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Keywords: macrophage, peritoneum, peritoneal cavity, pleural cavity, ontogeny

Abstract

For decades, it has been known that the serous cavities, which includes the peritoneal, pleural and pericardial cavities, harbour large numbers of macrophages. In particular, due to the ease of isolating these cells, the peritoneal cavity has been used as a convenient source of macrophages to examine many facets of macrophage biology over the last 50-60 years. Despite this, it is only recently that the true heterogeneity of serous cavity mononuclear phagocyte compartment, which includes macrophages and dendritic cells, has been revealed. Advances in technologies such as multi-parameter flow cytometry and the 'OMICs' revolution have uncovered the presence of distinct populations of mononuclear phagocytes in the serous cavities. Given that peritoneal macrophages have been implicated in many pathologies, including peritonitis, pancreatitis, endometriosis and acute liver injury, it is imperative to understand the biology of these cells. Here, we review the recent advances in understanding the identity, origin and function of discrete serous cavity mononuclear phagocyte subsets in homeostasis and how these may change when homeostasis is perturbed, focusing on peritoneal and pleural cavities and highlighting differences in the mononuclear phagocytes found in each.

Introduction

Mononuclear phagocytes (MPs), including macrophages and dendritic cells, are present in every tissue of the body where carry out important and distinct roles in protective immunity. However, it is increasingly clear that these cells are also crucial for the maintenance of tissue homeostasis, as well repair of damaged tissue following injury, infection or inflammation. The serous cavities, which includes the peritoneal, pleural and pericardial cavities, contain large numbers of MPs, but it is only recently that the heterogeneity of this compartment has been dissected. In this review, we will begin by discussing the recent advances in understanding the phenotypic identity, developmental origin and function of distinct MP subsets, and in particular, macrophages in the serous cavities during homeostasis before describing how these change in different disease contexts.

The Anatomy of the Serous Cavities

The peritoneal cavity is the small fluid filled space between the mesothelial lining of the abdominal wall (parietal peritoneum) and the equivalent lining of the abdominal organs (visceral peritoneum). With a similar surface area to that of the skin, the peritoneum is the largest serous membrane of the human body [1]. Notably the peritoneum differs between the sexes. Whereas in males the peritoneum forms a closed cavity, in females the peritoneum is discontinuous at the fimbrial openings of the fallopian tubes and the ovaries are covered in a single layer of cuboidal epitheloid cells, not visceral peritoneum [1]. Thus, the composition of the peritoneal fluid will differ between males and females due to the presence of ovarian exudate and retrograde passage of material from the reproductive tract. In contrast, male reproductive organs are located outwith the abdominal cavity. The pleural cavity is the serous cavity of the thorax and pericardial cavity surrounds the heart.

However, because the parietal and visceral mesothelia adhere to one another under normal physiological conditions in these cavities [2], they are often referred to as 'potential spaces'. In each of these cavities the mesothelium is a single layer of squamous epithelial cells which sits on top of a layer of connective tissue. The mesothelium continually secretes fluid, with around 5-20ml present in the human peritoneal cavity under normal physiological settings [1]. Similar to type II pneumocytes, mesothelial cells of the peritoneum, pleurae and pericardia have lamellar bodies, which are composed of lipid membranes and protein complexes of surfactant proteins [1]. Balanced release of lipids, surfactant proteins and fluid generates a glycocalyx over the surface of mesothelial cells, which creates a layer of static fluid that acts as lubricant and allows frictionless movement of the organs, for instance during intestinal peristalsis in the abdomen, expansion and contraction of the lungs in the thorax and the beating of the heart. However, the majority of cavity fluid is not static and moves in a well-defined manner. For instance, in the peritoneal cavity fluid moves upwards from the lower to upper abdominal cavity due to respiration and then returns under the control of gravity. The cavity fluid is rich in water, electrolytes, proteins and immune cells, including T- and B-cell subsets and mast cells that co-exist alongside the large mononuclear phagocyte (MP) compartment [3].

Unravelling Mononuclear Phagocyte Heterogeneity in the Serous Cavities

In mice, the peritoneal and pleural cavities are known to house at least two distinct macrophages subsets, which are present in a variety of strains, including C57BL/6, BALB/c, 129/S6, FVB/N, SJL/J and *Rag1*$^{-/-}$ mice [4]. These subsets were originally defined by their differential expression of the pan-macrophage marker, F4/80, and MHC class II (MHCII) [4]. The majority of macrophages in the healthy cavity express high levels of F4/80 and only low

levels of MHCII, and are sometimes referred to as 'large' peritoneal macrophages (LPM) [4] (Figure 1). These F4/80^{hi} cells possess characteristic macrophage morphology, including abundant cytoplasmic vacuoles, are highly phagocytic and are reliant on CSF1R signalling for their development and maintenance [4-8]. Furthermore, they express CD64 (the high affinity IgG receptor) and Mer tyrosine kinase (MerTK) [9], two markers that are now commonly used to identify tissue macrophages [9,10]. While there is general consensus that these F4/80^{hi} cells represent tissue macrophages, the composition of the F4/80$^{-/lo}$ MHCII^{+} population that co-inhabits the serous cavities has been a source of controversy [4-6,11-15]. This is due to divergent approaches taken to characterise these cells by different investigators and the realisation that the marker CD11c, which was previously considered to be dendritic cell (DC) specific, is expressed by many macrophages, including some of those present in the serous cavities [5,6,14,15]. Thus, while Ghosn et al. [4] were first to thoroughly compare the biology of F4/80^{hi} and F4/80^{lo} MPs, their exclusion of all CD11c^{+} cells as DC to identify the so-called 'small' peritoneal macrophages (SPM) will have underestimated the heterogeneity of the F4/80$^{-/lo}$ MHCII^{+} macrophage compartment. More recent studies have adopted CSF1R expression as a universal marker of cells of the macrophage lineage in the serous cavities [6,16,17]. Notably, unlike other tissues where CSF1R protein expression is difficult to measure, it can readily be detected on the surface of peritoneal exudate cells (PEC) (Bain & Jenkins, Methods in Molecular Biology, *In press*). Indeed, F4/80$^{-/lo}$ MHCII^{+} cells that lack the CSF1R represent conventional DC (cDC), since they arise from CCR2-independent precursors, rely on Flt3L for their development, and can be divided into cDC1 and cDC2 subsets based on expression of XCR1/CD103 and CD11b [6,15,18] (Figure 1), as in other tissues [19]. The vast majority of CSF1R expressing F4/80$^{-/lo}$ MHCII^{+} cells represent cells of the macrophage lineage, as they are acutely dependent on CSF1 for their

