



HHS Public Access

Author manuscript

Trends Immunol. Author manuscript; available in PMC 2018 July 01.

Published in final edited form as:

Trends Immunol. 2017 July ; 38(7): 526–536. doi:10.1016/j.it.2017.03.002.

Immunological functions of the omentum

Selene Meza-Perez and Troy D. Randall*

Department of Medicine, Division of Clinical Immunology and Rheumatology, University of Alabama at Birmingham, Birmingham, AL 35294

Abstract

The omentum is a visceral adipose tissue with unique immune functions. Although it is primarily an adipose tissue, the omentum also contains lymphoid aggregates, called milky spots (MS), that contribute to peritoneal immunity by collecting antigens, particulates and pathogens from the peritoneal cavity and, depending on the stimuli, promoting a variety of immune responses, including inflammation, tolerance or even fibrosis. Reciprocal interactions between cells in the MS and adipocytes regulate their immune and metabolic functions. Importantly, the omentum collects metastasizing tumor cells and supports tumor growth by immunological and metabolic mechanisms. Here we summarize our current knowledge about the development, organization and function of the omentum in peritoneal immunity.

Development of the Omentum and Milky Spots

The omentum is a visceral adipose tissue (VAT) derived from mesothelial cells [1], connected to the spleen, stomach, pancreas and colon [2, 3]. Although well known as a visceral fat depot, the role of the omentum in peritoneal immunity wasn't recognized until the early 1900's, when a British surgeon referred to it as "the policeman of the abdomen" due to its ability to attenuate peritonitis and promote surgical wound healing [4]. In fact, the omentum was noted to move about the peritoneal cavity and occlude sites of inflammation, such as ruptured ovaries, inflamed appendices, ulcerated intestines or wounds due to trauma or surgery [4]. Consistent with this observation, the omentum has remarkable angiogenic [5], fibrotic [6], stem cell [7, 8] and immune [9] activities, which together promote vascularization, accelerate wound healing and limit infection. However, these same activities are also likely involved in pathological responses, such as the growth rapid growth of omental tumor metastases [10].

In mice, the omentum is a relatively small strip of fat found anterior and slightly ventral to the stomach [11]. However, in humans the omentum is dramatically larger — reaching an area of 1500 cm² and resembling an apron that hangs in front of the abdominal organs [12].

*Correspondence to randallt@uab.edu (T.D. Randall), Department of Medicine, Division of Clinical Immunology and Rheumatology, University of Alabama at Birmingham, 1720 2nd AVE S, SHEL 507, Birmingham, AL 35294, Phone 205-975-3323, Fax 205-975-3322.

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The omentum in mice is a relatively small fat depot compared to those around the gonads and mesentery, whereas in humans, it is a major depot of abdominal fat. Nevertheless, the omenta of both mice and humans contain Milky Spots (MS), which are aggregates of leukocytes that in many ways resemble the follicles of secondary lymphoid tissues. In this review, we will concentrate on the immune functions of the omentum and the MS and how the activities of these tissues regulate peritoneal immunity.

The MS of the omentum were first described in 1874 in rabbits by the French anatomist, Ranvier, who gave them their name because of their whitish appearance amidst the yellow fat [13]. The MS are organized aggregates of leukocytes embedded between adipocytes just beneath the mesothelial cell layer that covers the omentum (Figure 1). Similar aggregates, known as fat-associated lymphoid clusters (FALCs), are found in other fat depots, including the pericardial and mediastinal fat in the pleural cavity [14–16] as well as the mesenteric fat in the peritoneal cavity [14, 17]. Although the leukocyte clusters in the omentum and the splenoportal adipose tissue are the only ones known as MS [18, 19], the MS and FALCs are structurally similar, contain similar populations of leukocytes and likely perform similar immune functions. Interestingly, the frequency of MS and FALCs are different depending on the tissue, with the omentum containing the highest frequency of clusters per gram of tissue, followed by the pericardial, mediastinal and mesenteric adipose tissues [14]. Perigonadal fat and subcutaneous fat have few, if any, leukocyte clusters that resemble MS or FALCs.

The MS in the omentum form during fetal development in both humans [20] and mice [14]. Although the development of most secondary lymphoid organs requires lymphotoxin and a subset of innate lymphoid cells (ILCs), known as lymphoid tissue-inducer (LTi) cells, for their development [21], the MS and FALCs do not require these interactions [9, 14]. In fact, MS develop independently of the transcription factors, ROR γ t and Id2 [9], which are essential for the differentiation of LTi cells and all ILCs, respectively [22]. Interestingly, mesenteric FALCs develop in normal numbers in *Rag2*^{-/-} mice and *Rorc*^{-/-} mice, but fail to develop in *Rag2*^{-/-}*Il2rg*^{-/-} mice [14], demonstrating that some type of innate or adaptive lymphocyte is important for their development. Thus, it is possible that ILC2 cells, which are relatively abundant in adipose tissues [23, 24], functionally replace LTi cells during the development of MS and FALCs.

