The peritoneum: healing, immunity and diseases

Annalisa Capobianco[1], Lucia Cottone[1,2], Antonella Monno[1], Angelo A. Manfredi[1,3], Patrizia Rovere-Querini[1,3]

[1]San Raffaele Scientific Institute, Division of Immunology, Transplantation, and Infectious Diseases, Milan, Italy; [2]University College London, Genetics and Cell Biology of Sarcoma Group, London, UK; [3]Vita-Salute San Raffaele University, Milan, Italy

Key words:

endometriosis, peritoneal carcinomatosis, peritoneal adhesions, autoimmune serositis, sterile inflammation, fibrosis, macrophages, angiogenesis

Running title:

Persisting repair fosters inflammatory peritoneal diseases

Correspondence to:

Annalisa Capobianco, PhD

Dibit1 2A1 San Raffaele Institute

via Olgettina 58, 20132, Milano

tel +39 0226434694

e-mail capobianco.annalisa@hsr.it

The authors declare that no conflict of interest exists.

Abstract

The peritoneum defines a confined microenvironment, which is stable under normal conditions, but is exposed to the damaging effect of infections,

This article has been accepted for publication and undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process, which may lead to differences between this version and the Version of Record. Please cite this article as doi: 10.1002/path.4942

surgical injuries, and other neoplastic and non-neoplastic events. Its response to damage includes the recruitment, proliferation and activation of a variety of haematopoietic and stromal cells. In physiologic conditions, effective responses to injuries are organized, inflammatory triggers are eliminated, inflammation quickly abates, and the normal tissue architecture is restored. However, if inflammatory triggers are not cleared, fibrosis or scarring occur and impaired tissue function ultimately leads to organ failure. Autoimmune serositis is characterized by the persistence of self-antigens and a relapsing clinical pattern. Peritoneal carcinomatosis and endometriosis are characterized by the persistence of cancer cells or ectopic endometrial cells in the peritoneal cavity. Some of the molecular signals orchestrating the recruitment of inflammatory cells in the peritoneum have been identified in the last few years. Alternative activation of peritoneal macrophages was shown to guide angiogenesis and fibrosis, and could represent a novel target for molecular intervention. This review summarizes current knowledge of the alterations to the immune response in the peritoneal environment, highlighting the ambiguous role played by persistently activated reparative macrophages in the pathogenesis of common human diseases.

The peritoneum: a peculiar (and crowded) microenvironment

The mesothelial membrane that lines the abdominal cavity is situated directly beneath the abdominal musculature (*rectus abdominis* and *transversus abdominis*) and comprises a thin layer of loose connective tissue covered by a single layer of mesothelial cells [1]. The latter is referred to as the peritoneum and collectively, the connective tissue and peritoneum are referred to as the serosa (Figure 1). Mesothelial cells are squamous cells of mesodermal origin, characterized by apical microvilli, fragility and high turnover [1,2]. The peritoneal membrane contributes to the protection of the abdominal cavity, providing an environment that facilitates response to mechanical stresses and in which organs are kept separate and slide on one another. Two layers of peritoneum line the abdomen: the *parietal* layer lines the abdominal wall, while the *visceral* layer lines the abdominal viscera. The narrow space within these two layers is referred to as the peritoneal cavity [2]. The peritoneum provides a route for entry of nerves, blood and lymphatic vessels. Pathogens and bacterial toxins are also readily absorbed and cause inflammation [3].

The peritoneum contains the peritoneal fluid (PF), continuously produced by mesothelial cells as a plasma transudate, and reabsorbed through the large surface area of the peritoneum. The PF facilitates frictionless movement of abdominal organs (*e.g.* during peristalsis), permits the exchange of nutrients, removes pathogens and cells ascending from the female genital tract, and allows reparative events [4]. The PF is in equilibrium with the plasma, even if it does not contain large molecules. The PF is highly fibrinolytic, an activity that may restrict the formation of adhesions in response to injury (see below).

Growth factors, nutrients, cytokines and chemokines, as well as leukocytes, are continuously exchanged between the PF and the blood. Monocytes and macrophages account for 50-90% of the leukocytes, and in normal conditions dispose of debris and pathogens [5]. Regulation of the composition of the peritoneal extracellular matrix (ECM) and of the receptors involved in matrix sensing (integrins and the α5β1 receptor in particular) shapes the mobilization of leukocytes from the bone marrow to the blood. Actively generated signals promote their active recruitment to the peritoneal cavity, in normal resting

conditions and upon induction of local acute inflammation [6, 7]. Matrix remodelling and clearance of apoptotic cells and other particulate substrates modulate the function of peritoneal macrophages, committing them to an alternatively activated state with the upregulation of chemokine receptors such as CXCR4 [8].

The second most represented cells are B1 lymphocytes. These are a source of natural antibodies (IgM and IgA, in particular) with broad specificity and low antigen affinity [9]. Although initial reports suggested a constitutive spontaneous production of antibodies by B1 lymphocytes, further evidence points towards a requirement for an activation signal for IgM production [10], followed by the relocation of these cells in secondary lymphoid organs [11]. B1 cells contribute to the removal of microbes early after infection and facilitate the switch from innate to adaptive immunity. Their survival in physiological conditions is tightly regulated, via a mechanism dependent on the inhibitory FcγRIIb receptor and modulated by B-cell activating factor (BAFF) and its receptor [12, 13]. T lymphocytes, dendritic cells, neutrophils, natural killer cells and mast cells are also represented [14].

The peritoneum is exposed to a variety of stressing events, including surgical or accidental injuries as well as viral and bacterial infection. Advanced liver or kidney failure cause the accumulation of PF, that upon infection leads to microbial peritonitis [15]. Damage-associated and pathogen-associated molecular patterns (DAMPs and PAMPs, released by dying cells and by invading microorganisms respectively) induce the recruitment, the proliferation and the activation of haematopoietic and non-haematopoietic cells, which together contribute to repair the tissue [16, 17]. The response leads to the elimination of the stimuli from the peritoneal cavity. In this case, inflammation abates and the tissue heals (Figure 2A). However, if the triggers persist, pathological fibrosis or scarring develop, impairing normal tissue function and leading to organ failure [18, 19] (Figure 2B).

Conditions in which inflammatory triggers are eliminated: healing *vs.* fibrosis

The recognition of microbes in the peritoneal cavity induces an inflammatory response, either localized or widespread. Archetypal inflammation is followed by oedema and production of fibrogenic exudates, with the formation of fibrotic tissue in the form of adhesions between serosal surfaces [20-22]. Peritoneal repair involves the proliferation of the normally quiescent mesothelial cells in response to inflammatory signals released by bystander injured cells and by inflammatory leukocytes in the early phases. Later on, angiogenesis, cell migration and regulated turnover of the ECM predominate [23, 24]. Repair occurs diffusely through the injured mesothelial membrane and not from the wound edges, as in the case of epithelial organs and tissues. The integrity of the peritoneum is usually soon restored, possibly because of the combined action of mesothelial cells migrating from the wound edges and detaching from the opposing surfaces and from distant sites [24]. Other precursors from the bone marrow may also float in the peritoneal fluid and adhere to the denuded surface of the serosa [25]. In all cases, the PF, now a high-protein exudate containing fibrin, histamines, monocytes, granulocytes, macrophages and mesothelial cells, guides the reparative process [5]. The fluid coagulates within few hours, yielding fibrinous bands between corresponding surfaces maintaining their contact. Later, neutrophils entangle in fibrin strands and macrophages cover the wound.