development/maintenance [6] (SJJ, unpublished observations) and, like their F4/80^{hi} co-inhabitants, express the macrophage-restricted transcription factor, MafB [20]. However, around a quarter of CSF1R^{+} F4/80$^{-/lo}$ MHCII^{+} cells are labelled in *Zbtb46*-GFP reporter mice [20], which have been used extensively to identify cells of the DC lineage [21,22]. Consistently, our recent work has shown that the CSF1R^{+} F4/80$^{-/lo}$ MHCII^{+} population is heterogeneous for CD11c expression and that the CD11c^{+} fraction is partially affected by Flt3L deficiency and comprises both CCR2-dependent and CCR2-independent cells. Thus, the CSF1R^{+} F4/80$^{-/lo}$ MHCII^{+} compartment seemingly contains a small population of DC. Notably, markers such as CD24, CD26, CD64, CD272 and MerTK, which have been used to distinguish macrophages and cDC in other tissues [9,10,19,23-25], are not useful for division of the CSF1R^{+} F4/80$^{-/lo}$ MHCII^{+} compartment in the serous cavities [5,15] (and CCB & SJJ, unpublished observations).

In addition to the phenotypic markers noted above, novel markers have been identified through genome-wide transcriptional profiling by the Immunological Genome Consortium (Immgen) and others [9,11,26,27], which aid identification of cavity macrophages. CD102 (intercellular adhesion molecule 2, ICAM2) has emerged as a signature marker of F4/80^{hi} macrophages, which also express high levels of CD73, CD93, CD9 and CD49F [11,13,26]. While most F4/80^{hi} macrophages also express Tim4, the phagocytic receptor that recognises phosphatidylserine on apoptotic cells, Tim4^{-} F4/80^{hi} macrophages are present under normal physiological conditions and, as discussed below, their number is highly dependent on the strain, age and sex of the animal. Notably, none of these markers are expressed by CSF1R^{+} F4/80$^{-/lo}$ MHCII^{+} macrophages to any significant level. Instead, CD226 (DNAM-1) has been established as a useful marker of mature CSF1R^{+} F4/80$^{-/lo}$ MHCII^{+} macrophages in the serous cavities under homeostatic conditions [5,14,15].

Similarly, we have recently shown that expression of CD206 (mannose receptor) and constitutive production of the immunoregulatory cytokine resistin-like molecule (RELM)α are key traits of these cells [5]. Of these, RELMα expression appears to best discriminate the macrophages from the DC component of $CSF1R^{+}$ $CD11c^{+}$ $F4/80^{-/lo}$ $MHCII^{+}$ cells. While these molecules are typically associated with 'alternative activation' of macrophages, expression of CD206 and RELMα is independent of the IL-4–IL-4R axis (CCB & SJJ, unpublished data) that defines 'alternatively activated' macrophages [28]. Thus, CD206 and RELMα are default properties of mature $CSF1R^{+}$ $CD11c^{+/-}$ $F4/80^{-/lo}$ $MHCII^{+}$ macrophages.

Studies examining the immune cell composition in the peritoneal fluid of humans have shown that mononuclear phagocytes are present in the peritoneal cavity, even in the absence of infection [29], and constitute around 50% of all leukocytes [30]. These display classical macrophage features, including expression of CD11b, CD14, CD68, CD64, MerTK, VSIG4 and CD49F, as well as having avid phagocytic activity, consistent with some of their counterparts in mice [29-31]. However, whether functionally distinct macrophage subsets exist amongst this population under normal physiological conditions requires further study.

The Ontogeny of Serous Cavity Macrophages

Classically, tissue macrophages have been considered to be replenished by blood monocytes, which themselves are rapidly replaced by highly proliferative bone marrow (BM) progenitors, as part of a linear mononuclear phagocyte system (MPS) first proposed by van Furth and colleagues in the 1970's [32]. However, as described elsewhere in this volume, our understanding of macrophage ontogeny has been completely re-written in recent years with the realisation that many tissue macrophages appear to exist independently of blood

monocytes and instead derive from progenitors arising from yolk sac mesenchyme or foetal liver (see review by Ginhoux & Guilliams [33]). These progenitors seed tissues during development and, in many cases, the 'embryo-derived' macrophages they give rise to are able to maintain themselves for much of adult life through *in situ* self-renewal and longevity, under normal physiological conditions and even following an inflammatory challenge [34,35]. The developmental origin of peritoneal macrophages has been a particular source of controversy. Although much of the historical work examining peritoneal macrophage origin concluded that these cells were of BM origin [36-39], these studies relied on techniques such as full body radiation BM chimeras, which suffer from the fact that radiation exposure results in ablation of tissue macrophages. Thus, the replacement under these conditions may not reflect mechanisms present under physiological conditions. More recently, fate mapping by genetic means has been developed. For instance, by using the *Cx3cr1*$^{\text{Cre-ERT2}}$.*Rosa26*$^{\text{eYFP}}$ strain in an attempt to label circulating monocytes, Jung and colleagues [40] concluded that peritoneal F4/80^{hi} macrophages exist independently of monocyte input, findings supported by studies using parabiotic mice [14,35] and dye-labelling studies [41]. Somewhat paradoxically, tracing of HSC-derived cells using an inducible fate mapping system based on Kit (CD117) expression suggested that peritoneal F4/80^{hi} macrophages are rapidly replenished by BM, at a rate faster than colonic macrophages [42], which are known to depend on monocytes for their maintenance [43,44]. We recently offered an explanation for the discrepancies in the literature, by using tissue-protected BM chimeric mice to demonstrate that the requirement for peritoneal F4/80^{hi} macrophage replacement by BM-derived cells is highly sex-dependent; high and low rates of replacement in male and female mice, respectively [5] (Figure 1). Interestingly, although identical populations of MPs are found in the pleural cavity, the turnover of pleural F4/80^{hi}

macrophages is high and unaffected by sex [5], suggesting that local environmental factors that control both the differentiation and rate of turnover of macrophages may differ in distinct cavities (see below).

An alternative mechanism for the replenishment of serous cavity F4/80^{hi} macrophages has been proposed recently. Audzevich et al. [45] have suggested that macrophages can also arise from pre/pro-B cells in both peritoneal and pleural cavities. By using the *Mb1*^{iCre}.*Rosa26*$^{LSL\text{-}eYFP}$ strain to fate-map B cell progenitors, high levels of labelling were detected in peritoneal and pleural macrophages, but not in most other tissue macrophages under steady state conditions. However, the relative dominance of these pre/pro-B cell derived macrophages with age and sex remains unclear, as does whether they differ functionally from their embryo- or monocyte-derived counterparts.

