

TISSUE IMMUNOLOGY

Immunobiology of the serous cavities

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The serous cavities are fluid-filled spaces that surround the lung, heart, and 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. Although these cavity-derived immune cells have been studied *ex vivo* for many years, the past decade has led to substantial advances in serous cavity biology. Importantly, immune mechanisms that occur in these fluid environments and communication networks between these cavities and the tissues that they contain have been elucidated. In this Review, we aim to summarize the current knowledge of cellular and molecular interactions that govern immunology across all serous cavities, comparing animal models and human studies. A deeper understanding of how the serous cavities provide immune protection to the tissues that they encompass is likely to reveal therapeutic avenues for manipulation of these cavities to improve disease outcomes.

INTRODUCTION

The peritoneal, pleural, and pericardial cavities, collectively termed the serous cavities, develop in close association with the organs that they encompass. Although 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 in the thorax and the peritoneal cavity sits in 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 (Fig. 1, A and B) (2). The size of the serous cavities differs between mammalian species because serosal fluid volume and surface area increase roughly in proportion to body mass (3). In contrast, the mesothelium itself is morphologically similar between species, 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 (~7 μm), whereas this is thicker in larger animals like humans (~30 to 40 μm) (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 harbor 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, as well as metastatic cancer cells and inherent changes in physiology such as effusion (11) and fibrosis. These immune cells can be suspended in the free-flowing fluid, associated with the mesothelial membranes, or organized in 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 (Fig. 1C), which will later separate into the mature peritoneal, pericardial, and pleural cavities (Fig. 1, D and E) (12). From this very early stage of development, the serous cavities are seeded by immune cells. Embryonic primitive hematopoiesis 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 bilayered structure that is observed in adults. Concomitantly, the fetal liver becomes seeded with hematopoietic cells (18) and will produce both myeloid and lymphoid progenitors. Around this time, B1 cells first appear in the cavity (19–21), and these cells function as a reservoir of B cells into adulthood. During this development, some of the mesodermal cells develop epithelial features such as basal-apical polarization 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 [~100 ml in the human peritoneal cavity (22, 23) and around 20 ml in the pleural cavity (24, 25)], which is

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generated from the systemic circulation via the mesothelial vasculature (26, 27). Female peritoneal fluid can also contain 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 2 hours (24), and roughly a liter of peritoneal fluid is generated daily. This huge fluid turnover is enabled via specialized structures called stomata, which are small holes interspersed in 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 in 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. Albumin, transferrin, and hemopexin

are found at high levels in the cavities, reflecting their 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 with serum (37). Additionally, hyaluronan and phospholipids such as phosphatidylcholine are present at high levels (5) and likely act together for tissue lubrication (38). Multiple studies report dramatic changes in serous cavity cytokine profiles after disease, and there are indications that the fluid composition differs between neighboring 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 in serous fluid, a better understanding of how fluid varies between different cavities and under distinct conditions is needed.

