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Review

The histophysiology and pathophysiology of the peritoneum

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ABSTRACT

The peritoneum is an extensive serous organ with both epithelial and mesenchymal features and a variety of functions. Diseases such as inflammatory peritonitis and peritoneal carcinomatosis can induce disturbance of the complex physiological functions. To understand the peritoneal response in disease, normal embryonic development, anatomy in healthy conditions and physiology of the peritoneum have to be understood. This review aims to summarize and discuss the literature on these basic peritoneal characteristics.

The peritoneum is a dynamic organ capable of adapting its structure and functions to various physiological and pathological conditions. It is a key element in regulation of inflammatory responses, exchange of peritoneal fluid and prevention of fibrosis in the abdominal cavity. Disturbance of these mechanisms may lead to serious conditions such as the production of large amounts of ascites, the generation of fibrotic adhesions, inflammatory peritonitis and peritoneal carcinomatosis.

The difficulty to treat diseases, such as inflammatory peritonitis and peritoneal carcinomatosis, stresses the necessity for new therapeutic strategies. This review provides a detailed background on the peritoneal anatomy, microenvironment and immunologic responses which is essential to generate new hypotheses for future research.

Contents

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1. Introduction

The peritoneum is the largest serous membrane of the human body. It has a unique structure and function. The peritoneum is of importance in facilitating the movements of intraabdominal organs and in maintaining an equilibrium in the abdominal cavity. In case of disease, these balances are disrupted leading to a variety of symptoms.

It can be argued that the peritoneum is involved in almost all intraabdominal conditions. For example, it is highly active in inflammation, it contributes to fibrotic adhesion formation subsequent to infection or surgery and it is a preferred localization for metastases of several types of epithelial malignancies, including ovarian, colon and gastric cancer. This last condition, called peritoneal carcinomatosis is often difficult to treat because it is characterized by numerous miliary tumor depositions throughout the abdominal cavity. Complete removal by surgery is difficult and often not feasible. Recurrent disease often presents on the peritoneum leading to obstructive or paralytic ileus of the bowel, with high morbidity and mortality rates. To understand how the peritoneum is affected and to generate new hypotheses for therapeutic strategies, for example strategies that interfere with the immune response of the peritoneum, fundamental knowledge of the histophysiology and pathophysiology of the peritoneum is essential. Therefore, this review of literature describes the embryology, the anatomy and the functions of the peritoneum.

2. Embryology

Embryonal development of the peritoneum starts in the fifth week of gestation at the gastrulation stage. During this stage, a trilaminar embryo develops with the innermost endoderm, the outermost ectoderm and in between the mesoderm (Sadler and Langman, 2012; Hesseldahl and Larsen, 1969; Langemeijer, 1976) (Fig. 1A). The mesoderm differentiates into the lateral plate mesoderm, the intermediate mesoderm and paraxial mesoderm (Fig. 1B). The lateral plate mesoderm separates into the parietal plate and the visceral plate, covering the amnion and the yolk sac, respectively. The parietal plate mesoderm together with the ectoderm form the embryonic body wall, including the future parietal peritoneum. The visceral plate mesoderm and endoderm form the embryonic gut wall and this will become the visceral peritoneum.

Between the visceral and the parietal plate mesoderm a body cavity develops which forms the embryonic coelome (intra-embryonic cavity) (Fig. 1C, D). The coelome is covered completely by the mesothelial membrane. The parietal layer of the mesothelial membranes lines the outside of the peritoneal, pleural and pericardial cavities and secretes serous fluid. The visceral layer of the mesothelial membranes covers the intra-abdominal organs including liver, spleen, stomach, bowels, and, in females, the reproductive organs. Double layers of peritoneum form mesenteries that suspend the gut tube from the abdominal wall and provide a pathway for vessels, nerves and lymphatics to and from the organs. In the fifth to the seventh gestational week, the embryonic coelome is further compartmentalized by a septum transversum and pleuroperitoneal membranes, separating the cavity in pericardial, pleural and peritoneal cavities (Fig. 1E). Simultaneously, in the fifth gestational week, thickening of the parietal coelomic peritoneum, in combination with the intermediate mesoderm gives rise to the bilateral gonadal ridges. During the sixth gestational week, proliferation of the gonadal ridges and migration of epithelial cells through the underlying mesenchyme, results in indifferent sex cords or gonads. The parietal mesothelium forms the surface epithelium of the future ovaries or testes, whereas the stroma develops from subcoelomic intermediate mesoderm (Fig. 1F). In females, after splitting of the future ovaries, the gonads enlarge until they fuse and eventually develop into the urinary bladder and the reproductive organs including uterus, fallopian tubes and the upper part of the vagina. In males, the gonads proliferate and form the future testes. During this development, the parietal mesothelium of the gonads folds continuously with the underlying developing organs, resulting in a perfectly covering layer of peritoneum (Larsen and Sherman, 2002).

3. Anatomy

3.1. Macroscopic anatomy

The peritoneum is the largest serous membrane of the human body. The peritoneum has a surface area of approximately 1.8 m^2, which is of similar size as the surface of the human skin. The parietal peritoneum lines the inner surface of the abdominal walls, whereas the visceral peritoneum integrates with the outer serosal layers of organs, thereby covering the visceral organs. The blood supply of the parietal peritoneum is derived from arteries of the abdominal wall and from parietal pelvic arteries. The blood supply of the visceral peritoneum is derived from the mesenteric, coeliac and visceral pelvic arteries. Venous blood of the visceral peritoneum drains into the portal vein, whereas the parietal peritoneum drains into systemic veins returning to the vena cava (Khanna and Krediet, 2009). Approximately 80% of all the lymphatic drainage of the abdominal cavity is regulated by the thoracic duct and the right lymphatic duct (Aguirre and Abensur, 2014). The innervation of the parietal peritoneum of the upper abdomen is supplied by the phrenic nerve, the thoraco-abdominal nerve, and the subcostal and lumbosacral nerves, whereas the obturator nerve innervates the parietal peritoneum in the pelvis (Aguirre and Abensur, 2014). The nerves that innervate the visceral peritoneum have not been clearly identified, but sensations are possibly supplied by splanchnic nerves, the celiac plexus superior and the mesenteric plexus (Snell, 2011; Skandalakis et al., 2004). The parietal peritoneum is sensitive to pressure, pain, temperature, and laceration. The visceral peritoneum is not susceptible for these sensations, but is sensitive to stretch and chemical irritation (diZerega, 2000). Thus, the visceral and parietal peritoneal surfaces have different sensibilities, despite similar embryonic development.