The origin of F4/80$^{-/lo}$ MHCII^{+} MPs has also been established recently. Fate-mapping of BM cells and monocytes, as well as parabiosis demonstrate that these cells are dependent on replacement from BM and are short-lived [5,8,13,14]. The majority of the CSF1R^{+} F4/80$^{-/lo}$ MHCII^{+} MPs are replenished in a CCR2-dependent manner, suggesting they depend on Ly6C^{hi} classical monocytes (Figure 1). Indeed, classical Ly6C^{hi} monocytes can be found in the naïve serous cavities where they appear to mature through a monocyte 'waterfall', whereby they lose Ly6C expression while gaining expression of MHCII to replenish the mature CSF1R^{+} F4/80$^{-/lo}$ MHCII^{+} MPs [5]. A small fraction of the CSF1R^{+} F4/80$^{-/lo}$ MHCII^{+} MPs that express CD11c but lack RELMα expression appear to be less dependent on CCR2, and most likely represent the small DC population within this population [5]. The CSF1R^{-} DCs amongst the F4/80$^{-/lo}$ MHCII^{+} MP compartment do not rely on cell intrinsic CCR2 signalling or their maintenance, suggesting that CCR2 utilisation is relatively unique to cells of the monocyte/macrophage lineage. Both subsets of CSF1R^{+} F4/80$^{-/lo}$ MHCII^{+} MPs

distinguished by CD11c also appear to have discernibly longer half-lives than the CSF1R^{-} DCs, as determined by pulse-chase studies [5].

As well as fulfilling discrete functions under normal conditions, CSF1R^{+} F4/80$^{-/lo}$ MHCII^{+} macrophages may also act as precursors of F4/80^{hi} macrophages. Indeed, our recent fate mapping using CD11c^{Cre}.*Rosa26*$^{LSL\text{-}eYFP}$ mice suggests that CSF1R^{+} F4/80$^{-/lo}$ MHCII^{+} macrophages can mature into F4/80^{hi} macrophages [5] and adoptively transferred F4/80$^{-/lo}$ MHCII^{+} peritoneal cells can adopt an F4/80^{hi} macrophage phenotype if there is niche availability [13]. Whether all CSF1R^{+} F4/80$^{-/lo}$ MHCII^{+} macrophages can mature into F4/80^{hi} macrophages or if this is a property of a subset of these cells is unknown.

While it has been known for years that macrophages have the ability to proliferate *in situ* [46], proliferation is often considered to be an exclusive property of embryo-derived macrophages, thereby explaining their ability to persist throughout adulthood. However, we have recently shown that both embryo- and BM-derived peritoneal F4/80^{hi} macrophages can, and do, proliferate. In fact, at least in the peritoneal cavity, BM-derived F4/80^{hi} macrophages tend to have a higher level of proliferation than their embryo-derived counterparts [5]. Consistently, lower levels of proliferation are observed in F4/80^{hi} macrophages from the cavities of monocytopenic *Ccr2*$^{-/-}$ mice (CCB & SJJ, unpublished observations). Furthermore, all F4/80$^{-/lo}$ MHCII^{+} MPs proliferate under normal physiological conditions [5], confirming that *in situ* proliferation is not an exclusive property of long-lived macrophages.

The parameters that limit the overall lifespan of the peritoneal F4/80^{hi} macrophage population remain unclear. It has been proposed that replacement by BM-derived cells may occur due to proliferative exhaustion of embryo-derived F4/80^{hi} macrophages. However, this does not appear to be the case in the serous cavities, as F4/80^{hi} macrophages of

different origins show identical proliferative responses to exogenous CSF1 administration [5]. Moreover, turnover of peritoneal F4/80^{hi} macrophages from the BM does not simply reflect a process of displacement that arises from competition with continually-recruited monocytes because sex-dependent differences in F4/80^{hi} macrophage turnover are also apparent in *Ccr2*$^{-/-}$ mice, in whom monocyte recruitment is markedly diminished. Thus, further work is needed to determine the factors that govern macrophage longevity.

Transcription Factors in Cavity Macrophage Differentiation

As well as identifying additional markers for more in-depth characterisation of cavity MPs, recent transcriptional profiling has also identified transcription factors involved in their differentiation. Three groups simultaneously identified the transcription factor GATA6 as a key regulator of peritoneal F4/80^{hi} macrophage differentiation, demonstrating that mice with myeloid-specific deletion of *Gata6* have fewer F4/80^{hi}CD102^{+} macrophages [11,17,26]. Furthermore, GATA6 deficiency affects survival, proliferation and function of F4/80^{hi} macrophages [11,17,26]. For instance, the TGFβ2-dependent support provided by peritoneal macrophages for B1 cell class switching was reduced in the absence of GATA6 in myeloid cells [26] (see below). Notably, GATA6 is also expressed by pleural F4/80^{hi} macrophages and similar defects in macrophage proliferation were seen in the pleural cavity [11]. Interestingly, similar breakdown in peritoneal F4/80^{hi} macrophage differentiation is seen in mice with global or myeloid-specific deletion of CCAAT/enhancer binding protein (C/EBP)β [13], although whether C/EBPβ and GATA6 control non-overlapping aspects of F4/80^{hi} macrophage differentiation is unknown. Rather than controlling survival, KLF2 and KLF4 appear to control the expression of apoptotic cell receptors, such as Tim4, and induce

negative regulators of TLR signalling, ensuring F4/80^{hi} macrophages clear apoptotic cells in a non-inflammatory manner [47].

CSF1R^{+} F4/80$^{-/lo}$ MHCII^{+} MPs are unaffected by GATA6 deficiency and instead rely on IRF4 for their differentiation, with markedly fewer of these cells in *Irf4*$^{-/-}$ and CD11c-Cre.*Irf4*$^{fl/fl}$ mice [14]. Interestingly, a proportion of CSF1R^{+} F4/80$^{-/lo}$ MHCII^{+} MPs remain in the absence of IRF4, but whether these represent a distinct IRF4-independent population remains unclear. Furthermore, the identity of other transcription factors involved in CSF1R^{+} F4/80$^{-/lo}$ MHCII^{+} MP differentiation remains to be determined.