In response to injury, macrophages increase their phagocytic activity, generate reactive oxygen species, an recruit and activate additional mesothelial cells and fibroblasts to prompt repair [26-28]. Adhesions are formed within 72 hours. Fibrinolysis counteracts this phenomenon and allows healing of the tissue. The plasticity of mesothelial cells is reflected by the “mesothelial-mesenchymal transition” phenomenon [29]. This results in a TGF-β-dependent formation of motile fibroblastoid cells that up-regulate alpha smooth muscle actin (α-SMA) and express type I collagen [24]. Mesothelial-derived myofibroblasts may play a role in the accumulation of ECM proteins and in the contraction of the repairing tissue, thus ensuring effective wound healing or prompting fibrosis [23, 30-34] (serosal adhesions in particular). The peritoneal microenvironments contain many components essential for healing, including collagens I and III, fibronectin, glycoproteins, fibroblasts,

macrophages, and blood and lymphatic vessels [30, 35]. The essential role of locally generated pentraxins, such as the prototypical long pentraxin PTX3, in stabilizing the provisional matrix and prompting effective healing has been recently demonstrated in various tissues [36-38].

Disruption of matrix assembly jeopardizes healing and/or favours adhesion formation [39-41]. It is known that hepatic fibrosis and even cirrhosis are potentially reversible if the underlying cause is removed [42]. Thus, at least in the liver, fibrosis is not the final outcome of a process leading to scar formation, but an actively maintained condition reflecting a maladaptive and sustained inflammatory response. This concept is relevant for the biology of peritoneal diseases.

Conditions in which inflammatory triggers are not eliminated: autoimmune serositis, cancer and endometriosis

When the inflammatory triggers are not eliminated, peritoneal inflammation does not abate, and leads to scar formation, impaired tissue function and eventually to organ failure. Examples comprise the response to self-antigens that induce autoimmune serositis in a transient-recurrent manner, or the response to neoplastic or ectopic cells, the main players of peritoneal carcinomatosis and endometriosis respectively.

Autoimmune serositis

Healthy individuals do not usually mount sustained adaptive responses to their own antigens; transient responses to damaged self-tissues do occur, but rarely cause tissue damage. Although self-tolerance is the rule, autoimmunity occurs in predisposed individuals. Consequently, tissue repair takes place and fibroplasia and granulation tissue are formed. Activated myofibroblasts produce a provisional ECM by excreting collagens and fibronectin. Because autoantigens cannot be eliminated, they elicit cycles of injury and repair and eventually overcome the ability of fibrinolysis to prevent fibrosis within the peritoneum.

Serositis refers to an inflammation of the lining of the lung, heart, or abdomen and peritoneum. Recurrent serositis is associated with autoimmune diseases such as Crohn’s disease, familial mediterranean fever (FMF) and systemic

lupus erythematosus (SLE). Crohn's disease is a characteristically segmental inflammatory bowel disease with extra-intestinal manifestations and immune-mediated features. The peritoneal serosa is usually spared, while the abdominal serosa is frequently involved. Rarely, inflammation of the lining of the lung or of the lung sacs occurs [43].

FMF is an auto-inflammatory disease associated with mutations in the *MEFV* gene that encodes the pyrin innate immunity regulator. In FMF, unrestrained production of IL-1β causes fever and polyserositis. Emotional factors, trauma and infection trigger both serositis and musculoskeletal pain. Menstruation plays an important role [44]; the pathophysiology underlying this relationship, and the role of blood accumulating in the peritoneal cavity as an inflammatory trigger (see below) are still unclear [45].

SLE is the prototypic autoimmune systemic disease, with antibodies specific for ubiquitous and abundant antigens, such as chromatin and proteins of the pre-mRNA splicing machinery. Inflammation of the peritoneum and the pericardium or pleuritis are frequent. Inflammatory fluid contains high levels of DNA and low levels of complement, suggesting that SLE serositis depends on deposition of immunocomplexes [46]. Inflammation abates with scar formation every time autoantigens are transiently targeted, and consequently the disease is exacerbated. Early appearance of serositis can be used to predict the risk of SLE development [47].

Peritoneal cancers and endometriosis

Tumours have been described as 'wounds that do not heal'. The signals promoting cell survival, proliferation and movement, as well as those favouring neo-angiogenesis, are useful for tissue repair. Conversely, they might be essential for the survival, growth and spreading of neoplastic cells. Most peritoneal tumors derive from extraperitoneal lesions. Primary peritoneal neoplasms of serosal origin are rare and usually of mesenchymal origin, deriving either from mesothelial cells (mesothelioma) or from adipose precursor cells in the stroma [48]. Mesothelioma is correlated to asbestos exposure, and affects all serosas [49]. Calcification and ascites formation are frequent [48]. Peritoneal carcinomatosis depends on the diffusion of cells from

carcinomas of the stomach, colon, ovaries, bladder, Fallopian tubes or pancreas [50]. Growing tumours eventually infiltrate structures contacting the visceral layer of the peritoneum and neoplastic cells detach and diffuse in the peritoneal cavity. Their fate within the peritoneal cavity has not been so far thoroughly investigated. Most cells die, but at least a fraction survive, attach to the mesothelium and – if the environment is permissive – yield metastatic lesions.

Islands of vascularized endometrial tissue at ectopic sites define endometriosis. During menstruation, the menstrual effluent is partially regurgitated through the Fallopian tubes into the peritoneal cavity. This is supposed to be necessary for endometriosis establishment [51]. It is not sufficient, though, since retrograde menstruation is common in healthy women [52]. The events that influence the ability of shed endometrium to survive, to attach and infiltrate the peritoneum and to recruit vessels have been only partially elucidated.

Peritoneal inflammation in endometriosis and carcinomatosis

Chronic inflammation, with persistent repair and eventual remodelling of the peritoneum, is a common feature of autoimmune serositis, cancer and endometriosis. Remodelling refers to the reorganization or renovation of the existing tissue, and sustains tissue alteration, diffusion, survival, spreading, and organization of ectopic and inflammatory tissue. It is achieved through the degradation and resynthesis of ECM components, orchestrated and guided by extracellular proteolysis and fibroblast activation [53]. Matrix metalloproteinases degrade ECM components and produce biologically active peptides, create space for cell migration and modify intercellular junctions, regulating the overall tissue architecture [54].

ECM dynamics result in altered synthesis or degradation of ECM components, influencing its architecture. ECM components are laid down, cross-linked and organized together *via* covalent and non-covalent modifications, determining the outcome of the interaction with stromal/inflammatory cells [55-58]. Thus the expression and function of ECM-modifying enzymes and stromal/inflammatory cells influence the

dissemination of ectopic or transformed cells, their diffusion in the peritoneal cavity and attachment to the serosa, specifically sustaining lesion vascularization. Each of these steps is discussed below.

Tissue remodelling by immune cells

Epidemiological studies and experimental findings support a role for chronic inflammation in fostering cancer [59, 60] and endometriosis [61, 62]. Recruited leukocytes possibly remodel the tissue, favouring tumour progression by supplying growth factors to sustain cell proliferation, survival factors to overcome cell death, and angiogenic factors and extracellular matrix-remodeling enzymes to foster angiogenesis [63]. Tumour-associated macrophages (TAMs) release proteases, cytokines and chemokines such as CCL2 and CXCL8, that promote tissue remodelling [64-68], as well as growth factors such as TGFβ, VEGFA, VEGFC, EGF and thymidine phosphorylase (TP), that promote angiogenesis and lymphangiogenesis under hypoxic conditions [69, 70]. Immune cells are crucial in the growth and vascularization of endometriotic lesions [71]. The presence of ectopic tissue in the peritoneal cavity is associated with overproduction of prostaglandins, cytokines and chemokines by infiltrating leukocytes [51]. Macrophages are a major source of inflammatory molecules that modify the peritoneal environment. They consistently infiltrate ectopic endometrial lesions, which in the absence of macrophages fail to establish and to grow in animal models [72, 73]. Thus the failure of endometriotic lesion establishment in these systems underscores the importance of leukocyte infiltration in the lesions.