The peritoneum adjacent to the female reproductive organs forms deep supportive parallel folds over the entire length of the fallopian tube. The thus formed ligament stretching out from pelvic wall to the uterus is collectively called the broad ligament. In accordance with the embryonic development, the peritoneum lining the abdominal walls and the visceral organs is similar throughout the abdomen, but is slightly different around the ovaries. It is composed of the mesovarium, the mesosalpinx and the mesometrium (Miller

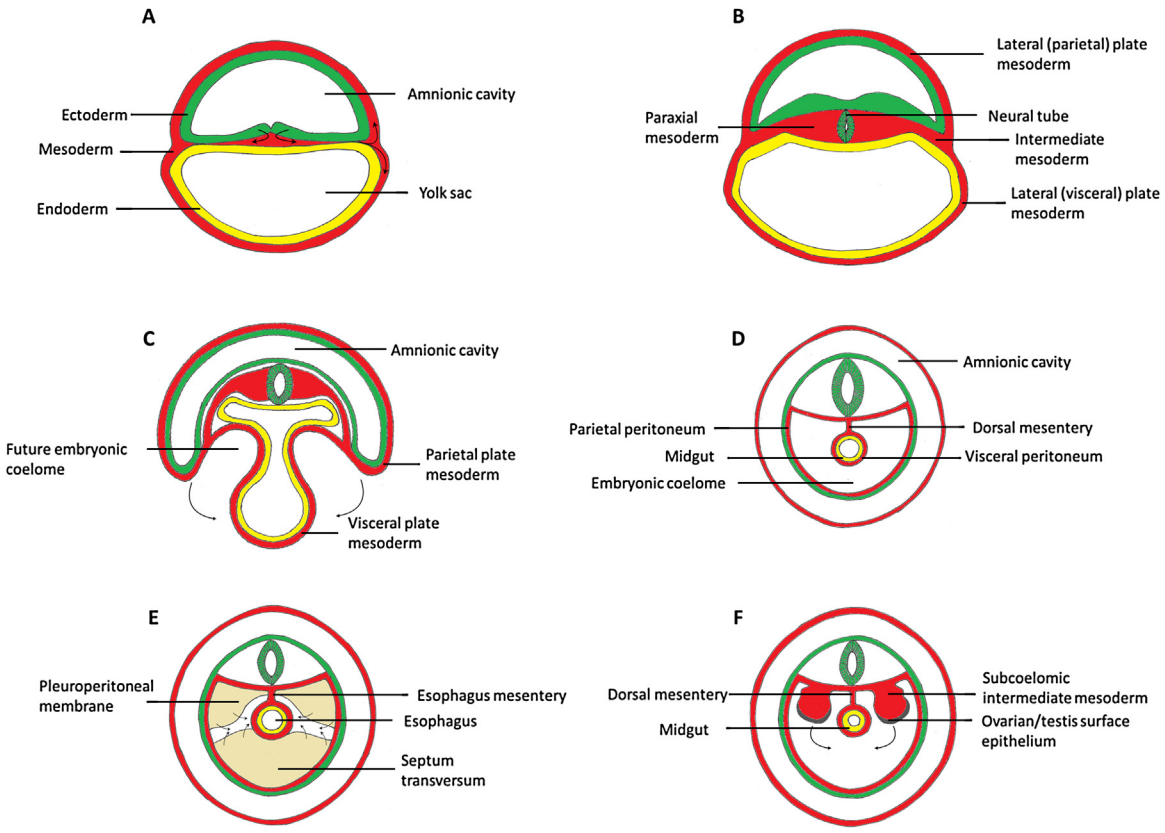

Fig. 1. Cross section cartoons of embryonic development of the peritoneum. A. Trilaminar embryo at 17 days. Inward migrating cells create sequentially the endoderm, mesoderm and ectoderm. B. Embryo at day 19. Mesoderm differentiation into lateral plate mesoderm, intermediate mesoderm and paraxial mesoderm. The lateral plate mesoderm splits into the parietal mesoderm and visceral mesoderm, the future parietal peritoneum and visceral peritoneum. C. During day 22 of gestation, the parietal plate mesoderm further elongates, eventually enclosing the endoderm and creating a newly formed cavity, the embryonic coelome. D. In gestational week 4, the embryonic coelome is created. The parietal peritoneum surrounding the embryonic cavity and the visceral peritoneum surrounding the organs is lined by mesothelial cells, derived from the mesoderm. E. Outgrowth of the mesoderm forms pleuroperitoneal membranes, which separate the pleural cavity from the peritoneal cavity and create the future diaphragm. F. During the 5th gestational week, the parietal coelomic peritoneum proliferates and together with the intermediate mesoderm create the ovarian or testicular surface epithelium.

et al., 2004). The ovaries are embedded in a membranous sac called the ovarian bursa, where the ovary bulges into the peritoneum towards the peritoneal cavity. At the dorsal side of the ovary, the mesovarium of the broad ligament attaches to the ovary. In fact, the ovary itself is not covered by peritoneum, but by a single-cell layer of cuboidal epitheloid cells, that is continuous with the peritoneum of the broad ligament (Eroschenko, 2012). The ovarian epithelium originates from the coelomic mesothelium, and has therefore similar morphological, immunohistochemical and molecular characteristics as the peritoneal mesothelium (Blaustein, 1984; Hoang et al., 1988; Anderson et al., 1976). The peritoneum is discontinuous at the fimbrial openings of the fallopian tubes. In contrast, the male reproductive organs are situated outside the abdominal cavity. Therefore, in males the peritoneum is a completely closed sac. Although the peritoneum is macroscopically identical throughout the abdomen, at microscopic level various cell types are found in the peritoneum.

