Seminars in Cell and Developmental Biology 92 (2019) 27–36

Contents lists available at ScienceDirect

Seminars in Cell & Developmental Biology

journal homepage: www.elsevier.com/locate/semcdb

Review

Embryology, anatomy, physiology and pathophysiology of the peritoneum and the peritoneal vasculature

Arnoud W. Kastelein[a,*], Laura M.C. Vos[a], Kees H. de Jong[b], Juliette O.A.M. van Baal[c], Rienk Nieuwland[d], Cornelis J.F. van Noorden[b,e], Jan-Paul W.R. Roovers[a], Christianne A.R. Lok[c]

[a] Amsterdam UMC, University of Amsterdam, Dept. of Obstetrics and Gynecology, Academic Medical Center, Meibergdreef 9, 1105 AZ Amsterdam, the Netherlands
[b] Amsterdam UMC, University of Amsterdam, Dept. of Medical Biology, Cancer Center Amsterdam, Academic Medical Center, Meibergdreef 9, 1105 AZ Amsterdam, the Netherlands
[c] Dept. of Gynecologic Oncology, Center for Gynecologic Oncology Amsterdam, The Netherlands Cancer Institute/Antoni van Leeuwenhoek Hospital, Plesmanlaan 121, 1066 CX Amsterdam, the Netherlands
[d] Amsterdam UMC, University of Amsterdam, Laboratory of Experimental Clinical Chemistry and Vesicle Observation Centre, Academic Medical Center, Meibergdreef 9, 1105 AZ Amsterdam, the Netherlands
[e] Department of Genetic Toxicology and Cancer Biology, National Institute of Biology, Ljubljana, Slovenia

HIGHLIGHTS

- The peritoneum is an extensive serous membrane with both epithelial and mesenchymal features, essential for maintaining an intra-abdominal homeostatic equilibrium.
- The peritoneum covers the abdominal walls and all intra-abdominal structures, with exception of the bare area of the liver. Comprehension of the anatomy of the peritoneum and its reflections is essential for surgeons performing intra-abdominal surgery.
- The peritoneum and the peritoneal vasculature play a central role in many intra-abdominal conditions such as peritoneal adhesions, the production of ascites and peritoneal carcinomatosis.
- The peritoneal microcirculation is located in submesothelial stroma and is characterized by a relatively low vessel density, but this may alter under pathological conditions.
- Understanding of the interaction between cancer cells, the peritoneum and the peritoneal vasculature is crucial for the development of new treatment strategies for peritoneal carcinomatosis.

ARTICLE INFO

Keywords:
Anatomy
Embryology
Microcirculation
Peritoneum
Physiology
Vasculature

ABSTRACT

The peritoneum is a large serous membrane with both epithelial and mesenchymal features, and is essential for maintaining an intra-abdominal homeostatic equilibrium. The peritoneum plays a central role in the pathogenesis of a number of disorders. Pathological processes affecting the peritoneum such as inflammation and carcinomatosis can have serious clinical consequences, but the pathophysiology of these conditions is poorly understood. Understanding peritoneal embryology, anatomy and physiology is crucial to comprehend pathophysiological mechanisms and to devise a new focus for research. The vascular response to pathological processes appears to be of considerable importance, since the peritoneal vasculature plays a pivotal role in most associated diseases. Therefore, this review summarizes currently available literature with special emphasis on the development, anatomy and function of the peritoneal vasculature. Pathological processes are described to illustrate physiological and pathophysiological characteristics of the peritoneum.

* Corresponding author.
E-mail addresses: a.w.kastelein@amc.uva.nl (A.W. Kastelein), l.m.vos@amc.uva.nl (L.M.C. Vos), k.h.dejong@amc.uva.nl (K.H. de Jong), j.v.baal@nki.nl (J.O.A.M. van Baal), r.nieuwland@amc.uva.nl (R. Nieuwland), c.j.vannoorden@amc.uva.nl (C.J.F. van Noorden), j.p.roovers@amc.uva.nl (J.-P.W.R. Roovers), c.lok@nki.nl (C.A.R. Lok).

https://doi.org/10.1016/j.semcdb.2018.09.007
Received 4 March 2018; Received in revised form 29 August 2018; Accepted 18 September 2018
Available online 09 October 2018
1084-9521/