Exposure to microbiota or microbial products enhances the postnatal maturation of MS and increases the number of observable FALCs in the mesenteric adipose tissue [14]. Conversely, the number of FALCs in the mesenteric fat is reduced by about half in germ-free mice. Moreover, the peritoneal administration of zymosan, a TLR-2-stimulating glucan, promotes the formation of additional FALCs in a process that is dependent on both TNF and CD1d-restricted NKT cells [14]. However, it is not clear whether this increase results from an expansion of previously existing, but very small clusters, or the *de novo* development of entirely new clusters. Regardless, these data demonstrate that both the primary development and post-natal enhancement of MS and FALCs uses mechanisms distinct from those used by conventional lymphoid organs and suggest that MS and FALCs should be categorized somewhere between true secondary lymphoid organs and tertiary lymphoid tissues.

Structure of Omental Milky Spots

The leukocyte clusters in MS are distinctly different from conventional secondary lymphoid tissues. For example, although the leukocytes in MS are supported by a reticular network of fibroblastic stromal cells that can be observed using the ERTR-7 antibody [9], they lack identifiable follicular dendritic cells (FDCs)[9, 25]. The B cell attracting chemokine, CXCL13, which is associated with FDC networks in conventional lymphoid organs [26], is also strongly expressed in the MS [27]. However, CXCL13 expression in the MS is observed outside the B cell clusters in an area with abundant FDCM1⁺CD11b⁺ cells [9, 27]. Given that macrophages are a potent source of CXCL13 in the peritoneal cavity and omentum [27], it is likely that these CD11b⁺CXCL13⁺ cells are macrophages. T cells in MS seem to be clustered around blood vessels [9], perhaps HEVs. However, T cells are also found in the B cell area, consistent with the placement of T follicular helper (Tfh) cells, although bona fide Tfh cells have not yet been identified in MS or FALCs. Despite the presence of both CD4⁺ and CD8⁺ T cells [25], it is difficult to discern a well-defined T cell zone. Moreover, it is not clear whether cells with markers of fibroblastic reticular cells (FRCs) are present in MS or whether they are restricted to a particular region. Thus, although MS do have a compartmentalized structure, it is strikingly different than that seen in conventional lymphoid organs.

The omentum as a whole is highly vascularized and the MS in particular are formed around a glomerulus-like knot of blood vessels [25, 28](Figure 1). Some of these vessels express markers of high endothelial venules (HEVs)[9, 25], including peripheral lymph node addressin (PNAd) and mucosal addressin cell adhesion molecule 1 (MAdCAM-1). MAdCAM is typically expressed by HEVs in mucosal lymphoid tissues, such as Peyer's patches and mesenteric lymph nodes [29], but not peripheral lymph nodes, and helps to recruit mucosal-homing lymphocytes from the blood [9, 30]. Not surprisingly, the mucosal-associated integrin, $\alpha 4\beta 7$, which is the ligand for MAdCAM, is involved in migration from the blood to the omentum [30, 31].

The lymphatic architecture of the omentum and MS is also distinct from that in conventional secondary lymphoid organs. For example, lymph nodes collect antigens via afferent lymphatic vessels that deliver cells and antigens to the subcapsular sinus, whereas Peyer's patches and other mucosal lymphoid tissues acquire antigens from mucosal surfaces via specialized M cells in the mucosal epithelium. In contrast, MS lack afferent lymphatics and collect cells and antigens from the peritoneal cavity through fenestrations in the mesothelial layer [9, 28, 31](Figure 1). Efferent lymphatic vessels, on the otherhand, originate around the MS or as a network of endothelial channels between adipocytes [3, 25, 28] and drain towards downstream lymph nodes. In humans, the lymphatic drainage of the omentum empties toward the subpyloric or splenic lymph nodes [32], whereas in mice, the lymphatic drainage empties to the mediastinal or perithymic lymph nodes.

Fluid is continuously drained from the peritoneal cavity, in large part, through the lymphatics of the omentum, carrying with it any free-floating cells, particulates or antigens. As a result, the MS function as filters for the peritoneal fluid, making them ideally situated to generate immune responses to any antigens or pathogens in the peritoneal cavity. Fluid

flow through the omentum can be increased, for example by peritoneal dialysis, which leads to a dramatic enlargement of the MS and ultimately promotes omental fibrosis [33, 34]. Conversely, tumor cells entrapped by MS form omental metastases that eventually plug the lymphatic drainage and allow the accumulation of ascites fluid in the peritoneal cavity [35].