3.2. Microscopic anatomy

The visceral and parietal peritoneum have a similar structural composition consisting of 3 distinctive layers: the mesothelium, a basal lamina and the submesothelial stroma (Fig. 2A). Throughout the whole abdomen, the mesothelium and basal lamina have a similar appearance, but the submesothelial stroma may vary in thickness. In the literature, the definition of the peritoneum is not consistent. The peritoneum is described either as a single-cell layer of mesothelial cells (Melichar and Freedman, 2002), or as a three-layered structure (Michailova and Usunoff, 2006). In this review, we will use the latter definition, and we describe mesothelium, basal lamina and submesothelial stroma separately. The microscopic anatomy of all structures of the peritoneum are described in the order beginning at the abdominal cavity and ending at the abdominal wall.

3.3. Peritoneal fluid

Under healthy conditions, a small volume of 5–20 mL peritoneal fluid is physiologically present in the peritoneal cavity. This is a mixture of plasma transudate and ovarian exudate. Furthermore, tubal fluid, retrograde menstruation and macrophage secretion contribute to the peritoneal fluid (Oral et al., 1996). Daily, approximately one liter of peritoneal fluid is produced to moisturize the peritoneal surfaces and exchange substances and immune cells between peritoneal fluid and plasma. Peritoneal fluid contains various types of immune cells, such as macrophages, natural killer cells, lymphocytes, eosinophils, mesothelial cells and mast cells (Gazvani and Templeton, 2002). In pathological conditions, the balance between peritoneal fluid secretion and drainage is often disturbed, causing an accumulation of fluid in the peritoneal cavity, known as ascites. The exact pathophysiology of this disturbance has not yet been identified but several etiologies have been proposed, such as portal hypertension and transudation of fluids into the peritoneum caused by liver disease, fluid production by a tumor,

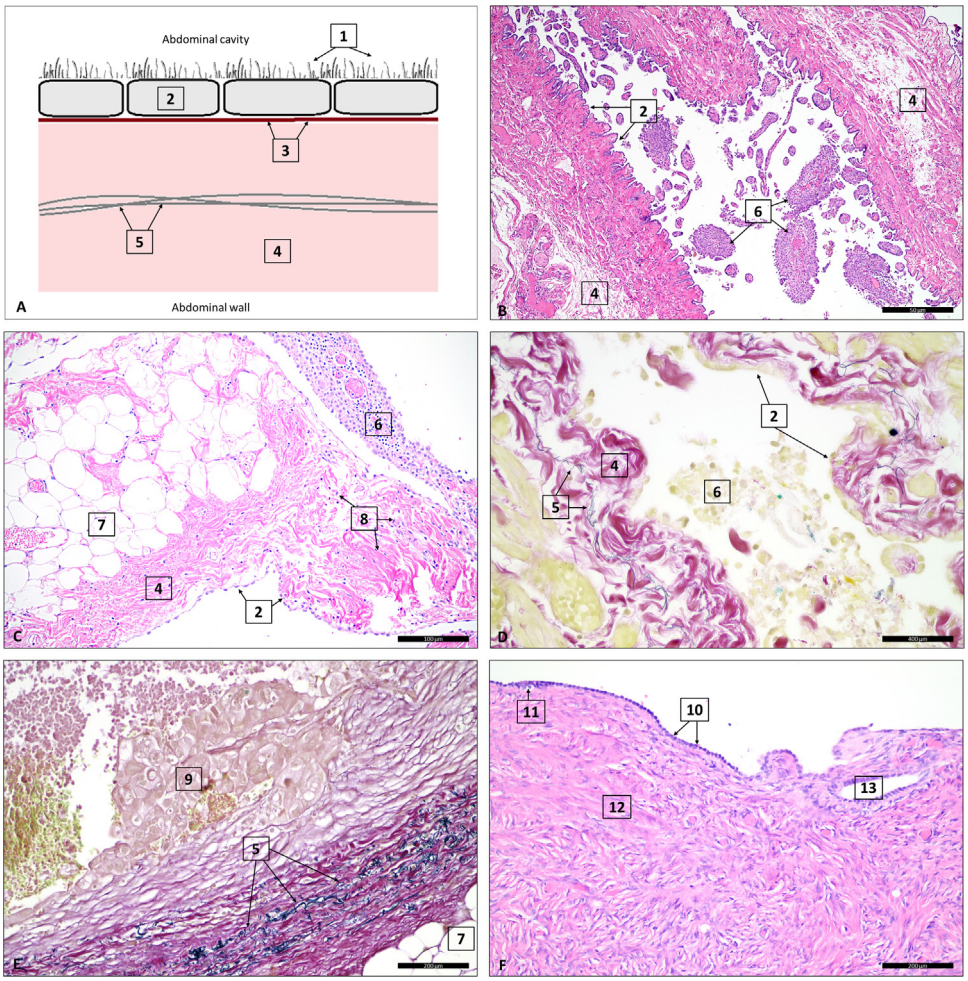

Fig. 2. Structure of the peritoneum. A. Cartoon of a cross-section of the peritoneum, demonstrating the various components of the peritoneum including glycocalyx (1), mesothelial cells (2), basal lamina (3), submesothelial stroma (4) and the elastic lamina (5). B and C. Microscopic images of hematoxylin and eosin staining of the peritoneum, demonstrating both the single cell layer mesothelium (2) and hyperplasia of stimulated mesothelium (6). Within the submesothelial stroma (4), fibroadipose tissue (7) and lymphocytes (8) are present. D and E. Microscopic images of Elastica van Gieson staining, demonstrating the elastic fibers of the peritoneal elastic lamina (5) and peritoneal depositions of metastatic ovarian carcinoma cells (9). F. Microscopic image of ovarian surface epithelium characterized with a mixture of cuboidal epitheloid cells (10) and columnar shaped epitheloid cells (11). Within the ovarian stroma (12), inclusion cysts (13) are often seen, developing after invagination of the ovarian surface epithelium.

lymphatic duct obstruction, hormonal stimulation and accumulation of inflammatory mediators (Miyoshi et al., 2015). Peritoneal fluid is transferred *via* a specific intra-abdominal circulation pattern from lower abdomen to upper abdomen and then returns to lower abdomen. This circulation pattern is created by gravity, resulting in a downward flow, and by respiratory movements, resulting in an upward flow.