1. Introduction

The peritoneum is a large serous membrane, essential for maintaining an intra-abdominal homeostatic equilibrium. Peritoneal structure and function can be affected by the following pathological processes: 1) adhesion formation as a consequence of surgical trauma, inflammation (peritonitis) or endometriosis, which in turn complicates surgical interventions and can lead to abdominal symptoms and female infertility; 2) fibrosis due to inflammation or long-term peritoneal dialysis and that can decrease the peritoneal diffusion capacity; 3) gynecologic or gastro-intestinal malignancies that can cause peritoneal carcinomatosis, which in turn can lead to ascites and impaired bowel function. However, the pathophysiology of the above-mentioned processes is not well understood. Despite extensive research and proposed interventions, peritoneal adhesions and fibrosis cannot be adequately prevented or treated. Additionally, peritoneal susceptibility for metastases in patients with cancer is still an enigma, and the behavior of carcinoma cells on the peritoneal membrane remains largely unexplained. This stresses the need for new insights into peritoneal physiology and pathophysiology. In turn these may guide research and development of new treatment strategies. Understanding basic principles is a necessary first step. We previously reviewed the literature on the histophysiology and pathophysiology of the peritoneum [1]. However, current knowledge on the peritoneal vasculature has not previously been reviewed, even though the vascular response to peritoneal pathology seems of considerable clinical importance. Therefore, this review summarizes currently available literature with special emphasis on the development, anatomy and function of the peritoneal vasculature.

2. Embryology

2.1. Embryology of the peritoneum

Embryonic development of the peritoneum starts during the gastrulation stage, at which point a 3-layered disc is formed and a layer of endoderm, ectoderm and mesoderm emerge [1–4]. The mesodermal layer consists of cells that have an irregular shape with large intercellular spaces and no recognizable extracellular matrix. Around Carnegie Stage (CS) 9 (25 days development), mesodermal cells start to transform into cubically shaped cells. This causes the intercellular spaces to merge and form larger cavities. These cavities, the so-called coelomic vesicles, eventually consolidate to one coelomic cavity, lined with a layer of cuboidal mesodermal cells. The caudal part of the coelomic cavity will give rise to the peritoneal cavity, and the layer of mesodermal cells will form the peritoneal membrane (Fig. 1) [5,6].

In later stages of the embryonic development, the shape of the embryo changes from a 2-dimensional embryonic disc to a 3-dimensional embryo (CS 10, 28 days development). In the cranial part of the embryonic coelomic cavity, the primitive pericardial region is formed first. From here, two extensions develop in a caudal direction: the pericardioperitoneal canals (Fig. 1). These expanding canals connect to the extraembryonic coelomic cavity (chorionic cavity). In this process, part of this extraembryonic coelom is incorporated in the embryo. This will form the future peritoneal cavity below the umbilicus [5,6] (Fig. 2).

The embryonic peritoneal cavity is separated from the pleural cavity by the formation of pleuroperitoneal membranes halfway along the pericardioperitoneal canals. These membranes are the cranial parts of the urogenital ridges. They do not contribute to the urogenital organs, but instead form part of the adult diaphragm. Once the peritoneal cavity is separated from the pleural cavity, a right and left cavity is present above the level of the umbilicus (which has developed from the pericardioperitoneal canals) and an undivided cavity is present below the level of the umbilicus (which has developed from the extraembryonic coelom) [5,6].

The peritoneal cavity is empty, but the embryonic gut protrudes in it. Mesodermal cells that line the protruding embryonic gut will form the future visceral peritoneum, and mesodermal cells that line the body wall and the septum transversum will form the future parietal peritoneum. Cells in the transition zone between visceral and parietal peritoneum (which become peritoneal 'reflections' in the adult) are "aggressive" towards their microenvironment, digesting underlying mesodermal cells. Therefore, the coelomic cavity has the ability to enlarge at the expense of non-differentiated sub-coelomic tissue. In this way, the liver (which will form in the septum transversum) is separated from the diaphragm, the foregut (i.e. esophagus, stomach and proximal duodenum) and the ventral body wall. Only the falciform ligament, the bare area of the liver (area nuda hepatis) with the surrounding coronary ligament and the lesser omentum persist. In the adult human, remnants of the septum transversum occur in these structures anterior to the embryonic foregut and below the embryonic pericardial cavity. The fact that the liver originates from the septum transversum explains why the future peritoneum covering the liver is derived from the embryologic parietal peritoneum instead of the visceral peritoneum (which covers most other abdominal organs) [5,6].