Cellular Composition of the Omentum and MS

The leukocyte populations in MS and other FALCs are also quite distinct from those in conventional lymphoid tissues [11, 27]. B cells make up the majority of lymphocytes in MS [9]. However, IgM^{hi}IgD^{lo} B1 cells outnumber IgM^{lo}IgD^{hi} follicular B2 cells in MS, whereas the opposite is true in conventional lymphoid organs [11, 20, 27, 36]. B1 cells are generated by fetal-derived hematopoietic progenitors, some of which contribute to local B1 lymphopoiesis in the omenta of both mice and humans [37, 38]. In adults, self-renewing B1 B cells are maintained in the omentum and peritoneal cavity [27, 37], a process that is dependent on the chemokine CXCL13 [9, 27]. Interestingly, parabiosis studies show that the majority of B1 cells are permanent residents of the omentum and peritoneal cavity [27], whereas the B2 cells in the omentum recirculate between the omentum and other lymphoid tissues.

The omentum also harbors recirculating CD4⁺ and CD8⁺ T cells, although at lower frequencies than in conventional lymphoid organs [25]. In contrast, the MS and other FALCs contain higher frequencies of CD1d-restricted NKT cells than conventional lymphoid organs [11]. These NKT cells are depleted (as a fraction of T cells or of total CD45⁺ cells) from the omenta of obese humans and those with cancer [39], a finding consistent with observations in obese mice [40]. Interestingly, fat-associated NKT cells are enriched for cells that produce IL-10 [41], suggesting an anti-inflammatory function for these cells. Consistent with this idea, most studies suggest that mice lacking NKT cells gain more weight on a high fat diet, have more inflammatory macrophages in adipose tissue and become insulin resistant [40, 42]. Although these metabolic studies did not test the role of NKT cells specifically in the omentum, the prevalence of these cells in this tissue undoubtedly influences a variety of local immune reactions, such as the expansion of FALCs in response to inflammatory stimuli [14].

The omentum also supports a unique population of VAT-associated CD4⁺ regulatory T cells (Tregs)[43], that express the chemokine receptors, CCR1 and CCR2, produce high levels of IL-10, and express proteins like CD36, which is involved in fatty acid metabolism [43, 44]. The phenotype of VAT-associated Tregs is conferred by the transcription factors, PPAR γ , BATF and IRF4 as well as by IL-33 signaling through ST2 [43, 45]. Although VAT-associated Tregs are mostly studied in large fat depots like epididymal fat, which lack MS, they are also found in the omentum [43], where they likely regulate local immune responses. Interestingly, obesity is associated with the loss of VAT-associated Tregs in epididymal fat and a corresponding increase in inflammatory cells and cytokines [43, 44]. Infact, the depletion of VAT-associated Tregs by blockade of the IL-33 receptor, ST2, increases adipose tissue insulin sensitivity [46], suggesting a direct role of Tregs in regulating metabolism. Moreover, in obese mice, the VAT-associated Tregs lose the gene expression signature typical of lean individuals and are less capable of suppressing inflammation [43]. Although

these data were obtained in fat depots like the epididymal fat, which does not contain MS, VAT-associated Tregs are found in the omentum and are likely important regulators of metabolism and inflammation in this tissue as well.

Innate lymphoid cells (ILCs), particularly ILC2 cells, are also found in adipose tissues, including the omentum [15, 24]. Like VAT-associated Tregs, ILC2 cells express ST2 and respond to local IL-33 [15]. Interestingly, the IL-33-induced expression of IL-5 by ILC2 cells in the FALCs of the pericardium promotes the differentiation of local B1 B cells into IgM-secreting cells [15]. Given that ILC2 cells are also present in the omentum, a similar process likely occurs in this location [47]. ILC2 cells also help regulate metabolic functions. For example, decreases in ILC2 cells in adipose tissue are associated with obesity in both humans and mice [24]. Similar to its role in VAT-associated Tregs, IL-33 is important for the maintenance of ILC2 cells in adipose tissue and in limiting adiposity in mice by increasing caloric expenditure [24]. IL-25 is also implicated in the homeostasis and activation of ILC2 cells in adipose tissue [48]. The administration of IL-25 to obese mice increases ILC2 cells in VAT and also promotes weight loss and improves glucose tolerance, as does the adoptive transfer of ILC2 cells. Conversely, the depletion of ILC2 cells in obese *Rag1*^{-/-} mice promotes weight gain and glucose intolerance [48]. Although the metabolism-regulating activities of ILC2 cells are not limited to the omentum, the omentum is the major depot of abdominal fat in humans and is particularly associated with metabolic disease [49].