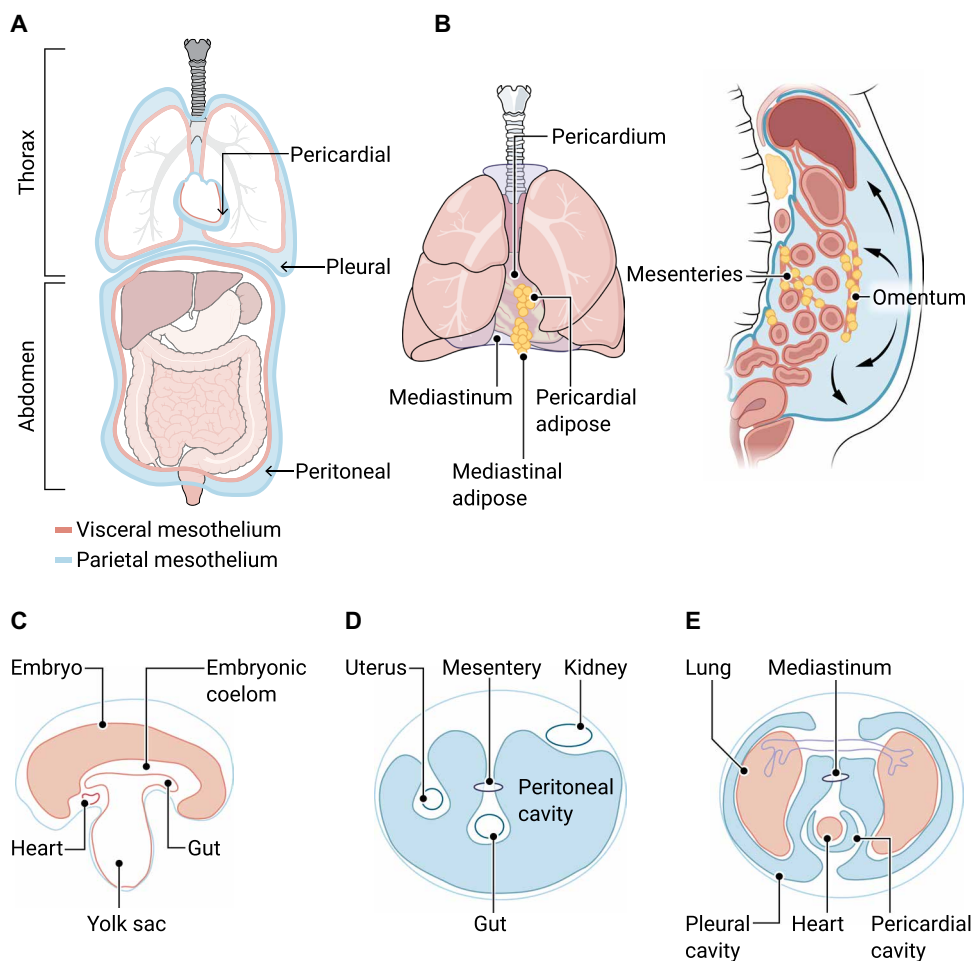


Fig. 1. Development dictates the formation of serous cavities and associated immune adipose tissues. (A) The pericardial, pleural, and peritoneal cavities. The parietal mesothelium lines the cavity wall and reflects back over the organs in each cavity, where it becomes known as the visceral mesothelium; each cavity contains a small volume of lubricating serous fluid. (B) Each serous cavity contains FALCs in specialized adipose depots. Serous fluid circulates because of gravity and internal pressure changes in the cavities. (C) Developing embryo showing relationship between embryonic coelom that forms the serous cavities, the yolk sac that 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 the 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.

Fat-associated lymphoid clusters

In addition to fluid-phase immune cells and the mesothelium, it has been recognized for more than 100 years (42) that other distinct structures in the serous cavities have immune functions (42–45). FALCs are small immune cell clusters present in immune-adipose tissues (primarily the pericardium, mediastinum, omentum, and mesenteries) of the serous cavities. FALCs are key coordinators of cavity immune responses, acting as hubs for immune cell activation in 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 in 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 (ILC2s) and are key portals for the entrance and egress of leukocytes in 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 (Fig. 2) (53). During infection and inflammation, stromal-immune cell