3.4. Mesothelium

The innermost surface of the peritoneum is formed by the mesothelium, a monolayer of mesothelial cells with a cell diameter of approximately 25 μm (Fig. 2B and C). Mesothelial cells are from mesodermal origin, but possess both epithelial and mesenchymal features (Table 1). In specific conditions, the mesothelial cell can become even more mesenchymal-like loosing its epithelial characteristics after a so-called mesothelial-to-mesenchymal transition (Sandoval et al., 2013; Aroeira et al., 2005). Various studies investigated mesothelial cells in both humans and animals and found 3 types of mesothelial cells (Barberini et al., 1977; Michailova et al., 1999; Michailova, 2004, 1995). In animal studies, the intestinal, omental and parietal mesothelium is characterized by flattened epithelial-like cells, an intermediate cell type is present in the gastric peritoneum, whereas a cubic cell type is found lining the serosa of the parenchymal organs and around lymphatic stomata (Michailova and Usunoff, 2006). The morphology of peritoneal cells surrounding parenchymal organs has not been investigated in humans yet. Stomata are lymphatic portals between mesothelial cells, that are directly connected to the lymphatic system (Wang et al., 2010; Li and Li, 2003; Li et al., 1996a). Stomata are profusely present on sub-diaphragmic peritoneal surfaces (Mutsaers, 2002). Mesothelial cells possess a well-developed system of intracellular vesicles, providing evidence of the formation of granules containing secretory products. Coalescence of the intracellular vesicles results into larger multivesicular bodies. Eventually, at the apical surface of the cell, the multivesicular bodies can be excreted as exosomes (Li et al., 1996b; Obradovic et al., 2001). Compelling evidence demonstrates that exosomes play an important role in intercellular communication (van der Pol et al., 2012). However, the exact function of mesothelium-derived exosomes and their role in either physiological or pathological conditions are yet to be identified.

Besides the presence of exosomes at the apical surface of mesothelial cells, numerous microvilli and occasional cilia are present in which lamellar bodies are embedded (Baradi and Rao, 1976). Lamellar bodies are organelles with secretory and storage functions, produced by mesothelial cells (Michailova and Usunoff,

Table 1
Specific epithelial and mesenchymal characteristics of mesothelial cells of the peritoneum under various conditions.

Variables	Epithelial characteristics	Mesenchymal characteristics
Expression of markers	Cytokeratins (intermediate filaments) Cell-cell adhesion markers	Vimentin Desmin α-Smooth muscle actin Fibronectin N-Cadherin[a]
Cell structure	Microvilli Basal lamina Actin cytoskeleton	Ability to change phenotype[a]
Cell polarity	Apical-basal axis	Lack of cell polarity[a]
Cell motility	Stationary cell	Migratory cell[a], invasiveness[a], resistance to apoptosis[a]
Morphology	Polygonally shaped	Spindle shaped[a]
Junctions	Tight junctions Gap junctions Desmosomes	No intercellular junctions[a]

[a] Mesenchymal cell characteristics after mesothelial-to-mesenchymal transition.

2006). Lamellar bodies were first identified in type II pneumocytes, and more recently in other cell types with lubricating and friction-reducing purposes, including mesothelial cells (Schmitz and Muller, 1991; Dobbie and Anderson, 1996). Dobbie (1996) examined the ultrastructure of mesothelial cells, among others, and discovered identical characteristics of lamellar bodies secreted by various cell types. Lamellar bodies are composed of lipid membranes and a protein complex of surfactant proteins SP-A, SP-B, SP-C and SP-D. To maintain a friction-free surface, balanced amounts of surfactant and lipids are mandatory. Pulmonary surfactant is phagocytosed and recycled by macrophages (Michailova and Usunoff, 2006; Schmitz and Muller, 1991; Wright, 1990). Although peritoneal surfactant has not been studied, the similarity with pulmonary lamellar bodies suggests a similar role of peritoneal macrophages. Besides creating a friction-free surface, surfactant proteins may have immunoregulatory functions. Especially SP-D, but also SP-A can recognize and bind to foreign antigens to stimulate phagocytosis by resident macrophages (Gaynor et al., 1995; Tino and Wright, 1996; Qaseem et al., 2013; Kishore et al., 2005). Furthermore, SP-D inhibits activation and proliferation of T-cells and contributes in this way to the adaptive immune system (Borron et al., 1998, 2002).

On top of the microvilli and lamellar bodies, a glycocalyx is present that entraps fluid and creates a stagnant fluid layer. This layer consists of proteoglycans and glycosaminoglycans (GAGs) and trapped fluid with various substances. The majority of GAGs in the glycocalyx belong to the hyaluronan family. By ensuring a constant fluid layer over the peritoneal surface, the lamellar bodies with phospholipids, together with microvilli, lubricate and protect the serosal surface from frictional damage arising from movement of organs and other surfaces (Dobbie and Anderson, 1996; Mutsaers, 2004). Additionally, the glycocalyx is of importance in intercellular contact, regulation of inflammation, tissue remodeling and possibly transport of growth factors and nutrients across the peritoneum (Evanko et al., 2007). Proteoglycans and hyaluronan create a negative polarity of the peritoneal surface, maintaining the integrity of a semipermeable diffusion barrier. Shape, length and quantity of microvilli and lamellar bodies vary depending on the localization on the peritoneum and can change under physiological and pathological conditions, which reflects functional adaptation (Dobbie and Anderson, 1996; Fang et al., 2004; Madison et al., 1979).

The monolayer of mesothelial cells expresses intercellular junctional complexes, including tight junctions, gap junctions and desmosomes (Table 1; Pelin et al., 1994; Ito et al., 2000; Simionescu and Simionescu, 1977). Tight junctions and desmosomes are anchored intracellularly to the cytoskeleton of the mesothelial cells. The intercellular junctions and their functions are shown in Fig. 3. As described before, stomatal openings are present between mesothelial cells, thus enabling communication between the peritoneal cavity and the lymphatic system by absorption and migration of cells from the peritoneal cavity to the lymphatic system (Wang et al., 2010; Michailova et al., 2005). Stomata are generally organized around milky spots. Milky spots are immune cell aggregates, mainly composed of lymphocytes, B-cells and macrophages. They are designated as secondary lymphoid organs, because of their ability to amplify B-cell and $CD4^+$/$CD8^+$ T-cell recruitment in response to intra-abdominal infection, as well as their contribution to antigen recognition.