Numerous macrophages are found in the omentum under steady-state conditions, although dendritic cells (DCs) are also present in MS [11, 27]. In particular, the omentum and peritoneal cavity hosts a distinctive subset of resident macrophages that is dependent on the transcription factor GATA6 [50]. Interestingly, the GATA6⁺ macrophages express high levels of retinaldehyde dehydrogenase-2 (RALDH2) [50, 51], an enzyme that generates retinoic acid (RA), which is a key factor in isotype-switching to IgA [52, 53]. The omentum also maintains macrophage precursors [54], and supports macrophage proliferation [55] via the production of macrophage colony-stimulating factor (M-CSF) by MS stromal cells [56]. Like B1 cells, macrophages are non-circulating residents of the omentum and peritoneal cavity [27]. A subset of peritoneal macrophages is also derived from CCR2-expressing monocyte precursors [57]. The differentiation of these monocyte-derived macrophages is dependent on the transcription factor, IRF4, and requires commensal microbiota [57], again suggesting a connection between the gut and the peritoneal cavity and omentum.

Given the unique populations of Tregs, ILC2 cells, NKT cells and macrophages in the omentum and MS, it is easy to imagine that these cells influence local immune responses, perhaps by dampening inflammatory responses. Other cells, such as B1 cells, seem poised to respond to bacterial antigens and to promote mucosal immunity in the gut. B1 cells also make IL-10 [58] and may contribute to the anti-inflammatory and perhaps tolerogenic environment of the omentum. Consistent with these ideas, the transfer of omental leukocytes from healthy mice to mice with DSS-induced colitis reduces inflammation, promotes healing of the damaged colon, restores body weight and reduces colitis-associated mortality [59].

Immune Responses in the Omentum

Consistent with its ability to collect antigens and cells from the peritoneal cavity, the MS of the omentum support both innate and adaptive immune responses to peritoneal antigens. For example, inflammation in the peritoneal cavity promotes the rapid migration of macrophages to the omentum — a process originally known as the macrophage disappearance reaction [60]. This process can be driven by sterile irritants, including LPS [61], zymosan [14] or thioglycollate [50], as well as inert particles, such as polydextran or silicone beads, which are carried to the omentum by macrophages. All of these stimuli promote the expansion of MS and the production of factors like vascular endothelial growth factor (VEGF) and chemokines like CXCL12 [62–64].

Similar events occur following peritoneal exposure to bacteria. For example, peritoneal administration of attenuated *Streptococcus pyogenes* triggers the activation of macrophages that engulf the bacteria, home to the omentum and increase both the cellularity and quantity of MS [65]. Importantly, increases in the cellularity of MS are not only driven by the influx of peritoneal cells, but are also due to the recruitment of cells from the blood. In fact, large numbers of circulating neutrophils migrate into the omentum during acute inflammation and sepsis [36]. This process occurs by trafficking across HEVs in the MS and requires PNAd as well as E-selectin, L-selectin and Mac-1 [66].

The inflammation-driven influx of cells from the peritoneal cavity also promotes adaptive immune responses. For example, infection or inflammation-driven production of IL-33 triggers the production of IL-5 by ILC2 cells, which in turn promotes the differentiation of local B1 cells in the FALCs and MS [15]. Peritoneal administration of LPS also promotes the migration of peritoneal B1 cells to the MS [50, 51, 61], where they differentiate into IgM-secreting and IgA-secreting cells, some of which colonize the intestine [67, 68], possibly by CXCR4-dependent mechanisms [69]. The omentum also supports the formation and local maintenance of IgM⁺ memory B cells and CD11c⁺ IgM plasmablasts in response to peritoneal infection [47]. Importantly, LPS-mediated peritoneal inflammation triggers the rapid accumulation of GATA6⁺ macrophages in the omentum, which produce RA [50, 51], a key factor in isotype switching to IgA [52, 53]. RA also imprints responding B and T cells with gut-homing receptors, such as $\alpha 4\beta 7$ and CCR9 [70, 71]. Surprisingly however, GATA6-dependent macrophages do not imprint $\alpha 4\beta 7$ and CCR9 expression on B cells responding to antigens in the peritoneal cavity and omentum [50].