Environmental Factors Controlling Macrophage Differentiation

Like most other tissue macrophages, those in the serous cavities depend on CSF1 for their differentiation and survival, and under normal conditions are independent of CSF2 [6]. However, the other local environmental factors that control the phenotypic and functional tissue-specific imprinting of serous cavity macrophages are only beginning to be uncovered. In the peritoneal cavity, the omentum has been implicated in the maintenance of F4/80^{hi} macrophages. The omentum is an intra-abdominal adipose tissue comprised of two layers of mesothelial cells that enclose a collection of adipocytes and leukocytes, with the latter aggregating in clusters known as 'milky spots' [48]. For decades, it has been appreciated that the omentum is important for peritoneal defence, principally due to its ability to adhere to sites of inflammation and remove foreign material [48]. Early studies suggested that the omentum was a local source of macrophage progenitors [49], which was supported by dye-labelling studies showing that macrophages appear to shuttle between the omentum and the peritoneal cavity [50,51]; a process facilitated by the lack of mesothelium over milky spots [48]. Moreover, omentectomy results in a reduction in the number of macrophages in

the peritoneal cavity [52] and peritoneal macrophages are known to accumulate in milky spots during peritoneal inflammation [26]. Despite this, definitive proof of a precursor-product relationship between omental macrophages and those in the peritoneal cavity is lacking. Studies of this nature have been hampered by the inability to distinguish resident omental macrophages from those potentially transiting to/from the peritoneal cavity, as both express F4/80 and CD11b, albeit at varying levels. However, with the identification of additional peritoneal macrophage markers such as CD102, it has been shown that cells with the phenotypic identity of peritoneal F4/80^{hi} macrophages are present in the omentum [26]. Nevertheless, the nature of these cells remains poorly understood.

Rather than acting as a source of peritoneal macrophages, other work has suggested that the omentum could be the source of factors that drive macrophage differentiation or a vessel for differentiation to occur. For instance, it was demonstrated that omental tissue could support macrophage differentiation from BM precursors, suggesting that omental cells are a rich source of CSF1 [51,53]. More recently, production of the vitamin A metabolite, retinoic acid (RA), by omental stromal cells has been proposed to control a large proportion of the transcriptional profile of F4/80^{hi} peritoneal macrophages through induction of GATA6 [26]. Indeed, mice reared and maintained on a vitamin A deficient (VAD) diet have fewer mature F4/80^{hi} macrophages, although notably, the effects of VAD are only evident after 9 weeks of age [26], suggesting other sources of RA may play a key role in early life or that there is a switch from independence to dependence on RA for macrophage maintenance with age. It must also be noted that maintenance on VAD diet can result in the generation of systemic inflammation, including in the peritoneal cavity [54]. Therefore, it could be that the breakdown in macrophage differentiation in VAD mice could be secondary to wider inflammatory effects [55]. The CSF1R^{+} F4/80$^{-/lo}$ MHCII^{+} macrophage

subset may also play a role in providing active RA, as they express high levels of retinaldehyde dehydrogenase A2 (RALDH2), one of the enzymes that catalyses the synthesis of RA from dietary vitamin A [5,14,56]. However, the significance of this has never been tested experimentally. Whether adipose in the pleural and pericardial cavities also acts to support macrophage differentiation in these sites is unknown.

The commensal microbiota and their products have been shown to influence the differentiation of a number of macrophage populations, including those in the colon, skin, lung and even the central nervous system [44,57-61]. Moreover, recent work has shown that administration of broad-spectrum antibiotics led to a selective loss of mature peritoneal CSF1R^{+} F4/80$^{-/lo}$ MHCII^{+} macrophages, suggesting their maintenance/differentiation is influenced by the presence of the commensal microbiota [14]. However, antibiotic treatment can result in cell stress, such as mitochondrial dysfunction [62], and it remains possible that CSF1R^{+} F4/80$^{-/lo}$ MHCII^{+} macrophages could be more susceptible to antibiotic-mediated stress. Thus, analysis of these cells from germ free mice will be valuable to dissect the role of the microbiota in their differentiation.

As mentioned above, the turnover of F4/80^{hi} peritoneal macrophages is also influenced by the sex of the animal and more of these cells are present in the peritoneal cavities of female mice [63,64]. Although the local factors responsible for creating this sex dimorphism are not yet clear, peritoneal macrophages express estrogen receptors and undergo transcriptional reprogramming and enhanced proliferation in response to exogenous estrogen [65]. Furthermore, oophorectomy (or ovariectomy) leads to a reduction in the number of peritoneal macrophages [63,65], suggesting the presence of the female reproductive tract in the female peritoneal cavity alters the biology of the resident macrophages.

Homeostatic functions of Cavity Macrophages

The presence of such phenotypically and transcriptionally distinct macrophage populations suggests specialised functions for each of these cells. As described above, F4/80^{hi} macrophages express an array of phagocytic receptors (including Tim4, MerTK, CD36)[9,16] and have avid phagocytic ability [4], suggesting that a primary function of these cells is to scavenge apoptotic and senescent cells (Figure 2). These properties may also allow them to regulate surfactant levels in serous cavity fluid similar to the regulation of pulmonary surfactant by alveolar macrophages. Indeed, F4/80^{hi} macrophages express genes that are involved in lipid uptake and metabolism, such as *Cd36*, *Alox15, Fabp4* and *Cav1* [9,11,66]. F4/80^{hi} macrophages also express high levels of CXCL13, the ligand for CXCR5 which is expressed highly by serous cavity B1 cells and is instrumental for their homing to the serous cavities [67]. Serous cavity B1 cells are rich sources of natural antibodies which are important for early protection against a variety of pathogens (see review [68]). However, B1 cells can also class switch to IgA production, a process that is promoted by TGFβ2 from F4/80^{hi} macrophages [26]. Local retinoic acid (RA) can also induce expression of gut homing molecules such as α4β7 and CCR9 on B1 cells, allowing them to migrate to the intestinal lamina propria where they can secrete IgA [69,70]. Thus, in addition to local roles, F4/80^{hi} macrophages may also support intestinal immunity. In addition to these homeostatic functions, F4/80^{hi} macrophages act as sentinels of the innate immune system and respond rapidly to microbial stimulation to recruit other innate immune effector cells (see below).

The homeostatic function of the F4/80$^{-/lo}$ MHCII^{+} MPs is less well understood. Compared with F4/80^{hi} macrophages, they appear less able to phagocytose apoptotic cells [13] but are more able to take up bacteria and produce nitric oxide in response to LPS stimulation *in vivo* [4] (Figure 2). In addition, their high expression of MHCII and

costimulatory molecules, such as CD80 and CD86, suggests a role for antigen presentation. Indeed, all subsets of F4/80$^{-/lo}$ MHCII^{+} MPs can drive T cell activation (IL-2 production) *in vitro*, although the DCs amongst these have a superior capacity [15]. The anatomical locale in which this occurs *in vivo* is unclear and is likely to be subset specific. For instance, although cells with the phenotypic identity of F4/80$^{-/lo}$ MHCII^{+} DC could be found in the LNs draining the peritoneal cavity, mature CSF1R^{+} F4/80$^{-/lo}$ MHCII^{+} MPs do not appear to have migratory capacity under steady state conditions [5], suggesting they may maintain T cells locally rather than participating in initial T cell priming in LNs. As stated above, another feature of steady state CSF1R^{+} F4/80$^{-/lo}$ MHCII^{+} MPs in the peritoneal and pleural cavities is their constitutive production of RELMα, a molecule known to have regulatory effects on T cells, and RALDH2 expression, from which RA could lead to imprinting of regulatory T cells. However, if and how RELMα and RA controls the behaviour of macrophages and/or other serous cavity leukocytes remains to be determined.