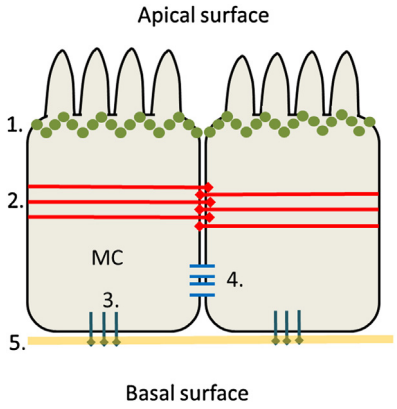

Fig. 3. Intercellular junctions of the mesothelial cells. Tight junctions (1) form the border between apical and basolateral membrane domains of mesothelial cells (MC) and prevent unregulated leakage of water-soluble molecules through intercellular spaces. In addition, tight junctions play an essential role in the maintenance of cell polarity. Desmosomes (2) of 2 neighboring cells adhere to bind the cells mechanistically to each other. Desmosomes are attached to intermediate filaments which are part of the cytoskeleton. Hemidesmosomes (3) containing integrins, bind the mesothelial cell to the basal lamina. Gap junctions (4) function as intercellular channels for exchange of small molecular hydrophilic compounds. A basal lamina (5) supports the mesothelial cells at the basal surface.

3.5. Basal lamina

In accordance with epithelial cells, a basal lamina supports the mesothelial cells at the basal surface (Figs. 2A and 3). The basal lamina consists of a layer of extracellular matrix with a thickness less than 100 nm, which is mainly composed of collagen type IV and laminin. Laminin interacts with the mesothelial cells *via* β1 integrins, which are expressed by mesothelial cells in regular conditions to facilitate adhesion (Yurchenco, 2011). The collagen type IV fiber network stabilizes the basal lamina. However, binding of the mesothelial cells to the basal lamina is weak and minor injuries

may already cause cell detachment, exposing the basal lamina and underlying stroma (Raftery, 1973a).

3.6. Submesothelial stroma

The mesothelial cells and the basal lamina are supported by connective tissue, also called stroma, of variable thickness. This supportive layer consists of collagen fibers, particularly type I collagen, fibronectin, proteoglycans, GAGs, (myo)fibroblasts, adipocytes, and lymphatic and blood vessels. In addition, Witz et al. (2001) demonstrated with light microscopy and confocal laser scanning microscopy, that laminin is also present in deeper layers of the submesothelial stroma. Stroma includes a complex of elastic fibers in a continuous layer, the elastic lamina (Fig. 2A, D and E; Knudsen, 1991). Despite the early discovery of the elastic lamina in animals (Rhodin, 1974), the understanding of its function is limited. Knudsen (1991) investigated the elastic lamina and its variable thickness in both the visceral and parietal peritoneum in humans. He described a relation between the thickness of the elastic lamina and the function of the organ that it covers. A prominent elastic lamina was found in organs with peristaltic movements, such as intestines and the gall bladder, whereas static organs, such as liver and the spleen, showed a less prominent elastic lamina. Lymph vessels are abundantly present in the stroma, in contrast to the generally low blood vessel density (Serini and Gabbiani, 1999; Saed and Kruger, 2004; Liu et al., 2001; Jorres et al., 1996; Hodge-Dufour et al., 1997; Saed and Zhang, 2001). The submesothelial stroma is an important source of immune cells. Generally, these cells are inactive and are found in low numbers in the stroma, but in specific (patho)physiological conditions immune cells are activated and angiogenesis is induced.

4. Function & dysfunction

Up to a few decades ago, the peritoneum was considered to be a permeable, passive membrane with exclusively a lubricating function, thereby facilitating intracoelomic movement. It is correct that with the stagnant fluid phase of the glycocalyx, a slippery, non-adhesive and protective surface is created, allowing the visceral and parietal serosa to move without friction. However, in the last 20 years additional functions of the peritoneum have been elucidated. The predominant role of peritoneal cells is regulation in the intraperitoneal homeostasis of the abdominal cavity. Other functions are transport of fluids, inflammation, antigen presentation and tissue repair (Mutsaers, 2002, 2004; Yung and Chan, 2007; Nachtsheim et al., 2006; Fig. 4). Furthermore, the peritoneum plays an important role in the development of peritoneal diseases such as endometriosis, mesothelioma and peritoneal carcinomatosis.

4.1. Transmembrane transport of fluids

The peritoneum is a semipermeable membrane, which enables passive transport of fluids and solutes by hydrostatic and osmotic pressure gradients *via* intercellular junctions and stomata and actively by (micro)pinocytic vesicle formation (Fedorko and Hirsch, 1971). The primary barrier for transport is the continuous endothelium which lines the capillaries and venules of the peritoneum (Khanna and Krediet, 2009). The stroma, the basal lamina and the mesothelium do not create resistance to transport of solutes and small molecules across the peritoneum (Flessner et al., 2003; Flessner, 2008). A network of GAGs, collagen, elastin and fibronectin and transcellular transport in mesothelial cells allows transport of large molecules (Khanna and Krediet, 2009). At present, the barrier function of the glycocalyx has not been clearly defined and there is no consensus in the literature regarding its filtering function (Flessner, 2008; Rippe, 2008).