In the dorsal body wall, two genital ridges develop from the mesonephros. The mesonephros is initially situated retroperitoneally and therefore covered with parietal peritoneum. Consequently, when the mesonephros proliferates and differentiates into ovaries or testes, these organs are covered with parietal peritoneum as well. The left and right genital ridges form a V-shape in the dorsal body wall, meeting in the midline at the caudal boundary of the peritoneal cavity. The peritoneal cavity enlarges in a caudal direction, and the caudal ends of the two genital ridges enlarge in a cranial direction, and move from a subperitoneal to an intraperitoneal position. As the caudal end of the genital ridges contains the fused genital ridges (which will from two Fallopian tubes, the uterus and the cranial part of the vagina in women) the latter moves in a similar manner. Consequently, these structures are covered with peritoneum of parietal origin [5,6].

The sensory innervation of the peritoneum is derived from migrating neural crest cells. An important difference in the number and type of sensory nerve receptors arises between parietal and visceral peritoneum. Precisely when receptor differentiation occurs and whether this is preceded by an embryologic event, is not clear yet [5,6]. Anatomical differences and nerve trajectories are discussed in more detail in paragraph 3.3.

2.2. Development of the (peritoneal) vasculature

The vascular system starts to develop when gastrulation is completed. Mesodermal cells differentiate into hemangioblasts in embryonic and extraembryonic mesoderm. The latter overlies the outer surface of the ectoderm (of the amniotic cavity) and endoderm of the yolk sac. At CS 6 (embryonic day 13 to 15), these cells form small clusters in a process known as blood island formation (Fig. 3). Around embryonic day 16, cells in the blood islands further differentiate into angioblasts (which will differentiate into endothelial cells) and hematopoietic precursors (which will differentiate into blood cells). Blood islands fuse and create a primitive vascular network of primordial blood vessels. The formation of endothelial cells from mesodermal cell precursors is defined as vasculogenesis [7–10] (Fig. 3).

From embryonic day 18 onwards, new blood vessels arise from vessels initially formed by vasculogenesis. When capillaries arise from pre-existing vessels, the process is called sprouting angiogenesis. During 'intussusceptive angiogenesis' an intussusceptive cylindrical tissue pillar is formed within an existing vessel, thus splitting the lumen of that vessel into two vessels. This form of angiogenesis is not well understood, partly because (and in contrast with sprouting angiogenesis) it is an intravascular process which cannot be visualized by light microscopy [11]. Intussusceptive angiogenesis can radically alter the structure of the microvasculature. During 'bridging angiogenesis', endothelial cells form bridges between capillary walls, thus creating two