Despite an obvious focus on B1 responses in the omentum, MS also support B cell germinal center responses to classic T-dependent antigens, such as haptenated OVA, when administered in the peritoneal cavity [9]. However, B cells responding to T-dependent antigens in MS are poorly selected for high-affinity variants [9], consistent with the lack of FDCs in MS. Nevertheless, T-dependent B cell responses in MS lead to high titers of antigen-specific serum IgG [9]. Importantly, these can occur in mice lacking conventional secondary lymphoid organs (Spleen, Lymph node and Peyer's patch-deficient — SLP mice) [47]. Thus, although some might argue that the primary purpose of the MS is to support the rapid differentiation of B1 cells into IgM and IgA-secreting cells, conventional, T-dependent B cell responses also occur in these sites.

The MS also support primary responses of conventional T cells. For instance, the initial activation and first divisions of OVA-specific CD4⁺ and CD8⁺ T cells occur in the omentum of SLP mice following peritoneal immunization with OVA [9]. Similarly, H-Y-specific CD8⁺ T cells are initially activated and proliferate in the omentum before appearing in the peritoneal cavity [31]. Moreover, CD11c⁺MHCII^{hi} DCs from the omentum are potent antigen-presenting cells with the ability to cross-present soluble antigens [31]. About 70% of these DCs highly express CD11b, whereas about 30% express CD103 — a ratio consistent with the composition of migratory DCs in a variety of non-lymphoid organs. Importantly, T cells primed in vitro by DCs from the omentum consistently express $\alpha 4\beta 7$, whereas T cells primed by splenic DCs do not [31], suggesting that omental DCs have mechanisms, such as RALDH2 expression, for promoting the differentiation of mucosal homing T cells. Although these DCs are distinct from GATA6⁺ macrophages, which also express RALDH2 [50], both cell types may promote the differentiation of mucosal homing T cells or inducible Tregs through the production of RA [70, 72, 73].

In addition to priming naïve T cells, the omentum also collects recirculating memory T cells that are generated at distal sites. For example, mice orally infected with *Heligmosomoides polygyrus*, a helminth restricted to the gastrointestinal tract [74], accumulate helminth-specific Th2 cells in the peritoneal cavity and omentum [9]. Similarly, mice nasally infected with influenza virus accumulate influenza-specific memory CD4⁺ and CD8⁺ T cells in the peritoneal cavity and omentum [9]. Both of these responses are mucosal, suggesting that mucosal-homing cells may preferentially home to the omentum. However, a direct comparison with antigen-specific T cells generated at systemic sites has not been performed.

The omentum and MS clearly have the cell types and immune mechanisms to promote anti-inflammatory or tolerogenic responses under steady-state conditions, perhaps as a way to maintain adipocyte homeostasis. The activities of the omentum and MS are also strongly linked to mucosal immunity and IgA production in the gut and may use these same mechanisms and cell types to suppress inflammatory responses to gut antigens and maintain intestinal homeostasis. However, there is no evidence that gut antigens or intestinal DCs are directly sampled by the MS unless the intestine is completely breached — a highly inflammatory and non-homeostatic event! If this is the case, then how do cells in the MS respond to antigens from the gut during homeostasis? (see Outstanding Questions)

Peritoneal Tumor Metastasis in the Omentum

Primary tumors of the omentum are uncommon. However, the omentum is the most common site of peritoneal metastasis for some tumors, including gastrointestinal and ovarian carcinoma [28, 75, 76]. In particular, ovarian cancer disseminates early and robustly to the omentum, where it is associated with poor prognosis and aggressive growth [10, 77, 78]. Despite the fact that immune responses can be initiated in the MS of the omentum, a protective immune response against tumors seems to not occur and metastatic tumor cells grow progressively [78].

Consistent with studies of inert antigens in the peritoneal cavity, live tumor cells injected into the peritoneal cavity are trapped in the MS [9, 28] — a finding that is consistent for

multiple tumor cell lines, including B16 melanoma, ID8 ovarian carcinoma, EG7 lymphoma, MC38 colon carcinoma, gastric carcinoma and EMT6 lung carcinoma [28, 79]. In each of these cases, tumor cells initially colonize the MS before being observed in non-MS areas of the omentum. In some cases, this phenomenon is attributed to the selective recruitment of CCR4-expressing tumor cells to CCL22-expressing macrophages in the MS [80]. However, the accumulation of tumor cells in the MS is not necessarily dependent on chemotaxis, as pertussis toxin-treated EL4 cells administered to the peritoneal cavity accumulate in the MS just as rapidly as untreated cells [9]. Thus, although chemokine-dependent migration of tumor cells to the omentum and MS undoubtedly occurs for some tumor cells, they can also accumulate passively due to fluid flow from the peritoneal cavity through the MS and omentum.

