Often asymptomatic; moderate fever, headache, oedema, skin rash, joint pains, fatigue neurological manifestations	Eosinophilia	(*141*, *142*, *174*)
Paragonimus westermani	Pleural (effusion, nodules), pericardial (effusion)	Eggs identified microscopically in pleural fluid and pleural nodules biopsied; serology positive for *Paragonimus*	Exudative eosinophilic pleural effusion, thoracoscopic pleural nodules causing chest pain, dyspnea and possible pericardial effusion	Th2-skewed eosinophilia in blood/fluid, granulomatous inflammation, elevated IgE	(*175*, *176*)
***Spirometra* spp.** (sparganosis)	Pleural (effusion)	Eosinophilic pleural effusion; worm-shaped larva removed from pleural fluid and identified by DNA sequencing	Chest pain, eosinophilic pleural effusion	Th2/eosinophil-rich inflammatory response	(*177*)
Toxocara canis/cati	Pleural (effusion), pericardial (effusion)	Eosinophilic pleural/pericardial fluid; positive anti-Toxocara serology in serum and effusion and associated imaging	Dyspnoea, chest pain, pericardial tamponade in myocarditis, ascites	Th2/eosinophil-rich inflammatory response in blood and fluid	(*178*, *179*)
Strongyloides stercoralis	Pleural (effusion), pericardial (effusion)	Hyperinfection in immunosuppressed hosts leads to larvae in serous fluids; direct detection or larva identified in fluid	Exudative eosinophilic pleural/pericardial fluid, often life-threatening dissemination and tamponade	Th2/eosinophil-rich systemic hyperinfection response	(*180–182*)
Echinococcus granulosus	Pleural and peritoneal (secondary rupture)	Ruptured hydatid cyst into serous space; imaging or surgical reports; serology positive in fluid or serum	Effusions, abdominal distension, dyspnoea; possible allergic/anaphylactic symptoms	Granulomatous/chronic inflammatory, eosinophils, IgG/IgE-mediated response	(*183–185*)
Trichinella spiralis	Pericardial (effusion)	Systemic larval migration; occasionally detected in pericardial fluid; imaging evidence plus serology	Fibrinous pericarditis, tamponade, dyspnoea, fever	Mixed inflammatory with eosinophils, myocarditic response	(*186*, *187*)
***Anisakis* spp.**	Pleural (effusion), pericardial (effusion)	Positive anisakis serology in serum and pleural/pericardial fluid; imaging and clinical context support parasitic migration across diaphragm or pericardium	Fever, dyspnoea, chest or abdominal pain, marked eosinophilic pleural effusion, possible pericardial effusion and tamponade	Th2/eosinophil-rich response, elevated total IgE, specific IgE/IgG positive in fluid and serum	(*188–190*)
Fasciola hepatica	Peritoneal involvement, pleural lesions	Juvenile fluke migration through peritoneum and rarely pleura; imaging shows pleural effusion and mesenteric/peritoneal lesions in ectopic cases	Abdominal pain, nausea, ascites, pleural/respiratory symptoms	Likely eosinophil-mediated Th2 response; possible hypersensitivity responses	(*191*, *192*)
Ascaris lumbricoides	Peritoneal	Live worms were recovered from the peritoneal cavity including one that was protruding through a rupture in the duodenum	Abdominal pain, clubbing of fingers, febrile, tachypneic, with raised blood pressure	Likely eosinophil and mast cell dominated with strong Th2 response and IgG/IgE production	(*193*, *194*)