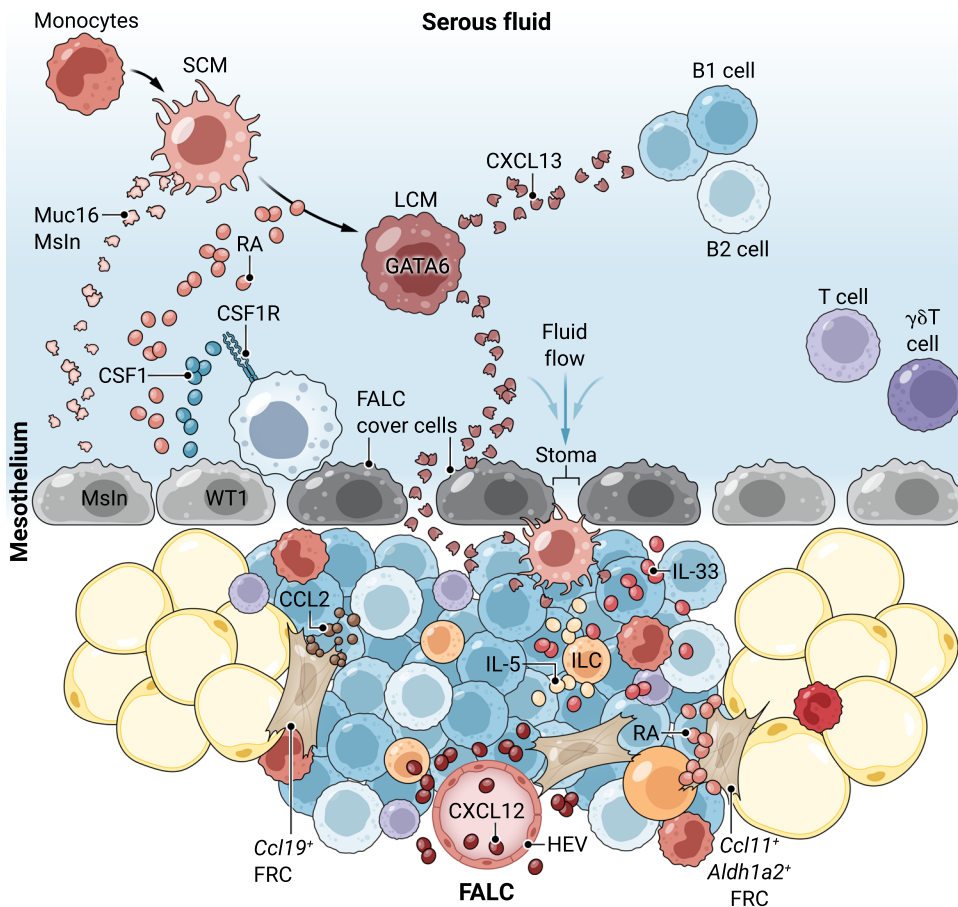


Fig. 2. Stromal-immune interactions define cellular position and phenotype in the serous cavities. Mesothelial-derived RA, Msn, and Muc16 released from mesothelial cells enhance fluid-phase macrophage acquisition of GATA6. Mesothelial-derived CSF1 directs mesothelial macrophage phenotype. Serous fluid flows through stomata in the mesothelium located over FALCs, facilitating contaminant and immune cell egress out of the cavity. Immune cells can also enter the cavities via HEVs in FALCs. FALC FRCs position monocytes via secretion of CCL2 and modify peritoneal B and T cells via RA secretion. IL-33 secretion from stromal cells activates ILC2s in FALCs, initiating IL-5 secretion. CXCL13 secretion from LCM and FALC cover cells positions B cells in the peritoneal fluid.

cross-talk facilitates de novo FALC formation and expansion that supports B cell activation, including the formation of germinal centers (47, 54, 55).

KEY IMMUNE CELL POPULATIONS IN THE CAVITIES

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

Lymphocytes

The murine serous cavities have large populations of B1 B cells (21) in addition to a smaller B2 population. B1 cells develop during fetal

hematopoiesis and are characterized by expression of CD11b in addition to CD19, which is also expressed by T-dependent B2 B cells (61). B1 B cells produce natural immunoglobulin M (IgM), which is polyreactive and recognizes self-antigens such as phospholipids (62). A large proportion of the abundant natural IgM antibodies in the serous fluid recognizes 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 to 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 in the peritoneal cavity, with a 40% reduction in entry after surgical removal of this tissue; however, B2 cells can still exit the peritoneal cavity of omentectomized mice (65). Although 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 in serous fluid (69).

T lymphocytes are key effectors of the adaptive immune response in the serous cavities and increase during infection. Conventional T cells can enter the peritoneal cavity via high endothelial venules (HEVs) in omental FALCs (70), and FALCs facilitate T cell-dependent responses to foreign antigens in the cavity (55). Studies detailing entry and egress of lymphocytes in the pericardial and pleural cavities are sparse in comparison with 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 are comparisons across cavities.

Innate lymphocyte populations are also present in the cavities with their contributions highly varied, and far more is still to be learned. For example, $\gamma\delta$ T cells, which are 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 have been documented in the serous cavities, with the latter originally identified in 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 in adipose depots including those that house FALCs. Eosinophils are linked to type 2 cytokines, most notably interleukin-5 (IL-5), which is required for their differentiation in the bone marrow and later activation in 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 in 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 Cohn (79), building on the identification of phagocytes by 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 (SPMs/LPMs) for studies undertaken in the peritoneal cavity (80). More recently, these cells have been referred to as cavity macrophages (SCMs/LCMs) to more broadly encompass the different serous cavities in which they are present (Fig. 3) (58, 81).

SCMs are typically F4/80^{Lo} and MHCII^{Hi}, contrasting with LCMs that 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. SCMs are recently derived from circulating monocytes (82–85) and depend on the transcription factor interferon regulatory factor 4 (IRF4) (82). They are a heterogeneous population, containing both monocyte-like and dendritic cell-like cells (86, 87). In contrast with SCMs, LCMs 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 (RA) produced by Wilms' tumor 1 (WT1)⁺ stromal cells (mesothelial and fibroblasts) (93), although other pathways are likely involved.