Diffusion and spreading

Peritoneal colorectal cancer dissemination was originally thought to follow a random pattern. However, it is now clear that lesions develop at preferential sites following the PF hydrodynamics and gravity. In contrast, in the absence of ascites, cancer cells are restricted in motion and implant nearer to the primary site [74, 75]. The neoplastic spreading in the peritoneum often depends on passive intraperitoneal seeding of cells exfoliated from exposed primary intraperitoneal tumors. Neoplastic cells detach spontaneously from the abdominal masses because of high interstitial fluid pressure, contraction of the interstitial matrix, increased osmotic pressure and down-regulation of

the molecules that ensure cell-to-cell adhesion within the primary neoplastic lesion [76]. Shed neoplastic cells are transported in the PF along mesentery and ligaments towards contiguous or non-contiguous organs. Malignant lesions accumulate preferentially where the fluid is deposited, including the liver surface (because of the negative pressure under the diaphragm) or ovaries (located in the *cul-de-sac* of the peritoneum). Antineoplastic treatments can also paradoxically favor the access of cancer cells to the peritoneal cavity. Surgery in particular facilitates the dissemination of tumors into the peritoneal cavity, with neoplastic cells being released from transected lymphatic vessels and from tumour-contaminated blood from the neoplastic specimen [77, 78].

Cancer cells also diffuse from primary lesions *via* lymphatic and blood vessels, which allow direct access to the sub-mesothelial space. Dissemination *via* lymphatic vessels occurs from regional to central nodes, and haematogenous spread occurs *via* the mesenteric arteries. Accordingly, regions of the peritoneum enriched in lymphatics are early sites of metastasis. Peritoneal lesions derived from various distant cancers, including mammary and lung carcinoma and malignant melanoma, have been described [79].

During menstruation, erythrocytes and leucocytes accumulate in the peritoneal fluid of most women [80-82]. Haemolysis and/or defective clearance of dying red blood cells results in iron release, with production of a wide variety of damaging free radical species by the Fenton reaction, with lipid peroxidation, protein and DNA damage. These signals favour adherence to the peritoneal wall of the endometrial fragments [71, 83-87]. Peritoneal macrophages are professional phagocytes, whose primary role is the clearance of particulate debris, including apoptotic leukocytes and senescent red blood cells. When their clearance ability is overwhelmed, and in the presence of an excess of free radicals, peripheral macrophages generate, through NF-κB, multiple inflammatory signals supporting recruitment of further phagocytes at the site. These events might be specifically involved in the persisting inflammatory status of endometriotic lesions, in which the endometrial tissue still responds to normal hormonal signals, but menstrual blood cannot be eliminated by the normal process of physiological shedding

[84, 88-93] . Generally, oxidative injury occurs when continued delivery of iron to the peritoneal macrophages is associated with inhibition of iron storage in ferritin [62, 84, 94-97] Macrophages also serve as a source of nitric oxide (NO) [84]. NO produced in abundance by the inducible form of NO synthase, induced by oxidant-sensitive transcription factors like NF-κB [98], exacerbates endometriosis [99, 100]. The exfoliated cancer or ectopic cells must then: i) survive in the peritoneal environment; ii) adhere to the surface of the serosa; iii) migrate into the sub-mesothelial space and iv) attach firmly via integrins to the mesothelial basement membrane. At later stages, cancer cells express matrix proteinases that disrupt the peritoneal blood barrier and invade the sub-peritoneal tissue. Angiogenesis is crucial for the further growth of established lesions [73].

Attachment/Dissemination.

Peritoneal cancer dissemination has been considered a random process for many years. However, lesions develop at preferential sites, possibly because of the pattern of PF flow and sites of stasis, which in turn are influenced by physical forces such as fluid hydrodynamics and gravity [74, 75]. In contrast, in the absence of ascites, cancer cells are restricted in motion and so implant near to the primary site. Peritoneal dissemination of cancer cells involves several steps: detachment of cells from the primary tumour, survival in the abdominal cavity, attachment to the peritoneum, invasion of the subperitoneal space and proliferation with angiogenesis. Various molecular events must thus cooperate for cancer cells to efficiently attach and adhere to the peritoneal lining, but limited information is available [101].

This is probably also the case for endometriotic lesions, even if endometrial fragments and not isolated endometrial cells adhere to the serosa. *In vitro* models have shown that the process is short and that the active participation of mesothelial cells is necessary [102, 103]. After adhesion, the endometrial tissue invades the underlying mesothelial basement membrane without the need for its physical disruption, as initially thought. It is a prerequisite for the organization of the ectopic endometrial cells in three-dimensional cysts [102]. Invasion *per se* is not sufficient: angiogenesis is necessary for the establishment of endometriotic lesions.

Ascites reflects the accumulation of protein-rich exudate in the abdominal cavity, and represents a presenting feature of advanced-stage ovarian cancer or a relatively late event in carcinomatosis associated with other neoplasm. Accumulation of PF depends on enhanced filtration and/or decreased drainage or clearance, because of: *i)* hindrance of lymphatic vessels by metastatic cells *ii)* VEGF-dependent increased permeability of the peritoneum-associated vasculature *iii)* hypoproteinaemia facilitating fluid movement to the peritoneal cavity *iv)* hepatic involvement with portal hypertension. Most PF accumulating in the peritoneal cavity depends on that part of peritoneal serosa which is not directly infiltrated by neoplastic cells [78]

Angiogenesis

The formation of new blood vessels in adult tissues (neoangiogenesis) is critical for the establishment of benign or malignant lesions in the peritoneal cavity. As the lesion burden grows, endothelial cells are recruited to form new blood vessels to meet the increased metabolic demands. This process depends on inflammatory cells and specifically on the ability to attract "reparative" macrophages that release growth factors and matrix-remodelling enzymes, promote neoangiogenesis, and might play a role in the ability of endometriotic and neoplastic cells to yield peritoneal lesions. This general paradigm well agrees with data obtained in humans and in experimental models of peritoneal disease, including ovarian cancer [50, 104] and endometriosis [72, 73].

Carcinoma cells release a prototypic DAMP/alarmin, HMGB1, which guides tissue regeneration and supports neo-angiogenesis. Exogenous HMGB1 accelerates leukocyte recruitment, macrophage infiltration, tumour growth and neoangiogenesis in experimental models [105-107]. Chemotherapeutic agents in animal models induce HMGB1 in the peritoneal cavity. This observation could underlie some paradoxical results of chemotherapeutic treatments in patients with peritoneal carcinomatosis [108]. HMGB1 is also released by mesothelial cells challenged with asbestos, an event implicated in the natural history of malignant mesothelioma [109-113]. Abdominal surgery results *per se* in the release of HMGB1 in the peritoneal cavity. In turn, HMGB1 might create a negative loop *via* the recruitment of inflammatory

leukocytes, in particular myeloid derived suppressor cells (MDSC), to promote the metastatization of colon cancer cells after surgery [114]. MDSC comprise cells phenotypically or morphologically similar to monocytes and cells closer to neutrophils [115]. The ability of HMGB1 to influence the metabolism, function and interaction of neutrophils with other innate immune cells [116-118] might be involved in the tumour-supporting action of MSDC.