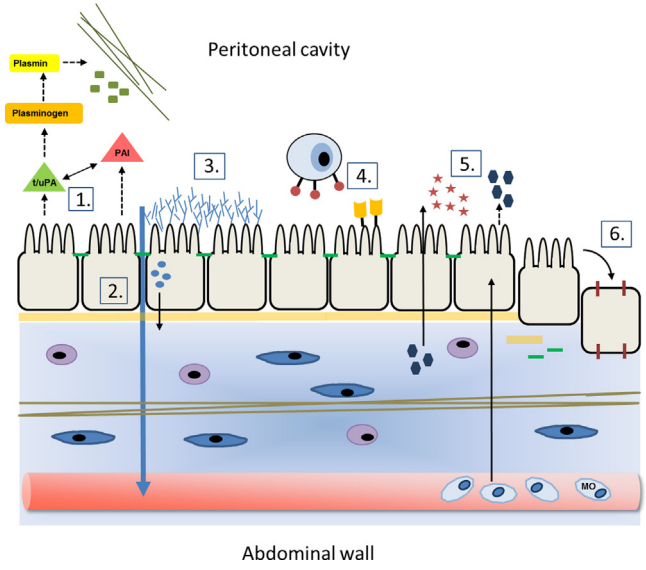

Fig. 4. Functions of the peritoneum. Cartoon of a cross-section of the peritoneum depicting the various functions of the peritoneum (1–6). 1) Mesothelial cells produce both tissue-type and urokinase-type plasminogen activators (tPA and uPA), which are proteases that contribute to fibrinolysis, by converting plasminogen into plasmin. This conversion is inhibited by the glycoproteins plasminogen activator inhibitors (PAI)-1 and PAI-2, which are also produced by mesothelial cells for the balance between fibrin deposition and degradation. 2) Transport of fluids and solutes across the peritoneum occurs passively *via* intercellular junctions (tight junctions) and stomata. Active transport occurs transcellularly *via* pinocytic vesicles. 3) A slippery, non-adhesive surface is formed by the glycocalyx. This friction-free surface is considered to prevent tumor adhesion and dissemination across the peritoneum. 4) Mesothelial cells contribute to the induction of inflammatory responses by their antigen-presenting function. Antigen presentation by the mesothelial cells enables recognition of foreign materials by T-helper cells *via* MHC-II molecules and secretion of inflammatory mediators. 5) An inflammatory response of the peritoneum in response to foreign material is initiated by leukocytes (mainly monocytes (MO)) that are attracted to the peritoneal cavity. Monocytes produce cytokines such as IL-1β, IFN-γ and TNF-α, which activate mesothelial cells to secrete inflammatory mediators that enhance inflammation (prostaglandins, cytokines, chemokines, nitric oxide, growth factors, phospholipids and proteoglycan species). A chemotactic gradient promotes migration of inflammatory cells towards the apical surface of the mesothelial cells, where the glycocalyx interacts with the recruited immune cells. 6) To initiate tissue repair and to stabilize the peritoneal microenvironment, mesothelial cells are able to transform into cells with a mesenchymal phenotype. This epithelial-to-mesenchymal-like transition is characterized by loss of cell-cell junctions, reorganization of the cytoskeleton and disappearance of apical and basal cell surface polarity.

The capacity of the peritoneum to transport fluids enables peritoneal dialysis, a renal replacement therapy for end stage renal failure. In response to the peritoneal dialysis solution, ultrafiltration and diffusion of water, salt and uremic toxins across the peritoneum occurs. However, chronic peritoneal dialyses evokes both morphological and functional adaptions of the peritoneum including inflammation, thickening of the submesothelial stroma, progressive fibrosis and angiogenesis, which eventually lead to loss of filtration capacity (Schilte et al., 2009; Witowski et al., 2015).

4.2. Inflammation

Serous membranes are susceptible to bacterial invasion. Hence, the anti-inflammatory role of the peritoneum is of importance to prevent infectious peritonitis, a disease which can develop into a potentially life-threatening condition. The inflammatory response of the peritoneum is a multi-step response that leads to the recruitment of immune cells (Topley and Williams, 1994). The inflammatory response is characterized by enhanced vascular perfusion, accumulation of macrophages with subsequent attraction of more infiltrating immune cells and the release of pro- and

anti-inflammatory mediators (Faull, 2000). Macrophages, resident within the peritoneal cavity and submesothelial stroma, play a key role in recognition and digestion of foreign material and subsequent recruitment of inflammatory leukocytes from blood, including monocytes, lymphocytes and neutrophils. Mesothelial cells secrete a number of inflammatory mediators in response to these recruited leukocytes (Topley et al., 1994; Jonjic et al., 1992; Li et al., 1998; Mazar et al., 2005). GAGs, located in the stroma and in the glycocalyx of the mesothelium, are able to bind chemokines (Johnson et al., 2004). The production, secretion and crosslinking of hyaluronan is increased during inflammation (Yung et al., 1995). The created cables of hyaluronan can mediate CD44-mediated leukocyte adhesion and migration (Evanko et al., 2007; Yung and Chan, 2011; Day and de la Motte, 2005). Furthermore, adhesion molecules such as vascular cell adhesion molecule (VCAM)-1 and intercellular adhesion molecule (ICAM)-1, expressed on the mesothelial cell surface, interact with the recruited leukocytes (Yung and Chan, 2012). Thus, peritoneal injury caused by either surgery, inflammation or ischemia triggers a complex peritoneal defense mechanism *via* several cross-reacting pathways. Exuberant immune responses may lead to angiogenesis, fibrosis and eventually destruction of the peritoneum. Peritoneal fibroblasts in the stroma and the mesothelial cells participate actively in the peritoneal immune defense and are able to respond to physiological and pathological changes within their microenvironment (Witowski et al., 2015).

4.3. Antigen presentation

The inflammatory response of the mesothelial cells is mainly regulated by T-helper cells. T-helper cells recognize foreign material presented by major histocompatibility complex (MHC)-II molecules by antigen-presenting cells (APCs) (Hausmann et al., 2000). APCs are highly-specialized cells that display fragments of antigens on their cell surface, necessary for T-cell activation. Mesothelial cells also have the ability to act as APCs. Valle et al. (1995) examined mesothelial cells for their antigen-presenting capacity in response to soluble antigens, tetanus toxoid and purified protein derivates, or particular antigens such as Candida albicans bodies. In this study, mesothelial cells expressed MHC class II molecules and were shown to present antigens to T-cells, and contributed thereby, along with resident macrophages, to T-cell activation. These data suggest that mesothelial cells effectively contribute to antigen presentation to T-cells to generate a cell-mediated immune response to pathogens.