LCMs are initially derived from the embryonic yolk sac (93, 94) but, over time, are replaced by circulating monocytes that infiltrate into the cavities and take on a SCM phenotype. These SCMs can further differentiate into LCMs analogous to the embryonically derived cells (82, 86). Monocyte infiltration into tissues is also a defining feature of classical inflammation, and inflammatory monocytes arriving in 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 α (IL-4R α) signaling (95). These IL-4R α -activated

macrophages produce type 2 effector molecules such as resistin-like molecule α and Ym1 (96, 97). Recent work has shown that in these settings, IL-4R α signaling can also drive incoming monocytes into the LCM pool via an intermediate converting cavity macrophage (CCM) population characterized by expression of markers such as lymphatic vessel endothelial hyaluronan receptor-1 (LYVE1) and folate receptor β (FR β) (Fig. 3) (81, 98).

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 with that in 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 affect the interaction between aging and disease pathogenesis.

Although GATA6⁺ LCMs have been found in the peritoneal (58, 99) and pericardial (100) spaces of humans, these cells are a far smaller population than that observed in mice. Instead, in the human peritoneal cavity, most 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, remain 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, specialized populations are intimately associated with the serosal membranes (Fig. 3) (101–103). Intravital microscopy initially revealed the presence of CD169⁺ sessile macrophages embedded in 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 (Fig. 3) (101). 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 in mesothelial linings. In particular, careful work on the mesenteric mesothelium identified LYVE1^{hi} CX₃CR1^{lo/-} and LYVE1^{lo/-} CX₃CR1⁺ populations. LYVE1^{hi} cells were found to be embryonically derived and to account for ~60% of the total macrophage population in the mesenteries (103). LYVE1^{hi} macrophages also exist in the parietal peritoneum and have a transcriptional profile enriched in modulation of extracellular matrix. In contrast with 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 tumor progression (Fig. 3) (102).

Stromal cells

Stromal cells are key regulators of immune cell function in the serous cavities. Like immune cells, they have 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 the environment, secreting a plethora of immune modulatory molecules (4).