In endometriosis, macrophages deliver signals that attract vessels, facilitating the survival of ectopic endometrial cells in the relatively hypoxic peritoneal cavity [62]. Subpopulations of macrophages are preferentially involved in angiogenesis [119, 120]. The best characterized are possibly those that express the Tie-2 receptor (TEM or Tie-2-expressing monocytes/macrophages), which sustain neo-angiogenesis in a variety of experimental tumour models. Circulating monocytes express limited amounts of Tie-2 in normal conditions. They up-regulate it after homing to hypoxic tissue, where they yield a subset of perivascular macrophages [121-123].

The VEGF family and associated receptors and the angiopoietin/Tie-2 systems connect hormonal levels to vessel remodelling [124-127]. Peritoneal macrophages are a source of VEGF and ovarian steroids regulate the production of this growth factor [128]. Estrogens act on various macrophage signalling pathways, influencing in particular those related to the ability to sustain the recruitment of inflammatory cells and the remodelling of inflamed tissues, such as mitogen-activated protein kinase, phosphatidylinositide-3-kinase/protein kinase B and NF-κB. As a consequence, a deregulated response to steroids might influence the survival of ectopic endometrial cells and promote the neoangiogenesis of the lesions [129, 130].

Endometriotic lesions do not contain neoplastic cells. However they share with neoplasm features such as unrestrained growth, invasion of adjacent tissues, defective apoptosis and sustained inflammatory responses. Endometriosis increases the risk of ovarian cancer, in particular invasive low-grade serous, clear-cell and endometrioid subtypes [131, 132]. As discussed above, macrophages are physiologically recruited to injured tissues, where they activate the neo-angiogenic switch, sustain resistance to apoptotic stimuli and stimulate the proliferation and invasion of precursor cells, in order to

prompt tissue regeneration. Macrophages recruited in the endometriotic lesions indeed activate neo-angiogenesis, sustain survival and prompt proliferation, possibly contributing to the evolution toward atypical endometriosis, metaplasia and then borderline or fully malignant ovarian cancer [133]. Interference with the recruitment or the function of angiogenic macrophages might prove valuable for targeted molecular intervention.

Inflammation in the peritoneum as a druggable target

The innate immune response plays a critical role in peritoneal cancers and endometriosis [14, 134], as summarized in Figure 3. Phagocyte depletion via clodronate treatment reduces neoplastic growth by limiting neoangiogenesis in mouse models of carcinomatosis [50, 108], reduces tumour burden, invasion and metastasis in a mouse model of mesothelioma [135], and delays tumour progression while leaving unaltered ascites formation in an orthotopic model of ovarian cancer [104]. Genetic ablation of macrophages in models of experimental colorectal cancer results in decreased infiltration by regulatory T cells, CCL20 production and tumour growth [136].

Endometriotic lesions fail to grow in the absence of macrophages, and develop a glandular and stromal architecture, due to impaired vascularization, while retaining the ability to adhere to and to infiltrate the serosal membrane in a mouse model [72]. Macrophages are critical for the continued growth of lesions, which in their absence fail to develop a glandular and stromal architecture due to impaired vascularization [72]. When TEMs are depleted, vessels and overall lesions are disrupted. TEMs preferentially localize in perivascular areas [137], where they provide survival and growth signals to endothelial cells and progenitors [138]. In experimental peritoneal carcinomatosis, pharmacological HMGB1 targeting resulted in substantial anti-neoplastic effects [105].

The interaction between neoplastic or ectopic cells and immune cells in the peritoneal environment is a critical area for drug development. The identification of new molecular targets is essential for progress in the treatment of these diseases, a largely unmet medical need.

Acknowledgements

The work of the authors has been supported by the AIRC (Associazione Itaiana Ricerca sul Cancro).

Author's contributions

A.C. and L.C. wrote the manuscript, A.M. performed immunohistochemistry analysis; A.A.M and P.R.Q supervised the work.

References

1. Di Paolo N, Nicolai GA, Garosi G. The peritoneum: from histological studies to mesothelial transplant through animal experimentation. *Perit Dial Int* 2008; **28 Suppl 5**: S5-9.

2. Di Paolo N, Sacchi G. Atlas of peritoneal histology. *Perit Dial Int* 2000; **20 Suppl 3**: S5-96.

3. Mais D. Quick Compendium of Clinical Pathology. *QuickQuick Compendium of Clinical Pathology 2nd Ed ASCP Press 2009* 2009.

4. Blackburn SC, Stanton MP. Anatomy and physiology of the peritoneum. *Semin Pediatr Surg* 2014; **23**: 326-330.

5. Heel KA, Hall JC. Peritoneal defences and peritoneum-associated lymphoid tissue. *Br J Surg* 1996; **83**: 1031-1036.

6. Sampaio AL, Zahn G, Leoni G*, et al.* Inflammation-dependent alpha 5 beta 1 (very late antigen-5) expression on leukocytes reveals a functional role for this integrin in acute peritonitis. *J Leukoc Biol* 2010; **87**: 877-884.

7. Brown RJ, Mallory C, McDougal OM*, et al.* Proteomic analysis of Col11a1-associated protein complexes. *Proteomics* 2011; **11**: 4660-4676.

8. Ariel A, Ravichandran KS. 'This way please': Apoptotic cells regulate phagocyte migration before and after engulfment. *Eur J Immunol* 2016; **46**: 1583-1586.

9. Stoermann B, Kretschmer K, Duber S*, et al.* B-1a cells are imprinted by the microenvironment in spleen and peritoneum. *Eur J Immunol* 2007; **37**: 1613-1620.

10. Choi YS, Dieter JA, Rothaeusler K*, et al.* B-1 cells in the bone marrow are a significant source of natural IgM. *Eur J Immunol* 2012; **42**: 120-129.

11. Baumgarth N. Innate-like B cells and their rules of engagement. *Adv Exp Med Biol* 2013; **785**: 57-66.

12. Amezcua Vesely MC, Schwartz M, Bermejo DA*, et al.* FcgammaRIIb and BAFF differentially regulate peritoneal B1 cell survival. *J Immunol* 2012; **188**: 4792-4800.

13. Sindhava VJ, Scholz JL, Cancro MP. Roles for BLyS family members in meeting the distinct homeostatic demands of innate and adaptive B cells. *Front Immunol* 2013; **4**: 37.

14. Mier-Cabrera J, Jimenez-Zamudio L, Garcia-Latorre E*, et al.* Quantitative and qualitative peritoneal immune profiles, T-cell apoptosis and oxidative stress-associated characteristics in women with minimal and mild endometriosis. *Bjog* 2011; **118**: 6-16

.

15. Merrell RC. The abdomen as a source of sepsis in critically ill patient. *Surgical Treatment Evidence-Based and Problem-Oriented* 2001.

16. Zhang Q, Raoof M, Chen Y*, et al.* Circulating mitochondrial DAMPs cause inflammatory responses to injury. *Nature* 2010; **464**: 104-107.

17. Bertheloot D, Latz E. HMGB1, IL-1alpha, IL-33 and S100 proteins: dual-function alarmins. *Cell Mol Immunol* 2017; **14**: 43-64.

18. Wynn TA, Ramalingam TR. Mechanisms of fibrosis: therapeutic translation for fibrotic disease. *Nat Med* 2012; **18**: 1028-1040.

19. Ramalingam TR, Gieseck RL, Acciani TH*, et al.* Enhanced protection from fibrosis and inflammation in the combined absence of IL-13 and IFN-gamma. *J Pathol* 2016; **239**: 344-354.