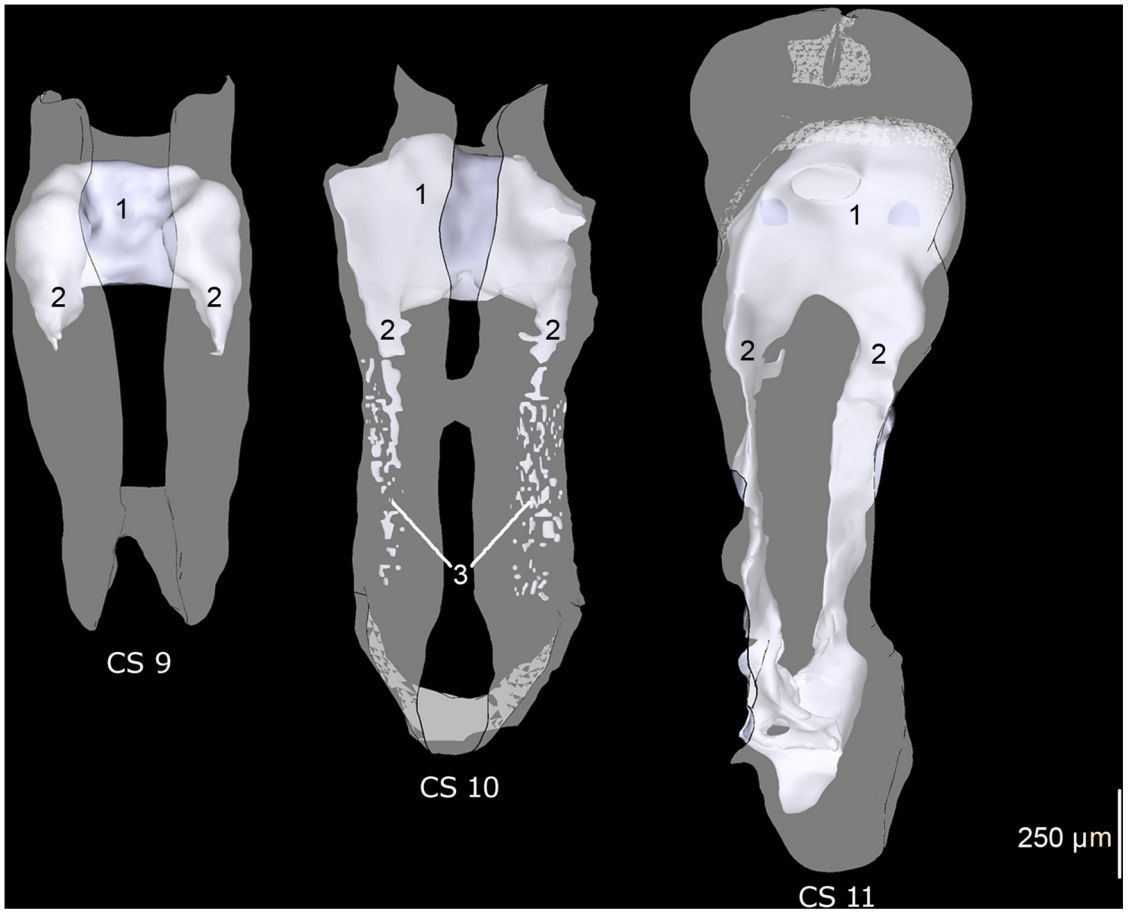

Fig. 1. Ventral view of reconstructions of human embryos. The coelom is reconstructed in white, the embryo is transparent. 1: pericardial cavity, 2: pericardio-peritoneal canals, 3: coelomic vesicles. From https://www.3dembryoatlas.com/ with permission of Bernadette de Bakker, Amsterdam UMC.

or more capillaries from one vessel (Fig. 3). Angiogenesis is responsible for the formation of the majority of the embryonic blood vessels and for vascularization of organs of endoderm and ectoderm origin [12–14].

Vasculogenesis is regulated by various growth factors. Fibroblast growth factors induce differentiation of mesodermal cells into hemangioblasts and signaling through Hedgehog ligands and their receptors is considered crucial for blood island formation [15]. Transforming growth factor-β (TGFβ) plays a critical role in vasculogenesis as well [15,16]. Three TGFβ ligands have been identified (TGFβ1, TGFβ2 and TGFβ3) that can bind to receptors on endothelial cells (type 1 receptor TGFβRII and type 2 receptors Alk1 and Alk5) [15,17]. When TGFβ signaling is altered, for example because of deletion of a ligand or receptor, this results in embryo lethality due to defective vasculogenesis in the yolk sac [18].

Vascular endothelial growth factor (VEGF) is a signaling protein that is essential in vasculogenesis and angiogenesis. The VEGF family consists of 6 members (VEGF-A, VEGF-B, VEGF-C, VEGF-D, VEGF-E and placental growth factor), of which VEGF-A is the most potent

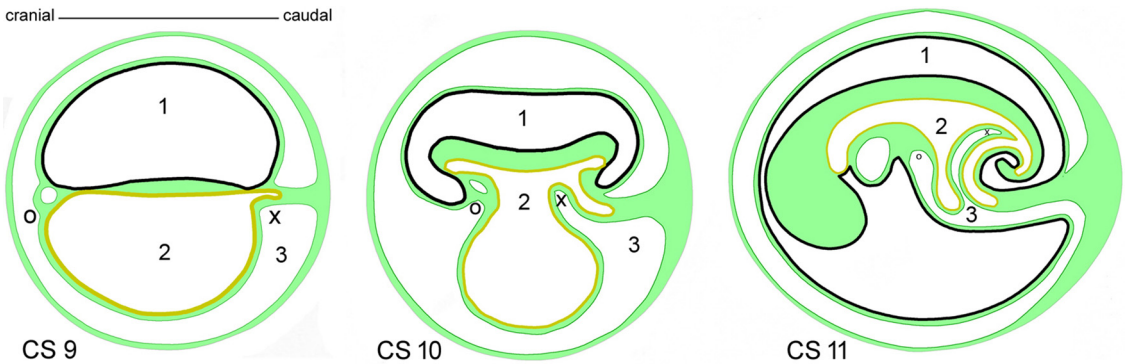

Fig. 2. Schematic drawing of a mid-sagittal section through a human embryo. 1: amniotic cavity, 2: yolk sac/gut, 3: coelom, o and x: parts of the extra-embryonic coelom that, due to the folding of the embryonic disc, become situated in the embryo as part of the embryonic coelom.
ectoderm
mesoderm
mesothelium coelomic cavity
endodermal lining yolksac and gut