4.4. Tissue repair

The peritoneum contributes to both formation and breakdown of peritoneal surface adhesions following surgical procedures or inflammation. A fine balance between these conflicting processes is crucial to prevent adhesion formation. Injured peritoneum, denuded from mesothelial cells, can create fibrotic adhesions with the opposite intact peritoneal surface. Injury (mechanical, thermal, chemical or ischemic) or ongoing inflammation of the peritoneum is accompanied by accumulation of inflammatory cells and fibrin precipitation. Mesothelial cells activate coagulation by production of tissue factor, the initiator of coagulation *in vivo* (Kothari et al., 2009). Normally, the activated fibrinolytic system will degrade these fibrin depositions. However, a disbalance of these mechanisms leads to fibrous adhesion formation. When the fibrinolytic system fails, extracellular matrix components are attracted to consolidate the fibrin depositions. Eventually, this fibrin matrix, containing fibroblasts, macrophages and multinucleated giant cells, adhere to both peritoneal surfaces (Cheong et al., 2001).

Mesothelial cells also contribute to fibrosis *via* their capacity to exert epithelial-to-mesenchymal-like transitions. This so-called mesothelial-to-mesenchymal transition (MMT) is a coordinated stepwise transformation of mesothelial cells by progressive loss of the mesothelial phenotype, into an invasive, migratory cell with a myofibroblastic phenotype and loss of intercellular adhesion (Yanez-Mo et al., 2003). MMT is initiated by several cytokines, including transforming growth factor (TGF)-β1, interleukin (IL)-1β, hepatocyte growth factor (HGF) (Thiery, 2003; Yang et al., 1999). In conditions such as lung fibrosis and liver fibrosis, the myofibroblastic cells stimulate fibrosis and epithelial injury through their production of stromal components, but also by the expression of inflammatory mediators and their contractile capacities *via* expression of α-smooth muscle actin (Hinz et al., 2007). The latter is typically expressed and often used as a marker for transformed myofibroblastic cells. However, the exact role of myofibroblastic cells in peritoneal fibrosis and peritoneal adhesion formation remains to be clarified.

Besides the capacity to promote formation of fibrin, mesothelial cells also have the capacity to promote its degradation. Mesothelial cells stimulate the conversion of plasminogen into plasmin by producing tissue plasminogen activators (tPA, uPA) that degrade fibrin, but they also produce their inhibitors (plasminogen activator inhibitors (PAIs)) that inhibit these fibrin-degrading enzymes (Sikkink et al., 2005). Furthermore, matrix metalloproteinases (MMPs) and their inhibitors (tissue inhibitor of metalloproteases (TIMPs)), produced by the peritoneum, degrade components of the stroma (Chegini et al., 2001). The proteolytic activity of MMPs and the inhibition by TIMPs contributes to remodeling of the stroma during adhesion formation. Physiological peritoneal healing can be established within one week, regardless of the size of the lesion in the peritoneum (Hubbard et al., 1967; Ellis et al., 1965; Raftery, 1973b). Thus, the peritoneum exhibits effects to either activate or prevent fibrin formation. However, injury of any cause can disrupt the fine balance, resulting in irreversible adhesions of fibrin matrix.

4.5. Peritoneal carcinomatosis

Besides the involvement in physiological conditions, the peritoneum can also play a role in various pathological conditions. The peritoneum is a preferred localization for metastases of epithelial cancers such as ovarian, colon or gastric carcinomas. In 70% of patients with epithelial ovarian cancer (EOC) multiple metastatic tumor deposits of only millimeters in dimension, adhere to the parietal and visceral peritoneal surfaces. This condition, designated as peritoneal carcinomatosis, is associated with an unfavorable prognosis as optimal curative treatment is often difficult. The exact mechanisms by which metastatic cancer cells attach to the peritoneum are unclear. EOC cells expose adhesion molecules which enable binding to both mesothelial cells and the submesothelial stroma. One type of such adhesion molecules are integrins, which are cell surface glycoprotein receptors that are abundantly expressed by epithelial cells and carcinoma cells such as EOC cells. Integrins are heterodimers, composed of an α- and a β-subunit. Ligands of integrins include components of extracellular matrix (ECM) in the stroma, such as collagen, laminin, fibronectin, fibrinogen and vitronectin.

Integrins expressed on EOC cells such as α5β1 integrin, are able to bind to fibronectin which is exposed by mesothelial cells (Burleson et al., 2004; Casey et al., 2001). Integrins can also bind to other adhesion molecules expressed by mesothelial cells, such as ICAM-1 and VCAM-1 (Alkhamesi et al., 2005; Slack-Davis et al., 2009). This binding leads to the production of inflammatory mediators such as tissue necrosis factor (TNF)-α, IFN-γ, IL-1β and IL-6 by mesothelial cells. The production of these inflammatory mediators results in upregulation of fibronectin production and activation of adhesion molecules on the mesothelial surface, further increasing EOC cell adhesion (Kenny et al., 2014; Klein et al., 1995). However,

Table 2
Non-integrin mediated tumor cell adhesion to the peritoneal mesothelium and the glycocalyx.

Adhesion molecules on EOC	Ligand on mesothelial cell	References
CD43	ICAM-1	Ziprin et al. (2004)
CD44	Hyaluronan	Burleson et al. (2004), Cannistra et al. (1993), Lessan et al. (1999), Gardner et al. (1995)
CA125/MUC16	Mesothelin	Rump et al. (2004), Gubbels et al. (2006)
L1CAM	Neutropilin-1	Stoeck et al. (2006)
GnRH	P-cadherin	Cheung et al. (2013)

CA125/MUC16 = Cancer Antigen 125/Mucin 16, L1CAM = L1 cell adhesion molecule, GnRH = Gonadotropin-releasing hormone.

adhesion of cancer cells to mesothelial cells is not solely established by integrins. Other adhesion molecules and their ligands involved in non-integrin mediated adhesion between EOC cells and mesothelial cells are summarized in Table 2.

An important component of the tumor microenvironment that contributes substantially to tumor growth, invasion and progression are cancer-associated fibroblasts (CAF) in stroma of the tumor. These CAF, originating from various sources depending on type of tumor, induce angiogenesis through the production of growth factors and components of the ECM (Orimo and Weinberg, 2006). Recently, it has become clear that CAF in peritoneal metastases are derived from mesothelial cells through MMT. The transformed mesothelial cells stimulate tumor progression through remodeling of the ECM and produce vascular endothelial growth factor (VEGF) to stimulate angiogenesis (Sandoval et al., 2013; Rynne-Vidal et al., 2015). Furthermore, several studies suggest that MMT also enhances integrin-dependent adhesion and thus amplifies progression of peritoneal carcinomatosis (Sandoval et al., 2013; Chen et al., 2015; Jiang et al., 2013).