20. Healy JC, Reznek RH. The peritoneum, mesenteries and omenta: normal anatomy and pathological processes. *Eur Radiol* 1998; **8**: 886-900.

21. Padwal M, Siddique I, Wu L*, et al.* Matrix metalloproteinase 9 is associated with peritoneal membrane solute transport and induces

angiogenesis through beta-catenin signaling. *Nephrol Dial Transplant* 2017; **32**: 50-61.

22. van Baal JO, Van de Vijver KK, Nieuwland R*, et al.* The histophysiology and pathophysiology of the peritoneum. *Tissue Cell* 2017; **49**: 95-105.

23. Rout UK, Saed GM, Diamond MP. Transforming growth factor-beta1 modulates expression of adhesion and cytoskeletal proteins in human peritoneal fibroblasts. *Fertil Steril* 2002; **78**: 154-161.

24. Mutsaers SE, Prele CM, Pengelly S*, et al.* Mesothelial cells and peritoneal homeostasis. *Fertil Steril* 2016; **106**: 1018-1024.

25. Bajpai R, Chen DA, Rada-Iglesias A*, et al.* CHD7 cooperates with PBAF to control multipotent neural crest formation. *Nature* 2010; **463**: 958-962.

26. Fotev Z, Whitaker D, Papadimitriou JM. Role of macrophages in mesothelial healing. *J Pathol* 1987; **151**: 209-219.

27. Riese J, Niedobitek G, Lisner R*, et al.* Expression of interleukin-6 and monocyte chemoattractant protein-1 by peritoneal sub-mesothelial cells during abdominal operations. *J Pathol* 2004; **202**: 34-40.

28. Koninckx PR, Gomel V, Ussia A*, et al.* Role of the peritoneal cavity in the prevention of postoperative adhesions, pain, and fatigue. *Fertil Steril* 2016; **106**: 998-1010.

29. Abelardo E, Roebuck D, McLaren C*, et al.* Right pulmonary artery sling in a single lung with bronchial isomerism. *J Card Surg* 2014; **29**: 256-258.

30. Buhimschi IA, Dussably L, Buhimschi CS*, et al.* Physical and biomechanical characteristics of rat cervical ripening are not consistent with increased collagenase activity. *Am J Obstet Gynecol* 2004; **191**: 1695-1704.

31. Gerarduzzi C, Di Battista JA. Myofibroblast repair mechanisms post-inflammatory response: a fibrotic perspective. *Inflamm Res* 2017; **66**: 451-465.

32. Witowski J, Kawka E, Rudolf A*, et al.* New developments in peritoneal fibroblast biology: implications for inflammation and fibrosis in peritoneal dialysis. *Biomed Res Int* 2015; **2015**: 134708.

33. Kawka E, Witowski J, Fouqet N*, et al.* Regulation of chemokine CCL5 synthesis in human peritoneal fibroblasts: a key role of IFN-gamma. *Mediators Inflamm* 2014; **2014**: 590654.

34. Burgess JK, Mauad T, Tjin G*, et al.* The extracellular matrix - the under-recognized element in lung disease? *J Pathol* 2016; **240**: 397-409.

35. diZerega GS. Biochemical events in peritoneal tissue repair. *Eur J Surg Suppl* 1997: 10-16.

36. Doni A, Garlanda C, Mantovani A. PTX3 orchestrates tissue repair. *Oncotarget* 2015; **6**: 30435-30436.

37. Cappuzzello C, Doni A, Dander E*, et al.* Mesenchymal Stromal Cell-Derived PTX3 Promotes Wound Healing via Fibrin Remodeling. *J Invest Dermatol* 2015.

38. Vezzoli M, Sciorati C, Campana L*, et al.* The clearance of cell remnants and the regeneration of the injured muscle depend on soluble pattern recognition receptor PTX3. *Mol Med* 2016; **22**.

39. Saed GM, Diamond MP. Molecular characterization of postoperative adhesions: the adhesion phenotype. *J Am Assoc Gynecol Laparosc* 2004; **11**: 307-314.

40. Roulis M, Flavell RA. Fibroblasts and myofibroblasts of the intestinal lamina propria in physiology and disease. *Differentiation* 2016; **92**: 116-131.

41. Nicolosi PA, Tombetti E, Maugeri N*, et al.* Vascular Remodelling and Mesenchymal Transition in Systemic Sclerosis. *Stem Cells Int* 2016; **2016**: 4636859.

42. Fallowfield JA. Future mechanistic strategies for tackling fibrosis--an unmet need in liver disease. *Clin Med (Lond)* 2015; **15 Suppl 6**: s83-87.

43. Mohammed AR, Babu S. Serositis and inflammatory bowel disease. *Br J Hosp Med (Lond)* 2008; **69**: 296-297.

44. Karadag O, Tufan A, Yazisiz V*, et al.* The factors considered as trigger for the attacks in patients with familial Mediterranean fever. *Rheumatol Int* 2013; **33**: 893-897.

45. Akar S, Soyturk M, Onen F*, et al.* The relations between attacks and menstrual periods and pregnancies of familial Mediterranean fever patients. *Rheumatol Int* 2006; **26**: 676-679.

46. Baroni G, Schuinski A, de Moraes TP*, et al.* Inflammation and the peritoneal membrane: causes and impact on structure and function during peritoneal dialysis. *Mediators Inflamm* 2012; **2012**: 912595.

47. Rees F. Early Clinical Features in Systemic Lupus Erythematosus: Can They Be Used to Achieve Earlier Diagnosis? A Risk Prediction Model. *Arthritis Care Research* 2016.

48. Bridda A, Padoan I, Mencarelli R*, et al.* Peritoneal mesothelioma: a review. *MedGenMed* 2007; **9**: 32.

49. Carbone M, Ly BH, Dodson RF*, et al.* Malignant mesothelioma: facts, myths, and hypotheses. *J Cell Physiol* 2012; **227**: 44-58.

50. Cottone L, Valtorta S, Capobianco A*, et al.* Evaluation of the role of tumor-associated macrophages in an experimental model of peritoneal carcinomatosis using (18)F-FDG PET. *J Nucl Med* 2011; **52**: 1770-1777.

51. Vercellini P, Vigano P, Somigliana E*, et al.* Endometriosis: pathogenesis and treatment. *Nat Rev Endocrinol* 2014; **10**: 261-275.

52. O DF, Roskams T, Van den Eynde K*, et al.* The Presence of Endometrial Cells in Peritoneal Fluid of Women With and Without Endometriosis. *Reprod Sci* 2017; **24**: 242-251.

53. Mezawa Y, Orimo A. The roles of tumor- and metastasis-promoting carcinoma-associated fibroblasts in human carcinomas. *Cell Tissue Res* 2016; **365**: 675-689.

54. Wang X, Page-McCaw A. A matrix metalloproteinase mediates long-distance attenuation of stem cell proliferation. *J Cell Biol* 2014; **206**: 923-936.

55. Lopez JI, Mouw JK, Weaver VM. Biomechanical regulation of cell orientation and fate. *Oncogene* 2008; **27**: 6981-6993.

56. Engler AJ, Chan M, Boettiger D*, et al.* A novel mode of cell detachment from fibrillar fibronectin matrix under shear. *J Cell Sci* 2009; **122**: 1647-1653.

57. Egeblad M, Rasch MG, Weaver VM. Dynamic interplay between the collagen scaffold and tumor evolution. *Curr Opin Cell Biol* 2010; **22**: 697-706.

58. Daley WP, Yamada KM. ECM-modulated cellular dynamics as a driving force for tissue morphogenesis. *Curr Opin Genet Dev* 2013; **23**: 408-414.