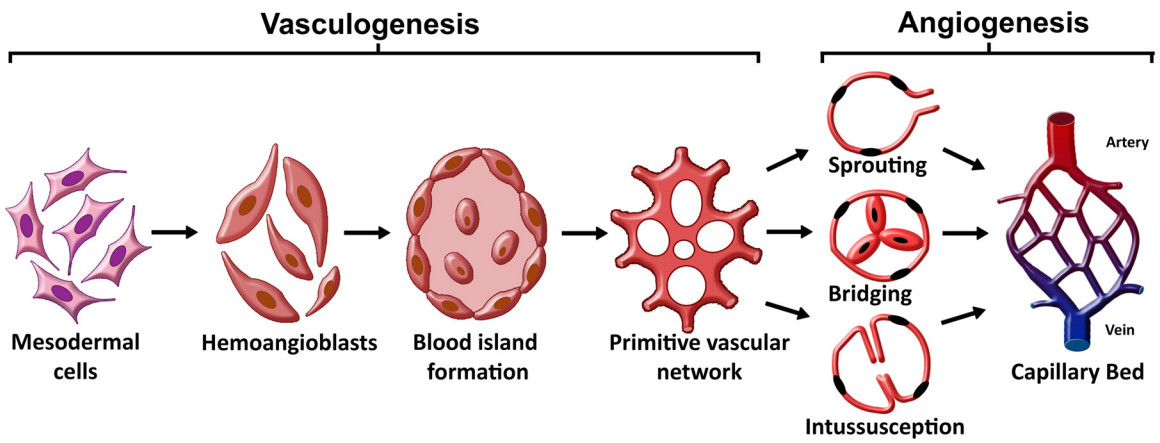

Fig. 3. Schematic drawing of the development of the vascular system within the mesoderm.

angiogenic factor. Three VEGF receptors have been identified, namely VEGFR1, VEGFR2 and VEGFR3 [14]. Signaling through VEGFR2 is considered the most important initiator of sprouting angiogenesis [19]. Knocking out of a VEGF receptor in mice results in lethal vascular defects during embryonic development. Deletion of a single VEGF allele results in lethal blood vessel formation defects [20].

Other signaling pathways are also involved in angiogenesis. For example, neuropilins act as co-receptors for VEGF-A and can bind VEGF ligands [21,22]. Notch receptors and ligands regulate proliferation and differentiation of endothelial cells [23]. Tie receptors in conjunction with angiopoietin ligands, regulate angiogenesis and vessel maturation [24].

In the dorsal mesentery, endothelial cells develop into dorsal-ventral cords during gut rotation. These cords become the major arteries supplying the midgut. To avoid strangulation of these vessels, vascular development is adapted to gut-rotation. Hence, formation of dorsal-ventral cords occurs solely in the left side of the dorsal mesentery. Asymmetrical development of the vasculature is regulated by the transcription factor pituitary homeobox 2 (Pitx2) [25].

3. Anatomy

3.1. General anatomy

The peritoneum has a surface area of approximately 1.8 m^2 [26]. Parietal peritoneum lines the abdomino-pelvic cavity whereas visceral peritoneum covers most visceral organs. As a consequence, the abdominal walls and all intra-abdominal structures are covered with peritoneum, with exception of the bare area of the liver. Most caudally in the abdomino-pelvic cavity, the peritoneum covers the dome of the bladder and the anterior rectal surface. Hence, the bladder and rectum are located 'under' the peritoneum, in the subperitoneal space. The uterus and uterine tubes are situated between rectum and bladder. These organs are initially situated in the sub- and retroperitoneal spaces, covered with parietal peritoneum. As these organs develop, they will protrude into the intra-abdominal cavity and are therefore covered for a large part by parietal peritoneum [27,28]. The double layers of peritoneum on the lateral sides of the uterus are identified as the broad ligament (consisting of mesometrium), the mesosalpinx and the mesovarium [29].

The uterus, Fallopian tubes and ovaries are covered with parietal peritoneum. The peritoneum covering the ovaries is also known as ovarian surface epithelium. This epithelium is continuous with the parietal peritoneum that covers the fallopian tubes, but has different properties [1]. The peritoneum is discontinuous at the fimbrial openings. Consequently, in women, there is a connection between the peritoneal cavity and the outer world, allowing transport of an oocyte from the peritoneal cavity, through the fallopian tubes to the uterus after ovulation. In contrast, the male reproductive organs are situated outside the peritoneal cavity. Therefore, in men the peritoneal cavity is a completely closed sac, continuously covered by peritoneum [27,28].