Serous Cavity Macrophages Under Non-Homeostatic Conditions

There are a number of pathological conditions that peritoneal macrophages have been implicated in, including, but not limited to, peritonitis, endometriosis, post-operative adhesions, pancreatitis, peritoneal cancer and acute liver injury. Thus, there is great need to understand the roles distinct MP subsets play when homeostasis is perturbed and the local factors that control their behaviour.

Regulation of serous cavity macrophages during disease

Experimental Peritonitis

Many studies have used sterile models of inflammation to assess macrophage population dynamics following perturbation of homeostasis. The commonest models include thioglycollate-, zymosan- and LPS-induced peritonitis. In each of these models there are major changes in the composition of the macrophage compartment, although the magnitude of these changes is highly dependent on the dose of the irritant used [12]. Nevertheless, a common feature of these models is the accumulation of pro-inflammatory F4/80$^{-/lo}$ MPs, which is abolished in *Ccr2*$^{-/-}$ mice, suggesting these arise from Ly6C^{hi} classical monocytes [4,15,16,71-73]. F4/80$^{-/lo}$ monocytes/macrophages elicited by thioglycollate express variable levels of MHCII and have a distinct transcriptional signature from the CSF1R^{+} F4/80$^{-/lo}$ MHCII^{+} macrophages that are present under normal conditions. Notably, cells bearing markers or transcriptional signatures of steady state CSF1R^{+} F4/80$^{-/lo}$ MHCII^{+} macrophages appear to persist throughout peritonitis induced by thioglycollate [16], zymosan [15] and a cell-free bacterial supernatant [15]. Whether these cells represent the same F4/80^{lo} population present prior to the onset of inflammation or newly recruited cells, remains unclear, although adoptive transfer experiments suggest the latter [15]. If so, there may be distinct fates for individual monocytes entering the inflamed cavity and it will be important to understand the factors controlling this process. Another common feature of these models is the loss of the F4/80^{hi} macrophages in the early stages of inflammation – a phenomenon known as the macrophage disappearance reaction (MDR). Again, the degree of loss is dependent on the dose of the irritant used to elicit inflammation [74]. The MDR has received much attention over the last 40 years, but whether there is unifying mechanism that underlies this response across models remains controversial (reviewed by [75]. Interestingly, in the context of liver infection, MDR by pyroptosis or necroptosis has been proposed to facilitate the recruitment of other immune effector cells to the site of infection

[76,77]. Whether this is the case in the serous cavities, especially in the context of sterile inflammation, remains unclear, however, the inability to undergo necroptosis appears to prevent the MDR in response to TLR ligation [78].

Further reorganisation of the macrophage compartment occurs as inflammation resolves. Co-incident with neutrophil clearance, the remaining F4/80^{hi} resident macrophages undergo elevated proliferation via a CSF1-dependent mechanism that, in the short term, re-establishes the bulk of the F4/80^{hi} population [12,74]. As with the MDR, the degree of repopulation that occurs is dependent on the dose and type of inflammatory stimulus [12], but whether this relates to differences in the initial extent of MDR or the delayed resolution of inflammation that arises with higher inflammatory burdens is not clear. Of note, higher numbers of F4/80^{hi} macrophages are found during peritoneal salmonellosis when inflammatory macrophage recruitment is defective [79], suggesting that the presence of inflammatory macrophages may, in some way, regulate F4/80^{hi} macrophage persistence. Other factors may also limit the rate and degree of repopulation, for example deficiency in the mTORC2 complex enhances repopulation by increasing the survival and proliferation of resident macrophages, due in part to negative regulation of GATA6 [80]. Whether retarded repopulation of F4/80^{hi} macrophages could be a contributory factor in the prolonged course of inflammation under certain conditions remains to be determined, but seems likely given the specialised role F4/80^{hi} macrophages play in clearance of apoptotic neutrophils (see below).

The fate of F4/80^{lo} inflammatory macrophages is less clear and is complicated by phenotypic heterogeneity within this compartment. While a minority may migrate to the draining lymph nodes [81], a significant proportion appear to die by apoptosis [16]. Despite this, many manage to persist alongside the endogenous F4/80^{hi} cells for at least several

weeks [12,16,71], and a subset defined by Ly6B expression undergo CSF1-dependent proliferation [74]. In the longer term (2-8wks), at least some cells recruited early during the inflammatory response go on to acquire a long-lived resident F4/80^{hi} MHCII^{lo} phenotype [40,71]. As in other tissues, many un-answered questions surround the fate of recruited and resident macrophages, particularly regarding the identity of factors that control whether a cell dies or persists, and importantly, how these events are co-ordinated and contribute to resolution of inflammation. An as yet unexplored factor is whether the fate of a monocyte is restricted by the point during inflammation at which it is recruited and this requires a more detailed understanding of the kinetics of monocyte recruitment during inflammation. Notably, although the Th2 cytokine IL-4 plays a negligible role in regulation of peritoneal macrophages under steady state conditions [82], administration of immunocomplexes of IL-4 and anti-IL-4, (IL-4 complex; IL-4c) can convert thioglycollated-elicited macrophages into F4/80^{hi}-like macrophages [83]. Consistent with this, IL-4 can enhance GATA-6 expression in peritoneal macrophages *in vitro* [80]. However, the relative contribution of elicited F4/80^{lo} macrophages to re-establishment of the F4/80^{hi} macrophage population during resolution of sterile peritonitis is not clear and a role for endogenous IL-4 in this process has so far not been reported.