59. Palucka AK, Coussens LM. The Basis of Oncoimmunology. *Cell* 2016; **164**: 1233-1247.

60. Coussens LM, Werb Z. Inflammation and cancer. *Nature* 2002; **420**: 860-867.

61. Gazvani R, Templeton A. Peritoneal environment, cytokines and angiogenesis in the pathophysiology of endometriosis. *Reproduction* 2002; **123**: 217-226.

62. Capobianco A, Rovere-Querini P. Endometriosis, a disease of the macrophage. *Front Immunol* 2013; **4**: 9.

63. Solinas G, Marchesi F, Garlanda C*, et al.* Inflammation-mediated promotion of invasion and metastasis. *Cancer Metastasis Rev* 2010; **29**: 243-248.

64. Cassetta L, Pollard JW. Cancer immunosurveillance: role of patrolling monocytes. *Cell Res* 2016; **26**: 3-4.

65. Murdoch C, Muthana M, Coffelt SB*, et al.* The role of myeloid cells in the promotion of tumour angiogenesis. *Nat Rev Cancer* 2008; **8**: 618-631.

66. Hamm A, Prenen H, Van Delm W*, et al.* Tumour-educated circulating monocytes are powerful candidate biomarkers for diagnosis and disease follow-up of colorectal cancer. *Gut* 2016; **65**: 990-1000.

67. Wang Y, Nakayama M, Pitulescu ME*, et al.* Ephrin-B2 controls VEGF-induced angiogenesis and lymphangiogenesis. *Nature* 2010; **465**: 483-486.

68. Kimura Y, Sumiyoshi M, Baba K. Antitumor and Antimetastatic Activity of Synthetic Hydroxystilbenes Through Inhibition of Lymphangiogenesis and M2 Macrophage Differentiation of Tumor-associated Macrophages. *Anticancer Res* 2016; **36**: 137-148.

69. Henze AT, Mazzone M. The impact of hypoxia on tumor-associated macrophages. *J Clin Invest* 2016; **126**: 3672-3679.

70. Mantovani A, Marchesi F, Malesci A*, et al.* Tumour-associated macrophages as treatment targets in oncology. *Nat Rev Clin Oncol* 2017; **14**: 399-416.

71. Lousse JC, Van Langendonckt A, Defrere S*, et al.* Peritoneal endometriosis is an inflammatory disease. *Front Biosci (Elite Ed)* 2012; **4**: 23-40.

72. Bacci M, Capobianco A, Monno A*, et al.* Macrophages are alternatively activated in patients with endometriosis and required for growth and vascularization of lesions in a mouse model of disease. *Am J Pathol* 2009; **175**: 547-556.

73. Capobianco A, Monno A, Cottone L*, et al.* Proangiogenic Tie2(+) macrophages infiltrate human and murine endometriotic lesions and dictate their growth in a mouse model of the disease. *Am J Pathol* 2011; **179**: 2651-2659.

74. Carmignani CP, Sugarbaker TA, Bromley CM*, et al.* Intraperitoneal cancer dissemination: mechanisms of the patterns of spread. *Cancer Metastasis Rev* 2003; **22**: 465-472.

75. Lemoine L, Sugarbaker P, Van der Speeten K. Pathophysiology of colorectal peritoneal carcinomatosis: Role of the peritoneum. *World J Gastroenterol* 2016; **22**: 7692-7707.

76. Worzfeld T, Pogge von Strandmann E, Huber M*, et al.* The Unique Molecular and Cellular Microenvironment of Ovarian Cancer. *Front Oncol* 2017; **7**: 24.

77. Lengyel E. Ovarian cancer development and metastasis. *Am J Pathol* 2010; **177**: 1053-1064.

78. Sodek KL, Murphy KJ, Brown TJ*, et al.* Cell-cell and cell-matrix dynamics in intraperitoneal cancer metastasis. *Cancer Metastasis Rev* 2012; **31**: 397-414.

79. Zhao YC, Ni XJ, Li Y*, et al.* Peritumoral lymphangiogenesis induced by vascular endothelial growth factor C and D promotes lymph node metastasis in breast cancer patients. *World J Surg Oncol* 2012; **10**: 165.

80. Bokor A, Debrock S, Drijkoningen M*, et al.* Quantity and quality of retrograde menstruation: a case control study. *Reprod Biol Endocrinol* 2009; **7**: 123.

81. Bulun SE. Endometriosis. *N Engl J Med* 2009; **360**: 268-279.

82. Bulun SE, Monsivais D, Kakinuma T*, et al.* Molecular biology of endometriosis: from aromatase to genomic abnormalities. *Semin Reprod Med* 2015; **33**: 220-224.

83. Carvalho LF, Samadder AN, Agarwal A*, et al.* Oxidative stress biomarkers in patients with endometriosis: systematic review. *Arch Gynecol Obstet* 2012; **286**: 1033-1040.

84. Donnez J, Binda MM, Donnez O*, et al.* Oxidative stress in the pelvic cavity and its role in the pathogenesis of endometriosis. *Fertil Steril* 2016; **106**: 1011-1017.

85. Turkyilmaz E, Yildirim M, Cendek BD*, et al.* Evaluation of oxidative stress markers and intra-extracellular antioxidant activities in patients with endometriosis. *Eur J Obstet Gynecol Reprod Biol* 2016; **199**: 164-168.

86. Da Broi MG, Navarro PA. Oxidative stress and oocyte quality: ethiopathogenic mechanisms of minimal/mild endometriosis-related infertility. *Cell Tissue Res* 2016; **364**: 1-7.

87. Gozzelino R, Arosio P. Iron Homeostasis in Health and Disease. *Int J Mol Sci* 2016; **17**.

88. Defrere S, Lousse JC, Gonzalez-Ramos R*, et al.* Potential involvement of iron in the pathogenesis of peritoneal endometriosis. *Mol Hum Reprod* 2008; **14**: 377-385.

89. Augoulea A, Alexandrou A, Creatsa M*, et al.* Pathogenesis of endometriosis: the role of genetics, inflammation and oxidative stress. *Arch Gynecol Obstet* 2012; **286**: 99-103.

90. Santanam N, Zoneraich N, Parthasarathy S. Myeloperoxidase as a Potential Target in Women With Endometriosis Undergoing IVF. *Reprod Sci* 2017; **24**: 619-626.

91. Alvarado-Diaz CP, Nunez MT, Devoto L*, et al.* Endometrial expression and in vitro modulation of the iron transporter divalent metal transporter-1: implications for endometriosis. *Fertil Steril* 2016; **106**: 393-401.

92. Nassif J, Abbasi SA, Nassar A*, et al.* The role of NADPH-derived reactive oxygen species production in the pathogenesis of endometriosis: a novel mechanistic approach. *J Biol Regul Homeost Agents* 2016; **30**: 31-40.

93. McKinnon BD, Kocbek V, Nirgianakis K*, et al.* Kinase signalling pathways in endometriosis: potential targets for non-hormonal therapeutics. *Hum Reprod Update* 2016; **22**.

94. Rishi G, Secondes ES, Wallace DF*, et al.* Normal systemic iron homeostasis in mice with macrophage-specific deletion of transferrin receptor 2. *Am J Physiol Gastrointest Liver Physiol* 2016; **310**: G171-180.

95. Jiang L, Chew SH, Nakamura K*, et al.* Dual preventive benefits of iron elimination by desferal in asbestos-induced mesothelial carcinogenesis. *Cancer Sci* 2016; **107**: 908-915.

96. Pirdel L, Pirdel M. Role of iron overload-induced macrophage apoptosis in the pathogenesis of peritoneal endometriosis. *Reproduction* 2014; **147**: R199-207.