Several virtual spaces can be distinguished between the pelvic organs. Males exhibit a recto-vesical pouch situated between the rectum and bladder. In women, the uterus divides this space into the vesico-uterine and recto-uterine pouch (or Douglas' pouch). In an upright position, the recto-vesical and recto-uterine pouches are the lowest parts of the peritoneal cavity [28]. Consequently, intra-abdominal fluid, e.g. peritoneal fluid, ascites, and blood, tends to accumulate here. Therefore, this region requires special clinical attention, for instance, when imaging the abdominal cavity [30,31].

A series of peritoneal 'folds' are situated at the anterior abdominal wall, below the umbilicus, where the peritoneum is reflected over (obliterated) structures. The median fold is formed by the obliterated urachus, the medial folds are formed by the obliterated umbilical arteries and the lateral folds overlie the inferior epigastric vessels.

The peritoneum also covers the intestines and contributes to the mesentery. The mesentery consists of connective tissue, adipocytes, the intestinal vasculature, lymphatics and two layers of mesenteric peritoneum, which are a further region of the visceral peritoneum [32]. The mesentery suspends the intestines and is characterized by a 'root', where the parietal peritoneal lining of the abdominal wall detaches, and where the celiac trunk branches and the superior and inferior mesenteric arteries enter the mesentery. The small intestinal mesentery, the transverse mesocolon and lateral mesosigmoid are mobile, whereas the left and right mesocolon and the medial mesosigmoid are flattened against the posterior abdominal wall [32].

The mesentery of the small intestine and colon have been considered separate entities, with the right and left mesocolon being 'fused' with the underlying retroperitoneum. However, between the right and left mesocolon and the underlying retroperitoneum, a separating layer of connective tissue (also known as Toldt's fascia) can be identified. This means that the mesentery is in fact continuous, from duodenum to rectum [32,33].

The transition zone between the visceral and parietal peritoneum is also termed 'peritoneal reflection'. In regards to the mesentery, the peritoneal reflection is important for colorectal surgeons, because dissection provides access to surgical planes, for example when detaching the mesentery during mesocolic or mesorectal surgery [33]. Toldt's fascia is also continuous, but has different names at different anatomic locations [32]. In the pelvis, surgeons know this fascia as the 'holy plane' of rectal surgery.

Superior to the mesenteric root, the peritoneum contributes to the greater omentum and forms the anterior layer of the lesser omentum.

The peritoneum almost covers the entire liver, except for the bare

area of the liver (area nuda hepatis), where the liver is attached directly to the diaphragm. The peritoneum around the bare area forms the coronary ligament, and the peritoneum around the obliterated umbilical vein (ligamentum teres hepatis) forms the falciform ligament, which is the most anterior remnant of the septum transversum, that forms the embryonic ventral mesentery. Finally, the peritoneum lines the lesser sac and contributes to the lieno-renal and gastro-splenic ligaments and covers the posterior wall of the stomach, where it folds into the greater omentum and continues posteriorly towards the posterior abdominal wall [27,28]. The described ligaments are mostly located where the peritoneum is reflected and changes from parietal to visceral peritoneum. In this sense, these ligaments can be considered as a transition zone between the two different types of peritoneum.

3.2. Microscopic anatomy

The peritoneum is often defined in literature as a 3-layer structure: a mesothelial cell layer, a basal lamina and submesothelial stroma [1,34]. In contrast, the peritoneum is sometimes defined as a single layer of mesothelial cells. According to the latter definition, the basal lamina and submesothelial stroma are not considered to be part of the peritoneum [27,35]. In the present review, the first definition is used because of the important role of the basal lamina and structures such as blood and lymphatic vessels in the submesothelial stroma in physiological and pathological processes.

3.2.1. Mesothelium

The mesothelial layer is the innermost layer of the peritoneum, and is in contact with the abdominal cavity. Mesothelial cells are mesodermal in origin and possess both epithelial and mesenchymal features. Three types of mesothelial cells have been described [36–38]. Flattened mesothelial cells are characteristic of the intestinal, omental and parietal mesothelia. A cuboidal cell type occurs in visceral peritoneum whilst the diaphragm and gastric peritoneum have an intermediate mesothelial cell type [34]. Morphologic heterogeneity suggests there are functional differences between mesothelial cells at different anatomical locations. Cuboidal cells contain more mitochondria and endoplasmic recticulum, a well-developed Golgi apparatus, microtubules and a greater number of microfilaments, suggesting increased metabolic activity in these cells [39].