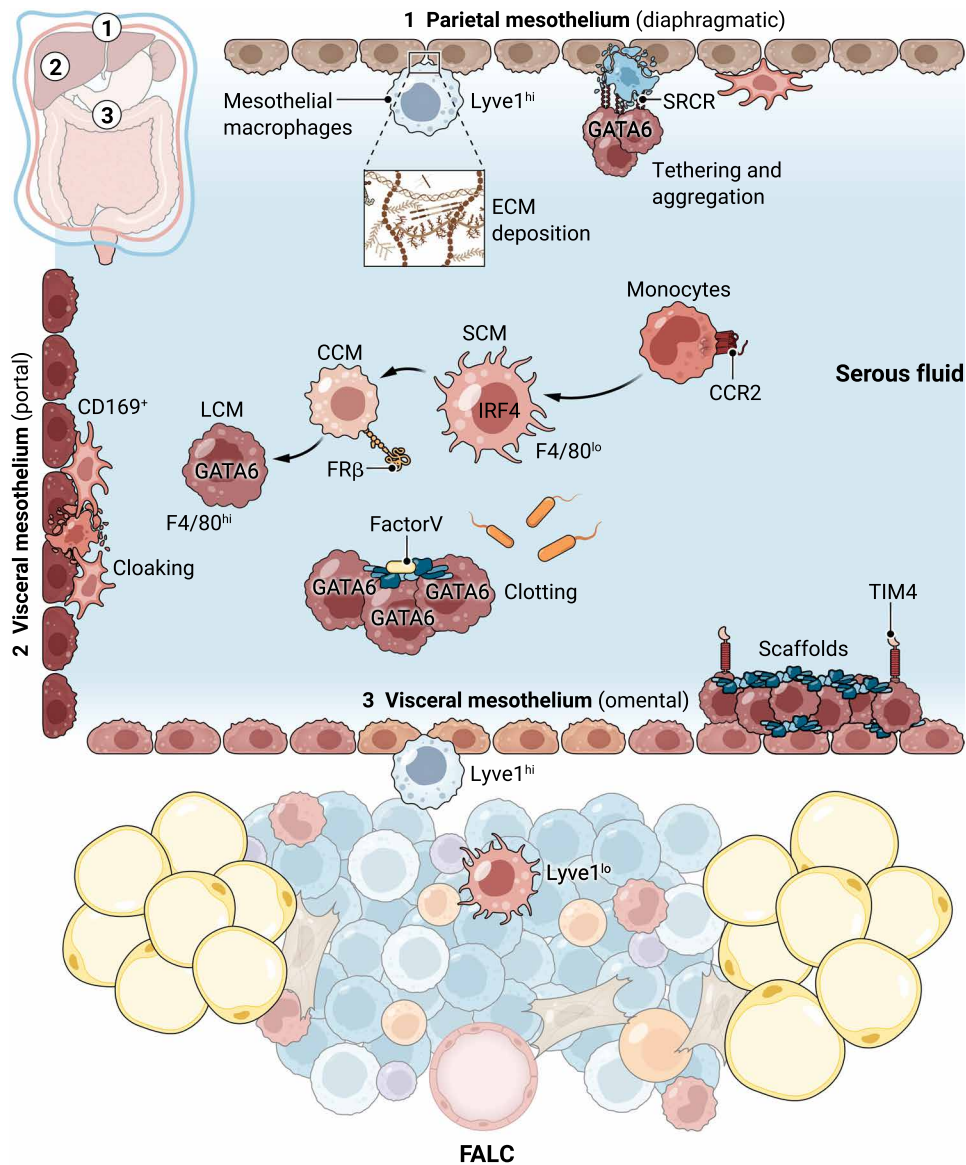


Fig. 3. Multiple macrophage populations contribute to functional immune protection in the serous cavities. CCR2⁺ monocytes, F4/80^{lo} SCMs, FRβ⁺ CCMs, and F4/80^{hi} LCMs occupy the fluid-phase serosal niche with additional populations of CD169⁺, Lyve1^{hi}, and Lyve1^{lo} macrophages associating with serosal linings and FALCs. Microinsults 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 microlesions, limiting neutrophil recruitment from the circulation. ECM, extracellular matrix; SRCR, scavenger receptor cysteine-rich; TIM4, T cell immunoglobulin and mucin domain containing 4.

Mesothelial cytokine secretion is highly polarized; 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 RA by WT1⁺ cells in the cavities specifies GATA6 expression in LCMs (93). In addition to RA, mesothelial cells also produce CSF1, which can drive peritoneal macrophage proliferation in vitro (105) and support mesothelial-associated macrophages (Fig. 2) (103). Fluid-phase macrophage specification is also influenced by mesothelin (MSLN) and mucin 16 (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 after inflammation (Fig. 2) (106).

FALC stromal cells are enriched in immune regulatory molecules and orchestrate immune responses in the cavities (107). FALC mesothelial cover cells act as coordinators of fluid-to-tissue immune activation, recruiting immune cells from the serous fluid to the cluster, whereas FRCs are key for recruiting immune cells to the peritoneal cavity and positioning them in 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 in naive omentum (107) and expresses high levels of *Aldh1a2* and aldehyde dehydrogenase activity (70), providing a nonmesothelial source of RA in 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 in 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, although the absence of ALDH1A2⁺ FRC led to fewer T cells and B1 and B2 B cells entering the peritoneal cavity, there was no impact on peritoneal LCMs (70). The authors suggest that this may be due to reduced endothelial CXCL12 expression in the absence of RA from FRCs (70), which would limit lymphocyte recruitment via omental HEVs (Fig. 2) (70). In contrast, LCMs have been described to respond to RA derived from WT1⁺ stromal cells that include both mesothelial cells and fibroblasts (93).

Together, these studies suggest that mesothelial-derived RA may be of greater importance than fibroblasts for specifying LCMs.

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

This brief overview of key players in 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 after 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 after 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 unsurprising 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 efforts of recruited neutrophils and monocytes, resident LCMs, 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 cecal 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 intraperitoneal delivery of *Escherichia coli*), neutrophils enter the peritoneal cavity via the HEVs of omental FALCs, and this contributes to protection from sepsis (111). Given that *E. coli* is 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) and results in rapid adhesion of aggregates to the mesothelium via fibrin-dependent aggregation of LCMs (Fig. 3) (114). Together, these macrophage-mediated pathways can effectively control peritoneal infection.