97. Lousse JC, Defrere S, Van Langendonckt A*, et al.* Iron storage is significantly increased in peritoneal macrophages of endometriosis patients and correlates with iron overload in peritoneal fluid. *Fertil Steril* 2009; **91**: 1668-1675.

98. Xiu-li W, Wen-jun C, Hui-hua D*, et al.* ERB-041, a selective ER beta agonist, inhibits iNOS production in LPS-activated peritoneal macrophages of endometriosis via suppression of NF-kappaB activation. *Mol Immunol* 2009; **46**: 2413-2418.

99. Beckman JS, Koppenol WH. Nitric oxide, superoxide, and peroxynitrite: the good, the bad, and ugly. *Am J Physiol* 1996; **271**: C1424-1437.

100. Detmers PA, Hernandez M, Mudgett J*, et al.* Deficiency in inducible nitric oxide synthase results in reduced atherosclerosis in apolipoprotein E-deficient mice. *J Immunol* 2000; **165**: 3430-3435.

101. Kanda M, Kodera Y. Molecular mechanisms of peritoneal dissemination in gastric cancer. *World J Gastroenterol* 2016; **22**: 6829-6840.

102. Nair AS, Nair HB, Lucidi RS*, et al.* Modeling the early endometriotic lesion: mesothelium-endometrial cell co-culture increases endometrial invasion and alters mesothelial and endometrial gene transcription. *Fertil Steril* 2008; **90**: 1487-1495.

103. Fassbender A, Overbergh L, Verdrengh E*, et al.* How can macroscopically normal peritoneum contribute to the pathogenesis of endometriosis? *Fertil Steril* 2011; **96**: 697-699.

104. Robinson-Smith TM, Isaacsohn I, Mercer CA*, et al.* Macrophages mediate inflammation-enhanced metastasis of ovarian tumors in mice. *Cancer Res* 2007; **67**: 5708-5716.

105. Cottone L, Capobianco A, Gualteroni C*, et al.* Leukocytes recruited by tumor-derived HMGB1 sustain peritoneal carcinomatosis. *Oncoimmunology* 2016; **5**: e1122860.

106. Wu T, Zhang W, Yang G*, et al.* HMGB1 overexpression as a prognostic factor for survival in cancer: a meta-analysis and systematic review. *Oncotarget* 2016; **7**: 50417-50427.

107. Jube S, Rivera ZS, Bianchi ME*, et al.* Cancer cell secretion of the DAMP protein HMGB1 supports progression in malignant mesothelioma. *Cancer Res* 2012; **72**: 3290-3301.

108. Cottone L, Capobianco A, Gualteroni C*, et al.* 5-Fluorouracil causes leukocytes attraction in the peritoneal cavity by activating autophagy and HMGB1 release in colon carcinoma cells. *Int J Cancer* 2015; **136**: 1381-1389.

109. Yang H, Rivera Z, Jube S*, et al.* Programmed necrosis induced by asbestos in human mesothelial cells causes high-mobility group box 1 protein release and resultant inflammation. *Proc Natl Acad Sci U S A* 2010; **107**: 12611-12616.

110. Qi F, Okimoto G, Jube S*, et al.* Continuous exposure to chrysotile asbestos can cause transformation of human mesothelial cells via HMGB1 and TNF-alpha signaling. *Am J Pathol* 2013; **183**: 1654-1666.

111. Napolitano A, Antoine DJ, Pellegrini L*, et al.* HMGB1 and Its Hyperacetylated Isoform are Sensitive and Specific Serum Biomarkers to Detect Asbestos Exposure and to Identify Mesothelioma Patients. *Clin Cancer Res* 2016; **22**: 3087-3096.

112. Pellegrini L, Xue J, Larson D*, et al.* HMGB1 targeting by ethyl pyruvate suppresses malignant phenotype of human mesothelioma. *Oncotarget* 2017; **8**: 22649-22661.

113. Yang T, Peleli M, Zollbrecht C*, et al.* Inorganic nitrite attenuates NADPH oxidase-derived superoxide generation in activated macrophages via a nitric oxide-dependent mechanism. *Free Radic Biol Med* 2015; **83**: 159-166.

114. Li W, Wu K, Zhao E*, et al.* HMGB1 recruits myeloid derived suppressor cells to promote peritoneal dissemination of colon cancer after resection. *Biochem Biophys Res Commun* 2013; **436**: 156-161.

115. Gabrilovich DI. Myeloid-Derived Suppressor Cells. *Cancer Immunol Res* 2017; **5**: 3-8.

116. Manfredi AA, Covino C, Rovere-Querini P*, et al.* Instructive influences of phagocytic clearance of dying cells on neutrophil extracellular trap generation. *Clin Exp Immunol* 2015; **179**: 24-29.

117. Manfredi AA, Baldini M, Camera M*, et al.* Anti-TNFalpha agents curb platelet activation in patients with rheumatoid arthritis. *Ann Rheum Dis* 2016; **75**: 1511-1520

.

118. Incerti E, Tombetti E, Fallanca F*, et al.* 18F-FDG PET reveals unique features of large vessel inflammation in patients with Takayasu's arteritis. *Eur J Nucl Med Mol Imaging* 2017; **44**: 1109-1118.

119. Qian BZ, Pollard JW. Macrophage diversity enhances tumor progression and metastasis. *Cell* 2010; **141**: 39-51.

120. De Palma M, Naldini L. Angiopoietin-2 TIEs up macrophages in tumor angiogenesis. *Clin Cancer Res* 2011; **17**: 5226-5232.

121. De Palma M, Naldini L. Tie2-expressing monocytes (TEMs): novel targets and vehicles of anticancer therapy? *Biochimica et biophysica acta* 2009; **1796**: 5-10.

122. Squadrito ML, De Palma M. Macrophage regulation of tumor angiogenesis: implications for cancer therapy. *Mol Aspects Med* 2011; **32**: 123-145.

123. Du R, Lu KV, Petritsch C*, et al.* HIF1alpha induces the recruitment of bone marrow-derived vascular modulatory cells to regulate tumor angiogenesis and invasion. *Cancer cell* 2008; **13**: 206-220.

124. Girling JE, Rogers PA. Regulation of endometrial vascular remodelling: role of the vascular endothelial growth factor family and the angiopoietin-TIE signalling system. *Reproduction* 2009; **138**: 883-893.

125. Mints M, Blomgren B, Palmblad J. Expression of angiopoietins 1, 2 and their common receptor tie-2 in relation to the size of endothelial lining gaps and expression of VEGF and VEGF receptors in idiopathic menorrhagia. *Fertil Steril* 2010; **94**: 701-707.

126. Elsheikh E, Sylven C, Ericzon BG*, et al.* Cyclic variability of stromal cell-derived factor-1 and endothelial progenitor cells during the menstrual cycle. *Int J Mol Med* 2011; **27**: 221-226.

127. Lash GE, Pitman H, Morgan HL*, et al.* Decidual macrophages: key regulators of vascular remodeling in human pregnancy. *J Leukoc Biol* 2016; **100**: 315-325.

128. McLaren J, Prentice A, Charnock-Jones DS*, et al.* Vascular endothelial growth factor is produced by peritoneal fluid macrophages in endometriosis and is regulated by ovarian steroids. *J Clin Invest* 1996; **98**: 482-489.

129. Cakmak H, Guzeloglu-Kayisli O, Kayisli UA*, et al.* Immune-endocrine interactions in endometriosis. *Front Biosci (Elite Ed)* 2009; **1**: 429-443.