Although the omentum efficiently collects tumor cells from the peritoneal cavity, ovarian tumor cells circulating in the blood also preferentially metastasize to the omentum. In fact, a recent study shows that parabiotic joining of a tumor-bearing mouse with a non-tumor-bearing mouse leads to ovarian tumor metastasis to the partner omentum [81]. Given that parabiotic mice have a joint circulation, but independent lymphatic systems, this study shows a metastatic preference for the omentum, even when tumor cells are freely circulating throughout the body [81]. In part, this preference can be attributed to ErbB2, also known as HER2/neu, a member of the epidermal growth factor receptor family [81], which is expressed by tumor cells, and its ligand, neuregulin 1 (NRG1), which is expressed by unknown cell types surrounding the omental vasculature. A similar phenomenon may occur in humans, in which an increase in ErbB2 expression in ovarian carcinoma cells correlates with advanced staging of the tumors [81]. Ovarian cancer cells also stimulate omental fibroblast proliferation via transforming growth factor (TGF)- β 1, which facilitates tumor cell implantation and subsequent dissemination [82]. Tumor cell implantation in the MS also promotes local angiogenesis due to the production of VEGF-C [79] and VEGF-A [28] by mesothelial cells. An additional explanation for the preferential tumor growth in omentum in ovarian cancer is attributed to the adipocytes themselves. Adipocytes express fatty-acid binding proteins (FABP)[83], including FABP4, which promotes lipid transfer from adipocytes to tumor cells and facilitates β -oxidation metabolism in tumor cells, thereby enhancing their proliferation and invasiveness [84]. Thus, the omentum is an ideal environment for tumor cell metastasis and subsequent growth.

How does the immune activity of leukocytes in the MS impact tumor growth? The initial colonization of tumor cells triggers an increase in MS size and number, mainly by macrophage recruitment from the peritoneal cavity [65]. Despite this apparent activation, the tumor cells continue to grow [76, 78], suggesting a lack of immune recognition or perhaps a potent immune-suppressive effect. Nevertheless, there are indications that ovarian cancer can be recognized by the immune system [85]. For example, the presence of tumor infiltrating lymphocytes (TILs), particularly CD8⁺ T cells, in both primary tumors (ovary) and metastatic tumors (omentum), positively correlates with overall survival [86, 87], whereas the absence of TILs correlates with treatment failure. Similarly, patients whose tumors have gene expression signatures of CD8⁺ T cells and antigen presentation pathways have a good prognosis [88, 89]. Conversely, the presence of Tregs in both malignant ascites and tumor mass is associated with poor outcomes [90].

The VEGF-driven accumulation of CD33⁺ myeloid-derived suppressor cells (MDSCs), particularly in the omentum, also correlates with a failure to accumulate CD8⁺ TILs, the suppression of T cell function and a poor prognosis in ovarian cancer patients [91]. Similarly, CD33⁺ MDSCs that accumulate in peritoneal ascites fluid of ovarian cancer patients express nitric oxide synthase-2 (NOS2) and produce NO [92], which promotes the differentiation of Th17 cells and impairs the function of Th1 and CD8⁺ T cells. Although Th17 responses can in some cases promote anti-tumor immunity [93], chronic IL-17-driven inflammation is also associated with tumorigenesis [94]. Thus, a feed-forward loop between Th17 cells and MDSCs in the peritoneal cavity and omentum is likely a driver of ovarian cancer metastasis and progression.

Given our understanding of the immune activities of the omentum and MS, it seems reasonable to devise immune strategies to target these sites and benefit local anti-tumor immunity. For example, phagocytic cells in the omentum can be targeted with antigen-loaded, oligomannose-coated liposomes, which promote tumor-antigen-specific CD8⁺ T cell responses and impair tumor growth [95]. Similarly, peritoneal vaccination with lethally irradiated tumor cells leads to a local NK-mediated immune response in the MS that impairs subsequent tumor growth [96]. Consistent with the immune suppressive properties of the omentum, TILs from human ovarian tumor fragments grafted in the omentum of immunodeficient mice are anergic [97]. However, the administration of IL-12 loaded liposomes promotes local T cell reactivation, impairs tumor growth and prolongs survival [97]. In addition to immunological interventions, physicians now use intraperitoneal chemotherapy to increase overall survival in ovarian cancer patients [98], although the role of the omentum or MS is unclear at this time. Together, these studies suggest that therapies that target antigens or drugs to the omentum may be important for controlling peritoneal tumors. However, surgeons often resect most or all of the omentum in the context of ovarian cancer to eliminate as much metastatic disease as possible [77, 78].