Zymosan-A is a fungal cell wall mixture isolated from *Saccharomyces cerevisiae* frequently used experimentally to induce peritonitis. Instillation of between 10 μg and 1 mg of zymosan intraperitoneally results in rapid neutrophil recruitment to the peritoneal cavity and loss of the resident LCM population. Replenishment by monocytes and SCMs occurs over the next 3 to 7 days, with resolution of inflammation, as evidenced by reduction of neutrophil and eosinophil numbers back to baseline by days 7 to 14 (115). Studies of zymosan-induced peritonitis revealed that release of CXCL1 by murine mesothelial cells in the omentum coordinates accumulation of peritoneal neutrophils on top of FALCs. The buildup of neutrophils is dependent on release of extracellular traps, and, if neutrophil extracellular trap (NET)-osis is blocked, then 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 (Fig. 3) (56, 116). Inhibition of coagulation via the delivery of heparin or

deletion of the clotting factor V in resident LCMs reverses the macrophage disappearance reaction induced by high-dose zymosan (56). LCMs also “disappear” from the fluid phase during experimental inflammation by recruitment to the omentum (91). Intraperitoneal infection with the single-celled protozoan parasite *Toxoplasma gondii* drives LCM recruitment to the omentum where, in contrast with conventional expectation, infected LCMs rather than DCs prime naive CD8⁺ T cells (117). This experimental system illustrates the importance of the tissue environment, even in 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 on competition for factors including RA (Fig. 2). After mild inflammation induced by low-dose zymosan, LCMs remain in the peritoneal cavity, and infiltrating SCMs persist but cannot acquire residency (118). After high-dose zymosan, when LCMs are ablated, RA availability increases and incoming monocytes can acquire residency (118). Inflammatory loss of LCMs from the peritoneal cavity also results in loss of CD11b⁺ B1 B cells after resolution of inflammation (118). This is because, in addition to FALC stromal cells, LCMs produce CXCL13, which is responsible for the sustained recruitment of B1 cells to the peritoneal cavity (Fig. 2) (49, 53, 118).

The examples above highlight that, even in a fluid environment, “niches” can form, either through resource availability, conversion from fluid phase to solid phase, or migration to local organized 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 tumor metastases (123). How deep into organs serous immune cells can infiltrate is a current topic of debate with different reports presenting data suggesting that serous cavity macrophages infiltrate deep in organs (100, 119, 121) or, alternatively, only accumulate on the surface (124). Improved understanding of how and why serous immune cells and particularly macrophages migrate into organs may enable their future repurposing for therapeutic use. More generally, understanding communication between the cavities and the organs that they encompass and how these cavities communicate with each other is directly relevant 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 extrapulmonary manifestations of this devastating disease. Pleural TB is a topic that has been comprehensively reviewed by others (125) and is characterized by the presence of neutrophils and monocytes and, subsequently, lymphocytes in pleural effusion. TB pleuritis is characterized by homing of memory T helper 1 (T_H1) cells to the pleural space, often 6 to 12 weeks after pulmonary TB (126). Local increases in interferon- γ are found in pleural fluid during TB pleuritis, which indicates a localized 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 the lung and/or heart by filtering the serous fluid has not been unequivocally demonstrated, in contrast with the peritoneal cavity where the omentum undertakes this function (107). Nonetheless, there is ample evidence for communication between these body systems. In preclinical models, particulate material delivered into the pleural space can be found in the FALCs of the pericardium and mediastinum, and labeled 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 the 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. *IL33* is expressed by FALC stromal cells, including mesothelial cells, cover cells, and fibroblasts (107), and IL-33 protein is released into the pleural space after intranasal instillation of *Alternaria* (50). Localized IgM antibody production in response to intranasal *Alternaria* occurs in the pleural cavity via IL-33-dependent activation of mediastinal and pericardial FALC-resident ILC2s, which produce IL-5 to activate FALC B1 and B2 B cells (50). IL-5 is also a key cytokine required for eosinophil differentiation in the bone marrow and later activation in 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 in 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⁺ ILC2s in the heart. Coculture 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. Intrapleurally injected eosinophils migrate into the hearts of eosinophil-deficient mice during pericarditis (52), highlighting the interniche movement of immune cells from serous fluid to organs housed in the cavities.

Fibrosis

In the context of prolonged or repetitive inflammation, the mesothelium can become fibrotic. Pleural fibrosis is characterized by remodeling 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 up-regulation of WT1 and migration of mesothelial cells into the lung parenchyma (133, 134). Increased expression of WT1 in the lung parenchyma is also seen in patients with IPF, 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). Together, these data fit with an idea that has been termed the “inside out model of pulmonary fibrosis” (133).

Fibrotic serous cavity adhesions are not only 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 and macrophage receptor with collagenous structure, also contributes to adhesion formation (Fig. 3) (57). 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 favor 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 extracellular matrix 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 in the serous cavities and how these contribute to both beneficial and harmful responses.