130. Pellegrini C, Gori I, Achtari C*, et al.* The expression of estrogen receptors as well as GREB1, c-MYC, and cyclin D1, estrogen-regulated genes implicated in proliferation, is increased in peritoneal endometriosis. *Fertil Steril* 2012; **98**: 1200-1208.

131. Yamaguchi K, Mandai M, Toyokuni S*, et al.* Contents of endometriotic cysts, especially the high concentration of free iron, are a possible cause of carcinogenesis in the cysts through the iron-induced persistent oxidative stress. *Clin Cancer Res* 2008; **14**: 32-40.

132. Yamaguchi K, Mandai M, Oura T*, et al.* Identification of an ovarian clear cell carcinoma gene signature that reflects inherent disease biology and the carcinogenic processes. *Oncogene* 2010; **29**: 1741-1752.

133. Wei JJ, William J, Bulun S. Endometriosis and ovarian cancer: a review of clinical, pathologic, and molecular aspects. *Int J Gynecol Pathol* 2011; **30**: 553-568.

134. Giudice LC, Kao LC. Endometriosis. *Lancet* 2004; **364**: 1789-1799.

135. Miselis NR, Wu ZJ, Van Rooijen N*, et al.* Targeting tumor-associated macrophages in an orthotopic murine model of diffuse malignant mesothelioma. *Mol Cancer Ther* 2008; **7**: 788-799.

136. Liu G, Ma H, Qiu L*, et al.* Phenotypic and functional switch of macrophages induced by regulatory CD4+CD25+ T cells in mice. *Immunol Cell Biol* 2011; **89**: 130-142.

137. De Palma M, Venneri MA, Galli R*, et al.* Tie2 identifies a hematopoietic lineage of proangiogenic monocytes required for tumor vessel formation and a mesenchymal population of pericyte progenitors. *Cancer Cell* 2005; **8**: 211-226.

138. Gordon S, Martinez FO. Alternative activation of macrophages: mechanism and functions. *Immunity* 2010; **32**: 593-604.

Figure legends

Figure 1. Anatomy and organization of the peritoneum. (A) Two layers of peritoneum cover the abdomen: the *parietal* layer lines the abdominal wall, while the *visceral* layer lines the abdominal viscera. The narrow space within these two layers is referred to as the peritoneal cavity. (B) The layer of mesothelial cells is referred to as the peritoneum and collectively, the connective tissue and peritoneum are referred to as the *serosa*. The serosa is situated directly beneath the abdominal musculature.

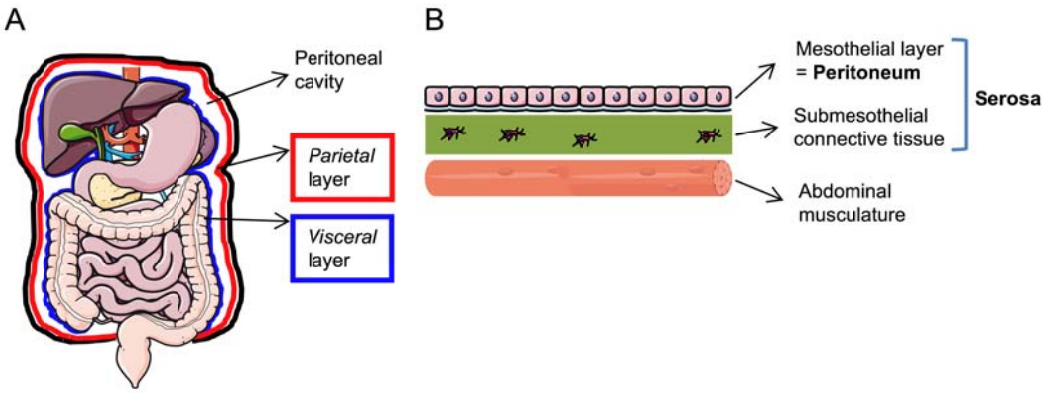

Figure 2. Peritoneal inflammation fosters homeostasis and/or tissue damage. Damage-associated molecular patterns (DAMPs) and pathogen-associated molecular patterns (PAMPs) released by dead and dying cells and by invading organisms elicit an inflammatory reaction in the peritoneal cavity. Under physiological conditions (A), the response is organized and controlled, these triggers are eliminated, inflammation resolves quickly and normal tissue architecture is restored. However, if the molecular triggers persist (B), the unrelenting tissue repair process leads to fibrosis or scarring, impairing normal tissue function and ultimately leading to organ failure and death.

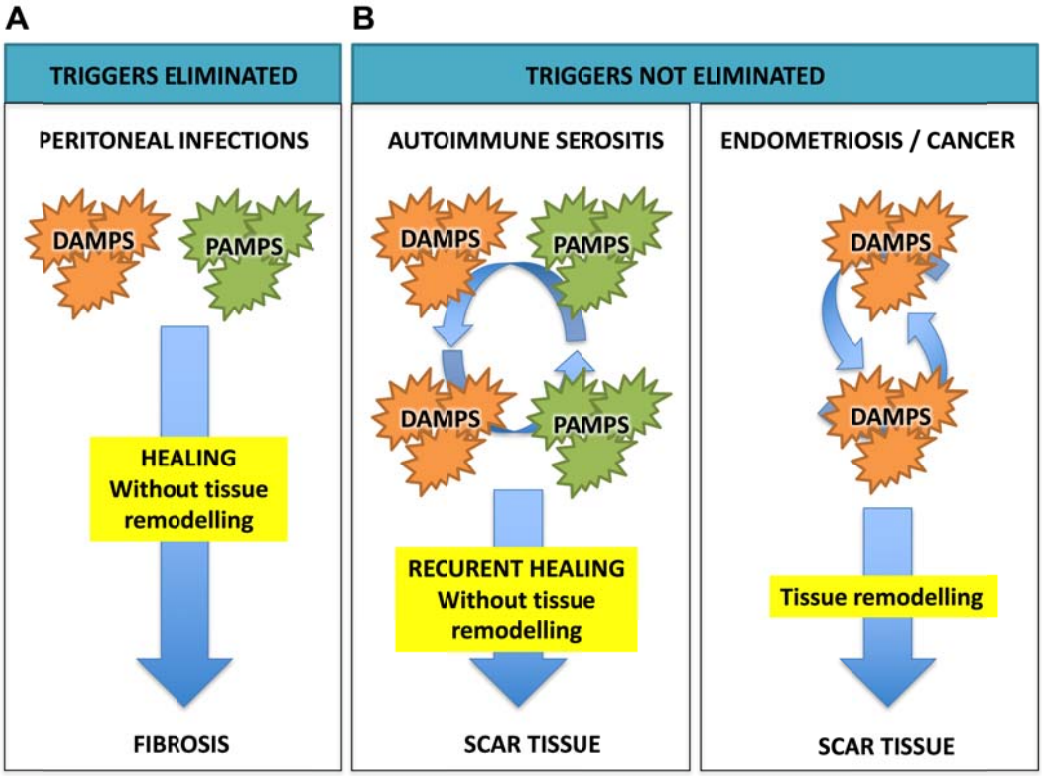

Figure 3. Common inflammatory themes in the establishment of ectopic and neoplastic peritoneal lesions. To yield lesions, exfoliated endometrial (light brown) or cancer cells (green) must: (i) survive the peritoneal environment; (ii) attract inflammatory phagocytes (macrophages, Mϕ and Tie2-expressing macrophages, TEM); (iii) adhere to the surface of the serosa and attach firmly, via integrins, to the basement membrane; (iv) attract novel vessels and grow, both processes being dependent on the prototypic DAMP/alarmin, HMGB1.