Type 2 inflammation

Regulation of serous cavity macrophages differs dramatically under conditions of strong Th2-polarised inflammation, where the MDR does not appear to occur and F4/80^{hi} macrophages accumulate by a process of elevated local proliferation. This first became apparent from studies of pleural exudate cells from mice infected with *Litomosoidies sigmodonitis*, a pleural cavity-dwelling filarial worm [84]. In this setting, proliferation is

largely dependent upon IL-4R signalling by macrophages [82]. Indeed, IL-4c is sufficient to drive proliferation and accumulation of F4/80^{hi} cavity macrophages, as well as other tissue macrophages [82,84] (and SJJ unpublished observations). However, it is now clear that additional signals are required for macrophage proliferation in response to IL-4 that provide a degree of tissue-specificity. These include ligands of myosin 18A, such as SP-A in the lung and the complement component C1q in the peritoneal cavity and liver [85]. Notably, C1q is one of the most significantly up-regulated genes in peritoneal macrophages stimulated with IL-4 [86] and IL-4 also increases surface expression of myosin 18A by these as well as other tissue macrophages [85]. However, in a marked disparity with their peritoneal counterparts, pleural macrophages do not require C1q to proliferate in response to IL-4 [85], and so far, no comparable pleural cavity-specific amplifiers of proliferation have been identified. Hence, discrete mechanisms may control macrophage responsiveness and behaviour at these anatomically similar sites. Another cytokine that can stimulate proliferation of cavity macrophages is the pro-Th2 cytokine IL-33. While IL-33 can stimulate proliferation in the absence of IL-4R, unlike IL-4, it does not promote 'alternative activation' directly and instead amplifies IL-4 and IL-13 signalling to the IL-4R [87]. Notably, whether macrophage proliferation is fundamental to e.g. helminth expulsion remains to be determined.

Function of serous cavity macrophages during disease

Peritonitis

The broad role of macrophages in the orchestration and resolution of the inflammatory events that underpin peritonitis have been studied extensively. However, comparably few studies have attempted to define the individual roles played by discrete mononuclear phagocyte subsets. For instance, although clodronate-depletion studies have been used to

show that peritoneal macrophages play a role in the increased vascular permeability seen in the very first phase of zymosan-induced peritonitis [88], whether this is a role of F4/80^{hi} or F4/80^{lo} macrophages remains unclear. Peritoneal macrophages are also implicated in the recruitment of neutrophils during initiation of acute peritonitis [89] and this is likely to involve the F4/80^{hi} population because neutrophil accumulation during thioglycollate- [72,73], zymosan- [71] and salmonella-induced peritonitis [79] is unaffected in *Ccr2*$^{-/-}$ mice, in whom the F4/80$^{-/lo}$ MHCII^{+} peritoneal macrophage population is essentially absent [5,14,15,26]. Notably, neutrophils can enter the cavity via high endothelial venules (HEV) in the omentum [90] and thus regulation of neutrophil recruitment could be a role for omentum-dwelling macrophages. However, this may by model-dependent, since neutrophil recruitment is normal during zymosan-induced peritonitis in mice with depleted macrophage compartments [11,91]. F4/80^{hi} macrophages that persist during peritonitis may also maintain a regulatory role by, for example, increased production of IL-10 [15]. Indeed, F4/80^{hi} macrophages appear to be the predominant myeloid source of IL-10 during peritonitis and enhanced neutrophil and inflammatory F4/80^{lo} macrophage accumulation is seen in global *Il10*$^{-/-}$ mice [15].

The function of inflammatory F4/80^{lo} macrophages during peritonitis remains relatively poorly understood, although it is clear that they produce high levels of pro-inflammatory cytokines, such as TNFα, IL-1β and IFNγ [79]. Combined with their superior ability to engulf microbial particles [92], inflammatory F4/80^{lo} macrophages appear to be the predominant iNOS expressing cell during peritoneal salmonellosis, suggesting they also play crucial role in bacterial elimination [79]. Notably, although many inflammatory F4/80^{lo} macrophages express MHCII, they are less able to present antigen to and cause activation of T cells [15], and fail to upregulate many of the signature genes of their homeostatic

F4/80^{lo} MHCII^{+} counterparts, including *Cd226, Fcrls* and *Aldh1a2* [15,16]. This may reflect the failure of inflammatory F4/80^{lo} macrophages to upregulate the transcription factor IRF4 [16], which is required for homeostatic differentiation of F4/80^{lo} MHCII^{+} macrophages [14]. Thus, differentiation of classical Ly6C^{hi} monocytes in the inflamed cavity appears to follow a distinct pathway. Interestingly, inflammatory F4/80^{lo} macrophages express high levels of the CSF2R [16], which could implicate CSF2 (GM-CSF) in their differentiation, although this remains to be determined experimentally.

Macrophages are also central players in the resolution of peritoneal inflammation. In particular, they are considered the main scavengers of dying cells during and following an inflammatory insult. In this way, clearance of the large number of neutrophils recruited at the onset of inflammation is considered an essential step in the promotion of the resolution of inflammation, and this is thought to induce an anti-inflammatory programme in inflammatory macrophages, including enhanced production of immunoregulatory cytokines, such as IL-10, TGFβ and RELMα [71,93]. This may support the expansion of regulatory T cells that is reported to occur during peritonitis resolution [71]. Uptake of apoptotic cells (efferocytosis) also blunts production of pro-inflammatory cytokines, and at least in the case of TNFα, is dependent on CD73, the enzyme that catalyses conversion of AMP to adenosine and is a signature marker of F4/80^{hi} macrophages [94]. Efferocytosis can occur via a variety of receptors but most of these require specific ligands on the surface of target cells, such as phosphatidyl-serine, to be bound by secreted 'opsonins', such as milk fat globule-EGF factor 8 (Mfge8) protein [95]. However, in the peritoneal cavity, F4/80^{hi} resident macrophages express exceptionally high levels of Tim4 , a receptor that directly recognises phosphatidyl-serine on the surface of apoptotic cells [96,97]. Notably, although depleted in terms of cell number, F4/80^{hi} macrophages appear to be the most efficient at uptake of

apoptotic cells [16]. Moreover, their capacity to sequester free Mfge8 by expressing modified lipids on their cell surface, limits efferocytosis by Tim4$^{-/lo}$ inflammatory macrophages [98], which express high levels of Mfge8 [16]. Hence, it seems a strategy has evolved that allows efficient and preferential apoptotic cell removal by resident F4/80^{hi} macrophages. While the purpose of this mechanism is unclear, deficiency in the enzyme 12/15-lipoxygenase (encoded by *Alox15*), which is required by F4/80^{hi} to modify lipids, results in the development of lupus-like disease, and this has been attributed to uptake of apoptotic cells by recruited monocyte-derived 'inflammatory' macrophages [98]. That Tim4 deficient mice develop antibodies to dsDNA following immunisation, would seemingly support this hypothesis [97]. Indeed, induction of Tim4 expression by peritoneal F4/80^{hi} seems to accompany increased expression of negative regulators of TLR signalling, and loss of expression of TLR9, the cytosolic TLR that recognises DNA [47]. Thus, mechanisms exist to allow safe removal of apoptotic cells in the peritoneal cavity.