Mesothelial cells are linked by intercellular junctions, including tight junctions, gap junctions and desmosomes (Fig. 4) [1,40–42]. At the junction of two or more mesothelial cells, stomatal openings may be present. These openings are 3–12 μm in diameter and provide direct access to the submesothelial lymphatic system, allowing rapid transportation of fluid [1,43–46]. It is suggested that stomata provide a gateway between pleural and peritoneal cavities [46]. Lymphatic stomata are extensively present in the mesothelium, but the distribution of stomata has not been characterized for all mesothelial regions (e.g. for different regions of the mesentery) [43].

At the apical mesothelial cell membrane, numerous microvilli are present [46,47]. On top of these microvilli, a glycocalyx is present, which creates a stagnant fluid layer consisting of proteoglycans and glycosaminoglycans to promote lubrication [39]. This glycocalyx has an anti-inflammatory function and plays an important role in intercellular contacts, tissue remodeling and possibly transport of growth factors and nutrients across the peritoneal membrane [46,48].

Mesothelial cells contain a number of intracellular vesicles with secretory products. These vesicles can be excreted as exosomes at the apical cell membrane [49]. The exact function of mesothelium-derived exosomes is unknown, but they may play a role in intercellular communication [50]. Mesothelial cells also contain lamellar bodies. These organelles have a lipid storage function [34]. In fact, the main function of lamellar bodies is to supply lipid components to the apical membrane [51]. Lamellar bodies in general were first identified in type 2 pneumocytes. In these cells, lamellar bodies store alveolar surfactant. In mesothelial cells, lamellar bodies produce a similar surfactant-like substance, that helps to provide a friction-free peritoneal surface [52,53]. Besides lubrication, surfactant proteins may also have immunological functions [1].

A recent study has suggested that mesothelial cells are also a potential source of adipocytes. The authors demonstrated that visceral fat depots (which are associated with metabolic dysfunction) have a layer of mesothelial cells, that can differentiate into adipocytes [54].

3.2.2. Basal lamina

The basal lamina supports mesothelial cells. It is less than 100 nm thick and consists of an extracellular matrix, mainly composed of collagen type IV and laminin [1]. The collagen type IV fiber network acts as a skeleton of the basal lamina, whereas laminin provides binding sites for adhesion of mesothelial cells via hemi-desmosomes [55]. Binding of mesothelial cells to the basal lamina is not strong, explaining why minor injuries can result in cellular detachment [56].

3.2.3. Submesothelial stroma

Stroma underneath mesothelial cells and basal lamina provides support to the mesothelial cell layer. This layer consists of collagen type I fibers, laminin, fibronectin, proteoglycans, glycosaminoglycans, fibroblasts, adipocytes, blood and lymph vessels and nerves [57]. The thickness and composition of submesothelial stroma varies with age [58] and can change in response to disease [59]. Within the stroma, a continuous layer of elastic fibers is present as elastic lamina [60]. Knowledge of its function is limited, but a relation has been described between the thickness of the elastic lamina and motility of the organ the peritoneum covers [60]. Organs with peristaltic movements are covered by peritoneum with a more prominent elastic lamina, whereas the elastic lamina is thinner in static organs. In some organs, such as the omentum and bladder, the elastic lamina is absent, although it is not clear whether this holds for both lesser and greater omentum.

The submesothelial stroma can also be described as ‘interstitium’. A recent study has suggested that the interstitium consists of macroscopically visible spaces within tissues through which interstitial fluid flows [61]. These authors consider the submesothelial layer of the mesentery an interstitium, that functionally communicates with the lymphatic drainage of the gastrointestinal tract. Another study also demonstrated that the submesothelial stroma of the mesentery is connected to the intestinal serosa, which means that intestinal and mesenteric connective tissues are continuous [32]. These findings are of clinical importance, for example in inflammatory bowel disease or with respect to the spread of cancer cells.

In the mesentery, adipose tissue in the submesothelial layer has been identified as a source of C-reactive protein (CRP). This protein is widely used as marker for inflammation and previously was considered as exclusively produced by the liver. However, emerging data suggests that mesenteric fat tissue can also contribute to the inflammatory response by producing CRP, and that this may be relevant in patients with Crohn’s Disease [61].

3.3. Anatomy of the peritoneal (micro)vasculature, lymphatics and nerves

3.3.1. Microvascular anatomy

The blood supply of the parietal peritoneum is provided by arteries of the abdominal wall and by parietal pelvic arteries. In contrast, blood flow to the visceral peritoneum comes from mesenteric, coeliac and visceral pelvic arteries. Venous blood from the visceral peritoneum drains into the portal vein, whereas vessels of the parietal peritoneum drain into the inferior vena cava [62].