Insights from tissue-dwelling metazoan parasites

Multicellular metazoan parasites, or helminths, that live in the tissues represent a very common evolutionary event with nearly 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. Whereas few species reside directly in 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 fibrinohemorrhagic 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 affect 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 in 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 edema and huge increases in eosinophils and IL-4R α -activated

Table 1. Nonclassical multicellular metazoan parasites that modify immunobiology in the serous cavities.

Parasite	Cavities involved	Route to cavity/evidence	Symptoms	Prevailing immune response	References
<i>Mansonella</i> spp.	Peritoneal, pleural, and pericardial	Recovered from connective tissue in serous cavities during surgery or autopsy	Often asymptomatic; moderate fever, headache, edema, skin rash, joint pains, fatigue, and neurological manifestations	Eosinophilia	(141, 142, 174)
<i>Paragonimus westermani</i>	Pleural (effusion and nodules) and pericardial (effusion)	Eggs identified microscopically in pleural fluid and pleural nodules biopsied; serology positive for <i>Paragonimus</i>	Exudative eosinophilic pleural effusion, thoracoscopic pleural nodules causing chest pain, dyspnea, and possible pericardial effusion	T _H 2-skewed eosinophilia in blood/fluid, granulomatous inflammation, and elevated IgE	(175, 176)
<i>Spirometra</i> spp. (<i>sparganosis</i>)	Pleural (effusion)	Eosinophilic pleural effusion; worm-shaped larva removed from pleural fluid and identified by DNA sequencing	Chest pain and eosinophilic pleural effusion	T _H 2/eosinophil-rich inflammatory response	(177)
<i>Toxocara canis/cati</i>	Pleural (effusion) and pericardial (effusion)	Eosinophilic pleural/pericardial fluid; positive anti- <i>Toxocara</i> serology in serum and effusion and associated imaging	Dyspnea, chest pain, pericardial tamponade in myocarditis, and ascites	T _H 2/eosinophil-rich inflammatory response in blood and fluid	(178, 179)
<i>Strongyloides stercoralis</i>	Pleural (effusion) and 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	T _H 2/eosinophil-rich systemic hyperinfection response	(180–182)
<i>Echinococcus granulosus</i>	Pleural and peritoneal (secondary rupture)	Ruptured hydatid cyst into serous space; imaging or surgical reports; serology positive in fluid or serum	Effusions, abdominal distension, and dyspnea; possible allergic/anaphylactic symptoms	Granulomatous/chronic inflammatory, eosinophils, and IgG/IgE-mediated response	(183–185)
<i>Trichinella spiralis</i>	Pericardial (effusion)	Systemic larval migration; occasionally detected in pericardial fluid; imaging evidence plus serology	Fibrinous pericarditis, tamponade, dyspnea, and fever	Mixed inflammatory with eosinophils and myocarditic response	(186, 187)
<i>Anisakis</i> spp.	Pleural (effusion) and pericardial (effusion)	Positive <i>Anisakis</i> serology in serum and pleural/pericardial fluid; imaging and clinical context support parasitic migration across diaphragm or pericardium	Fever, dyspnea, chest or abdominal pain, marked eosinophilic pleural effusion; possible pericardial effusion and tamponade	T _H 2/eosinophil-rich response, elevated total IgE, and specific IgE/IgG positive in fluid and serum	(188–190)
<i>Fasciola hepatica</i>	Peritoneal involvement and 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, and pleural/respiratory symptoms	Likely eosinophil-mediated T _H 2 response; possible hypersensitivity responses	(191, 192)
<i>Ascaris lumbricoides</i>	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, and with raised blood pressure	Likely eosinophil and mast cell dominated with strong T _H 2 response and IgG/IgE production	(193, 194)

macrophages in the cavity. Using this model, the capacity of IL-4 to drive local macrophage proliferation was discovered (95) as was a new understanding of monocyte-to-LCM dynamics as described above (81). These LCMs that expand during infection in response to T_H2 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 in 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, although the importance of peritoneal versus liver eosinophils was not assessed (144). Similarly, infection with the gastrointestinal parasite *Heligmosomoides polygyrus* increases effector T_H2 cells (145) and IL-4R α -activated macrophages (146) in the peritoneal cavity. In addition to mounting direct responses during infection, the serous cavities harbor memory immune cell populations, both in the mesenteric adipose (110) and the peritoneal fluid (147). After infection with *H. polygyrus*, the gut, draining lymph nodes, and peritoneal cavity all harbor memory T_H2 cells (147).