Interestingly, omentectomy is also used in combination with gastric bypass surgery to promote weight loss and reduce symptoms of metabolic syndrome [99–101]. Although some studies suggest that omentectomy lowers inflammatory markers in skeletal muscle [99], and reduces C-reactive protein in serum [102], more recent trials find that omentectomy provides no additional benefit over gastric bypass alone with regards to metabolic parameters [100, 101]. These data may suggest a differential role of the omentum in regulating inflammatory and metabolic processes, perhaps due to its immune functions. Unfortunately, we have no information on peritoneal immune responses following omentectomy in patients with obesity or ovarian cancer.

Concluding Remarks

We now understand that the immune activity of the omentum is highly specialized and that its unusual leukocyte composition is likely evolved to maintain adipocyte homeostasis, protect the unique environment of the peritoneal cavity and promote the differentiation of mucosal-homing cells that recognize gut antigens. Importantly, this model suggests that perturbations of omental functions that may occur in the context of obesity, tumor metastasis, peritoneal dialysis or most extremely, omentectomy, may also have unpredictable

effects on immune regulation in the gut and peritoneal cavity, the progression of metabolic disease, tumor progression or even systemic inflammation. Thus, the omentum is an immunologically important, albeit poorly understood and often overlooked, regulator of regional immune responses.

Acknowledgments

This work was supported by NIH grant RO1-CA216234 to TDR and by the UAB Comprehensive Cancer Center P30-CA013148.

Glossary

Omentum

The omentum is a specialized adipose tissue in the peritoneal cavity that is connected by a mesothelial layer to the spleen, stomach, transverse colon and pancreas. In mice it appears as a thin strip of fat, whereas in humans the omentum is an apron-like sheet that hangs in front of the visceral organs

Milky spots (MS)

MS are clusters of leukocytes embedded in adipose tissue, primarily in the omentum and the splenic-portal fat. They function similar to lymph nodes, in that they collect and respond to local antigens. However, the cellular composition of MS more closely resembles the cells in the peritoneal cavity than cells in conventional secondary lymphoid organs like lymph nodes and spleen

Fat-Associated lymphoid clusters (FALCs)

FALCs are similar to MS in that they are clusters of leukocytes embedded in adipose tissue, primarily in mesenteric and pleural fat. However, FALCs are partially dependent on microbiota for their formation and are smaller and less frequent than the MS of the omentum. Their function may be similar

Visceral adipose tissue (VAT)-associated Tregs

VAT-associated Tregs are a subset of FoxP3⁺ Tregs that reside in adipose tissue, including the omentum. These cells depend on the transcription factor, PPAR γ , that is normally associated with adipocyte differentiation. They are found in perigonadal fat, which lacks MS or FALCs

Mesothelial cells

Mesothelial cells are a thin layer of cells that covers the omentum and other visceral and pleural organs. The surface of mesothelial cells is slippery to reduce friction between organs. Mesothelial cells are a potent source of TGF β in the omentum

SLP mice

Spleen, Lymph node and Peyer's patch-deficient mice are generated by surgically removing the spleen from lymphotoxin-deficient mice (which lack lymph nodes and Peyer's patches) and irradiating splenectomized Lta^{-/-} mice and reconstituting them with WT BM. The omentum and MS remain in these mice, allowing investigators to isolate their activity from other lymphoid organs

Parabiosis

Parabiosis is a surgical technique in which two mice, usually expressing distinct markers, are surgically joined by the skin, side-by-side, so that they share a circulation. This technique allows cells in the blood to circulate between the joined animals, and is used to analyze whether cells are circulating or resident (based on the presence of cells with both markers, or the host alone, respectively)

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Trends box

VAT-associated Tregs are a transcriptionally and functionally unique population of Tregs that regulate immune responses and metabolic process in adipose tissues, including the omentum.

ILC2 cells are found in adipose tissues like the omentum, where they regulate local immune responses and adipocyte metabolism

The omentum is a well characterized site of ovarian cancer metastasis due to its ability to collect tumor cells from the peritoneal cavity and to support tumor cell metabolism and growth

Despite the immune functions of the omentum, it appears unable to promote adaptive immune response to tumors that implant in the milky spots.