Other mechanisms to ensure successful removal of apoptotic/necrotic cells from the peritoneum have been uncovered recently. For instance, production of CD5L (also known as apoptosis inhibitor of macrophage; AIM) by macrophages may also facilitate removal of necrotic cell material, as the resolution of zymosan-induced peritonitis is delayed in CD5L deficient mice [99]. However, the source of CD5L is unclear because both homeostatic F4/80^{hi} macrophages and inflammatory F4/80^{lo} cells express high levels of *Cd5l* [9,16]. Furthermore, macrophages present during the resolution phase of zymosan-induced peritonitis produce high levels of CCL5 [71] which may act to recruit other pro-restorative leukocytes, but also enhance efferocytosis by binding to the atypical chemokine receptor ACKR2 (also known as D6) on neutrophils [100].

Type 2 Inflammation

Th2-dominated inflammation, such as that associated with helminth infection, is characterised by high levels of IL-5, IL-10, IL-13, and in particular IL-4. In addition to inducing *in situ* proliferation of macrophages, IL-4R signalling is known to cause 'alternative activation' of macrophages, which is characterised by production of arginase, RELMα, Ym-1 and TGFβ [101]. Alternatively activated macrophages are important for the wound healing following helminth invasion, which may involve promoting eosinophil recruitment [102]. Moreover, alternatively activated macrophages produce growth factors such as insulin-like growth factor (IGF)-1 and platelet-derived growth factor (PDGF), which promote collagen deposition, fibroblast proliferation and myofibroblast differentiation to facilitate effective tissue repair following injury/insult [103]. However, while eosinophils have a well-defined roll in helminth expulsion in the serous cavities [104], the relative roles for these macrophage-derived products in this process remains to be determined with certainty. Importantly, it has recently been shown *in vivo* that helminth-expanded F4/80^{hi} macrophages can switch to bactericidal, iNOS-expressing macrophages during a subsequent salmonella challenge [79], demonstrating that functional plasticity exists in resident serous cavity macrophages in an infectious setting.

Role of serous cavity macrophages in non-cavity conditions

While much of the work examining the properties of peritoneal mononuclear phagocytes during disease has utilised models of sterile inflammation of the cavity directly, recent data suggest that these cells could have wider roles in regulating inflammation in neighbouring tissues. For instance, infection with the intestinal parasite *Heligmosomoides polygyrus* leads to elevated proliferation and alternative activation of peritoneal F4/80^{hi} macrophages

[79,82], while *Alternaria alternata*-induced airway inflammation generates the same response by resident F4/80^{hi} pleural macrophages [87]. The significance of bolstering the macrophage compartment of the serous cavity in response to inflammation in neighbouring tissues remains unclear, although this may rely on IL-33 to promote tissue repair functions by these cells. Indeed, as discussed above, IL-33 can induce proliferation and alternative activation of cavity macrophages [87], and adoptive transfer of IL-33-treated peritoneal macrophages appears to protect mice from 2,4,6-trinitrobenzene sulfonic acid (TNBS)–induced colitis [105] and promote expulsion of the intestinal parasite *Heligmosomoides bakeri* [106]. Whether serous cavity macrophages enter these neighbouring tissues to promote repair remains unclear, although they have been shown to migrate to the liver in a CD44-dependent manner following thermal injury of the liver capsule [107]. Here they undergo alternative activation, characterised by high levels of arginase and CD206 expression, to promote tissue repair [107]. While this represents a novel reparative function of these cells, it will be important to determine if peritoneal F4/80^{hi} macrophages play a similar role in e.g. acetaminophen-induced liver injury, which represents a more clinically relevant model of liver injury.

While macrophages can perform beneficial, pro-restorative roles, they are also implicated in many chronic inflammatory pathologies and cancer. One such pathology of the peritoneal cavity is endometriosis, a condition characterised by ectopic endometrial tissue on the peritoneum that affects 10% of women of reproductive age [108]. In addition to increases in their numbers, peritoneal macrophages obtained from women with endometriosis have heightened basal production of pro-inflammatory cytokines, including TNFα, IL-1β and IL-8, and exaggerated responses to stimulation with TLR ligands, such as LPS [109,110]. Endometrial lesions are rich in immune cells and, in particular, macrophages.

High levels of monocyte/macrophage chemoattractants CCL2, CCL3 and CCL5 present in lesions attracts macrophages [111,112], although it remains to be shown definitively that mature peritoneal macrophages, or particular subsets, enter endometrial lesions. Similarly, peritoneal macrophage function is altered in acute pancreatitis [113], where they show enhanced levels of pro-inflammatory cytokine production, but the subset responsible for this and if these migrate to the pancreas remains unclear.

Macrophages are also implicated in the formation of peritoneal adhesions, a common issue following abdominal surgery. However, their exact role remains unclear because although depletion of macrophages using the Macrophage Fas-Induced Apoptosis (MAFIA)-mouse [114] was shown to elicit peritoneal adhesions [115], depletion with clodronate liposomes led to reduced adhesion formation in post-operative adhesion model, which was attributed to a reduction in macrophage-derived epidermal growth factor (EGF) [116]. Thus, more work is needed to elucidate the role of peritoneal macrophages, and their subsets, in this condition.

The peritoneum is also a common site for metastases of epithelial cancers, such as ovarian, colon and gastric carcinomas [1]. Moreover, malignant mesothelioma is a highly aggressive cancer resulting from neoplastic transformation of mesothelial cells in the body cavities, although around 95% of cases affect the pleurae. That clodronate-mediated depletion of macrophages reduced tumour burden and metastasis in a model of peritoneal mesothelioma [117] and ovarian cancer [118], suggests serous cavity macrophages promote tumorigenesis. Notably, phenotypic and functional alterations have been reported in mononuclear phagocytes from patients with ovarian carcinoma [119], and pleural effusion from malignant mesothelioma patients induces differentiation of macrophages with enhanced suppressive capacity *in vitro* [120]. However, again, how cavity macrophages

contribute to tumour establishment and growth requires further study and like in different cancers, cavity macrophages are likely to play dichotomous roles depending on the stage of the disease [121].

Conclusions and future perspectives

The last decade has seen unprecedented advances in our understanding of mononuclear phagocyte heterogeneity, origin and function. Thus, while once simply considered a convenient source of macrophages, the serous cavities are now considered to have a highly diverse mononuclear phagocyte system. Nevertheless, how distinct populations of macrophages contribute to disease pathogenesis and/or tissue repair, and the factors that control their function in different contexts remain poorly characterised. Therefore, the focus now must be to understand these processes in clinically-relevant models of disease affecting the serous cavities and the organs they cover.