In conclusion, compelling evidence suggests that integrins, but also other adhesion molecules, are involved in cancer cell adhesion to the peritoneum. In addition, the mesothelial cells acquire a fibroblastic phenotype that contributes to tumor progression. Further insights into the mechanism of cancer cell adhesion to the peritoneum and the effects of MMT on tumor progression may generate new hypotheses for treatment of peritoneal carcinomatosis. Clearly, translational studies are needed to address these questions.

4.6. Mesothelioma

A rare malignancy that can be found on the pleural or peritoneal membranes, is malignant mesothelioma. Peritoneal malignant mesothelioma arises from mesothelial cells of the peritoneum. Three types of mesothelioma tumors are distinguished: the epithelial, mesenchymal and mixed type, reflecting the multipotent character of mesothelial cells. The presence of malignant mesothelioma in the peritoneal cavity is rare. Generally, the macroscopical appearance of peritoneal mesothelioma is similar to that of peritoneal carcinomatosis of EOC, and is characterized by multiple miliary tumor depositions localized on the peritoneum. This aggressive disease strongly correlates with a history of asbestos exposure. Studies on peritoneal mesothelioma are scarce since 93–95% of the mesotheliomas arise in the pleural cavity (Soeberg et al., 2016a, 2016b). After exposure to asbestos, fiber depositions can provoke breaks in DNA strands and induce the release of free radicals including reactive oxygen and nitrogen species by mesothelial cells (Walker et al., 1992). Due to disruption of the mesothelial cell layer, chemokines and growth factors including IL-1α, IL-1β, IL-6, TNF-α, TGF-β, VEGF and platelet-derived growth factor (PDGF) are recruited to enhance proliferation of the mesothelial cells (Izzi et al., 2012; Mossman et al., 2013). A chronic inflammatory response is generated, which further stimulates carcinogenesis of mesothelial cells (Mossman et al., 2013). In summary, the ongoing inflammation, the production of free radicals and the activated immune system can enhance the development of malignant mesotheliomas.

4.7. Endometriosis

Apart from malignant cell growth, the peritoneum can be involved in growth of benign ectopic cells. Endometriosis is a condition that is characterized by endometrial tissue deposition outside the endometrium and myometrium, often involving the pelvic peritoneal surfaces. Generally, endometrial lesions consist of endometrial epithelium, stroma cells, blood vessels and lymphocytes. The exact mechanisms of the development of peritoneal endometriosis are unclear, but 2 hypotheses have been proposed: 1) metastases of endometrial tissue *via* retrograde menses through the fallopian tubes to the peritoneum, or 2) coelomic metaplasia of peritoneal cells (Young et al., 2013). With regard to the metastatic theory, immune cells and their mediators play a crucial role in the establishment of endometriosis. An impaired natural killer (NK)-cell activity has been demonstrated in patients with endometriosis, possibly reducing detection and effective removal of ectopic endometrial tissue (Quaranta et al., 2006). In addition, a reduced T-lymphocyte-mediated immune response to ectopic endometrial cells was observed in patients with endometriosis and the degree of cellular immune failure correlated with the extent of the disease (Steele et al., 1984). These studies suggests that immune responses and the escape from immune surveillance play an important role in the establishment of endometriosis.

Similar to peritoneal carcinomatosis, several adhesion molecules expressed by mesothelial cells such as integrins, cadherins, VCAM-I and ICAM-I, facilitate attachment of endometrial tissue (Chen et al., 2002; Gullberg et al., 1992; Witz et al., 2000; Zeillemaker et al., 1996; Kyama et al., 2008a,b). Possibly, changes of the mesothelial cell morphology after MMT enable further invasion of adhered endometrial tissue (Demir et al., 2004; Dunselman et al., 2001). To promote cell proliferation, endometrial cell adhesion and angiogenesis, an inflammatory response is provoked with recruitment of macrophages (Tran et al., 2009; Lin et al., 2006), as reflected by an increase of macrophage-released cytokines such as IL-1β, IL-6, TNF-α (Kyama et al., 2008a,b, 2006; Vigano et al., 1998; Song et al., 2003; Sikora et al., 2016). Furthermore, production of several growth factors including TGF-β and HGF (Kyama et al., 2006) by mesothelial cells is significantly increased and contributes together with the pro-inflammatory cytokines to cell proliferation and neovascularization (Kyama et al., 2006). In summary, peritoneal endometriosis has been thoroughly investigated, although most research so far was focused on the characteristics of endometrial tissue, instead of peritoneal characteristics and cellular adaptions. There is increasing evidence showing an important role of the immune response of the peritoneum in the development of endometrial lesions.

5. Concluding remarks

Over the past decades, functions of the peritoneum and its characteristics have been elucidated, but many questions remain. The peritoneum is a large serous organ, in appearance only a thin, elastic structure, that is in fact a complex organ with a number of functions able to respond to changes in (patho)physiological circumstances. The peritoneum is highly specialized in the regulation of homeostasis, prevention or initiation of inflammatory responses, fibrin formation and degradation. In order to develop new therapeutic regimens for peritoneal carcinomatosis, fundamental understanding of the peritoneal functioning including embryonic development, anatomy, histology and physiology is of great importance. Our review presents a clear overview of the peritoneum, including its anatomy, immune responses and cancer cell adhesion. During the development of peritoneal diseases such as peritoneal carcinomatosis, malignant mesothelioma and endometriosis, the peritoneal cells adapt their responses to various stimuli involving production of specific adhesion factors to provide attachment of ectopic cells, MMT to acquire a mesenchymal phenotype, escape from immune surveillance by ectopic cells, and by triggering an inflammatory response. This fundamental knowledge of the peritoneum may help to develop new hypotheses with respect to therapies for peritoneal diseases that could interfere with these processes, for example, new immune therapy-based treatments for peritoneal metastases, but also to resolve questions regarding the preferred location of peritoneal metastases on the peritoneum, its restricted growth and depth of invasiveness. Therefore, our review of the literature may help to inspire new research and allow for the development of novel therapies.

Conflict of interest

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