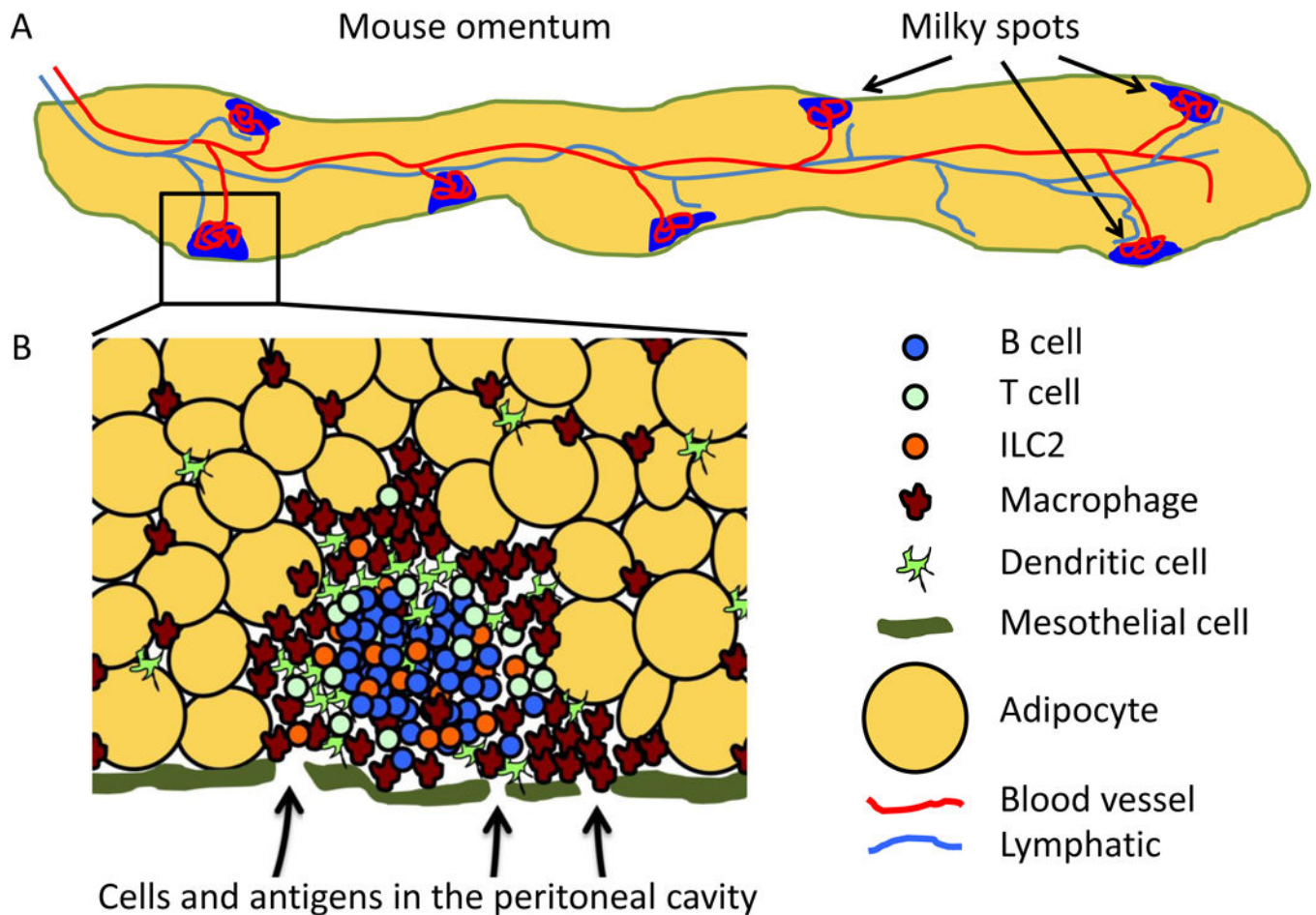


Figure 1. Structure of Milky Spots in the Omentum

A. Schematic of whole omentum in mice. The omentum is a thin strip of fat (yellow) that is covered by a layer of mesothelial cells (green). Milky spots (blue) are located just beneath the mesothelial layer embedded between adipocytes. The omentum is well vascularized with an extensive network of capillaries (not shown) running between the adipocytes that connect to a large central blood vessel (red). Blood vessels also connect to the milky spots and form a glomerulus-like knot of blood vessels in the lymphoid clusters. A large central lymphatic vessel (light blue) also runs down the center of the omentum and branches from this vessel lead to milky spots as well as to areas of the omentum that lack milky spots. The human omentum is much larger and resembles an apron hanging in front of the abdomen, but also contains milky spots. **B. Structure of milky spot.** Milky spots are loose collections of leukocytes embedded between adipocytes (yellow) just beneath the mesothelial layer (green). B cells (blue) form a central cluster, whereas macrophages (brown) and dendritic cells (light green) tend to accumulate around the outside of the milky spot and are also found individually throughout the omentum. T cells (green circles) and ILCs (orange) can be intermixed with the B cells or may cluster around blood vessels (not shown). Cells and antigens are passively collected from the peritoneal cavity through fenestrations in the mesothelial layer by fluid flow or may be actively carried by phagocytic cells like

macrophages. Cells can also enter the milky spots from the blood through HEVs (not shown).

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