Figure Legends

Figure 1: Heterogeneity, ontogeny and growth factor dependence of peritoneal mononuclear phagocytes. Resident macrophages in the healthy serous cavities are characterised by their high expression of F4/80, CD11b and CD102, as well as low levels of MHCII. They also express high levels of CD93, CD73, CD49F and many express the phagocytic receptor Tim4. These F4/80^{hi} macrophages dominate the cavity under normal physiological conditions and rely on number of transcription factors for their full differentiation, including GATA6, C/EBPβ, KLF2 and KLF4 [11,13,17,26,47]. Although F4/80^{hi} macrophages initially arise from embryo-derived precursors, these are progressively displaced by bone marrow-derived macrophages in a process that is highly influenced by age, and in the peritoneal cavity, the sex of the animal [5]. F4/80^{hi} macrophages exist alongside a much smaller population of 'F4/80^{lo}' macrophages that express high levels of CSF1R, MHCII, CD226 and the immunoregulatory cytokine RELMα. F4/80^{lo}MHCII^{+} macrophages are short-lived and are continually replaced by Ly6C^{hi} classical monocytes, which enter the cavity in a CCR2-dependent manner and mature locally under the control of CSF1. The microbiota or its derivatives may also influence this differentiation process, along with other, as yet unidentified, environmental factors. These are distinct from conventional dendritic cells that are replenished by CCR2-independent precursors, rely on Flt3L for their development and can be divided into cDC1 and cDC2 subsets on the basis of CD103/XCR1 and CD11b expression, respectively [5,6,15]. F4/80^{lo}MHCII^{+} macrophages may also act, in part, as precursors of F4/80^{hi} macrophages [5]. Peritoneal macrophages are known to be able to migrate to the omentum and the differentiation of F4/80^{hi} macrophages relies on the vitamin A metabolite, retinoic acid, which is thought to be provided by cells in the omentum

[26]. However, whether differentiation of F4/80^{hi} macrophages occurs locally in the peritoneal cavity or if cells are 'educated' in the omentum remains unclear.

Figure 2: Homeostatic functions of peritoneal macrophage subsets. Resident F4/80^{hi} macrophages express an array of phagocytic receptors, such as Tim4, MerTK and CD36 that allows them to take up and eliminate apoptotic cells. Notably, apoptotic cells accumulate when this process is defective [97]. They may also control the composition of the serous cavity fluid by regulating the levels of surfactant in serous cavity fluid. F4/80^{hi} also play a crucial role in immune surveillance and their high phagocytic activity means that they can capture and destroy any pathogenic intruders. Through their production of the chemokine CXCL13, they also regulate the recruitment and maintenance of B1 B cells, which are key producers of natural IgM [122]. The functions of F4/80^{lo} MHCII^{+} macrophages are less well understood, although their high levels of MHCII and costimulatory molecules indicates a role in antigen presentation. These cells do not actively migrate to lymph nodes during homeostatic conditions, suggesting that they may be involved in local antigen presentation and maintenance of the serous cavity T cell pool. A defining feature of F4/80^{lo} MHCII^{+} macrophages under homeostatic conditions is the constitutive production of RELMα. Furthermore, they also express high levels of RALDH2, suggesting they may be a rich source of retinoic acid. The role of macrophage-derived RELMα and RA in serous cavity homeostasis remain unclear.

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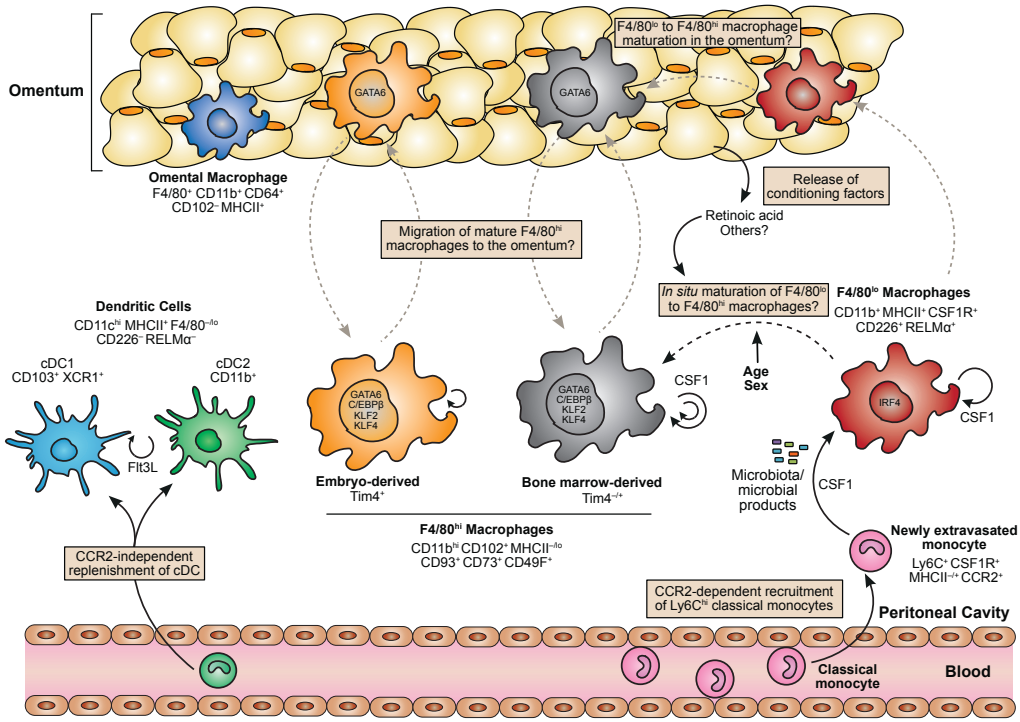

Figure 1: Heterogeneity, ontogeny and growth factor dependence of peritoneal mononuclear phagocytes

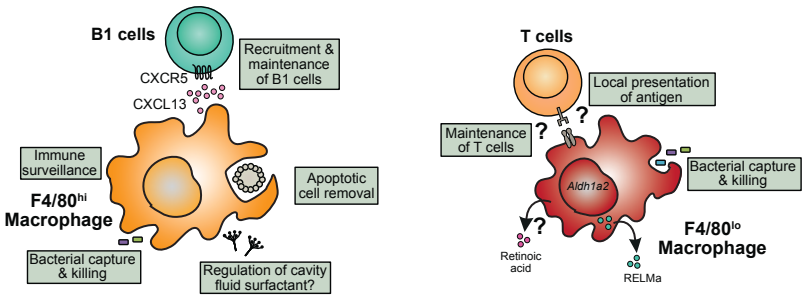

Figure 2: Homeostatic functions of peritoneal macrophage subsets