The consequences of an intestinal T_H2 response extending into the cavities are 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 after 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-4R α -activated LCMs present after *H. polygyrus* infection did not enhance susceptibility to *Salmonella enterica* ser. *Typhimurium* (146). Instead, nematode-expanded LCMs up-regulate canonical type 1 markers such as nitric oxide synthase 2. However, although the LCMs generated by nematode infection demonstrate the capacity to become antimicrobial, 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 in 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 also 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, although it predominantly affects the pleural mesothelium, peritoneal mesothelioma does occur. After inhalation, asbestos fibers migrate into the pleural cavity where macrophages attempt to phagocytose them. Short fibers are efficiently cleared; however, longer fibers are too big to be phagocytosed resulting in macrophages becoming "frustrated" (150). These frustrated cells release reactive oxygen and nitrogen species 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 fibers becoming lodged in the mesothelium (151). Importantly, long biopersistent fibers other than asbestos can also cause mesothelioma in preclinical 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 the development of malignant pleural mesothelioma has not been investigated. However, there is normally a decade-long delay between fiber exposure and development of mesothelioma, which has made assessment of the immune processes leading to tumor development difficult to dissect in patient cohorts. Murine models of disease are beginning to facilitate assessment of the immune trajectory of mesothelioma development after asbestos exposure (153, 154), but more work is needed in this area.

Metastatic niches in the cavities

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

Studies in the pleural space have extended these findings to show that Kirsten rat sarcoma viral oncogene homologue (KRAS)-expressing tumor 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 LCMs reduce metastasis, decrease tumor burden, and extend survival in a B16F10 melanoma model (123). The role of mediastinal FALCs in metastasis to the pleural cavity is underinvestigated despite this cavity being a key site to which cancers of the breast and lung metastasize (159). The role of FALCs in peritoneal metastasis has been more comprehensively investigated, particularly the frequent metastasis of ovarian cancers to the omentum (102, 160).

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

Serous macrophages in cancer

Macrophages in peritoneal fluid and omentum are also a key link that can capture cancerous cells and facilitate tumor development in FALCs, supporting the metastatic spread of ovarian cancer (102, 161). Macrophage inflammatory protein 1 β secretion by macrophages acting on mesothelial cells facilitates tumor 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 on 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 RA receptors RXR α and RXR β have reduced LCM and expanded SCM populations. This has implications for ovarian cancer progression because RXR α β -deficient

mice have reduced peritoneal LCM infiltration of early ovarian tumors, which reduces tumor progression (164). Depletion of embryonically derived CD163⁺Tim4⁺ tissue-resident macrophages using diphtheria toxin reduces the volume of ascites, the number of tumor cells in peritoneal fluid, and the development of invasive disease in a mouse model of metastatic ovarian cancer (102). Peritoneal LCMs isolated from mice with ID8-derived ovarian carcinoma promote tumor 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). Together, these studies support a protumor role for fluid-phase peritoneal LCMs 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 affecting ~190 million women worldwide and is characterized 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 comprise a mix of progenitor, glandular epithelial, and stromal cells. The presence of endometriotic lesions in 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 in the soil of an activated mesothelium (168). Additionally, endometrial cells have been proposed to metastasize to the peritoneal cavity via vascular and lymphatic spread (166). Additional sequelae of endometriosis include the formation of adhesions in 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 estrogen (168, 169), a known risk factor for disease development.

Extrauterine endometrial tissue that has passed into the peritoneal space can contain endometrial-resident immune cells and recruit 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 after 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 that, in both contexts, fluid-phase monocytes are protective. Monocyte-derived cells were subsequently revealed by single-cell RNA sequencing to become prodisease once recruited into the lesions (171), suggesting that tissue-derived factors in the lesion modulate macrophage phenotype. The immune environment of patients with endometriosis has been characterized as T_H2 skewed (172), as well as having a substantial population of T_H17 cells in the peritoneum (173). These responses have parallels with those mounted against helminths, perhaps suggesting that the presence of misplaced multicellular endometrial tissue activates similar immune processes to those that have evolved to combat migrating multicellular worms.

CONCLUSIONS

Together, the data from multiple studies show that serous cavity cells not only respond to challenges in 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 in these sites and act as a defense behind the mucosal front line. Unraveling the complex communication occurring between the serous cavities and the organs that they encase remains a major challenge in immunology.

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