The peritoneal microcirculation is located in submesothelial stroma and comprises arterioles, venules and capillaries. The morphology of these vessel types differs: arterioles have a round lumen of 20–130 μm, whereas the lumen of venules is often not round and can be larger than that of arterioles. Capillaries located between arterioles and venules

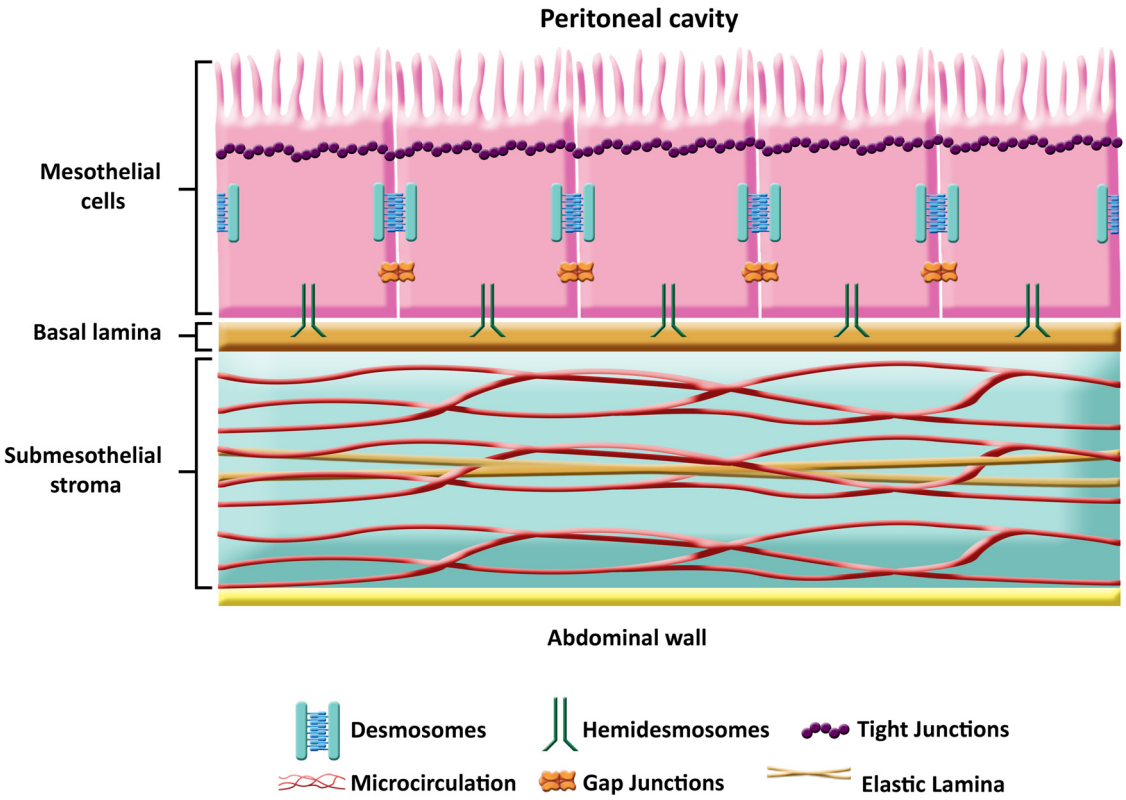

Fig. 4. Schematic representation of the peritoneum.

have a diameter of 5–10 μm [63,64]. The walls of arterioles and venules consist of several layers. From lumen to adventitia, the following layers can be identified: endothelium, tunica elastica interna, tunica media, tunica elastica externa and tunica adventitia. The thickness of the tunica media differs between arterioles (thick) and venules (thin). The wall of a capillary is morphologically different from that of arterioles and venules and consists of a single endothelial cell layer, on top of which pericytes are located [63,64]. Pericytes are morphologically heterogenous cells that play a key role in blood flow regulation and endothelial proliferation [65]. Trans-sectional imaging of the peritoneal submesothelial stroma demonstrates that vascular networks are situated in three horizontal planes [58] (Fig. 4).

Arterioles and venules are transport vessels, which means that no exchange of substances between these vessels and surrounding tissues occurs [63]. Exchange of substances occurs in capillaries. In the capillary bed, hormones, gases (like oxygen and carbon dioxide), immune cells, nutrients, water and waste products are exchanged between the capillary lumen and surrounding tissue [66].

The solute and water transport capacity of the peritoneum depends on the capillary density (the spatial arrangement of capillaries) and perfusion of these [67]. The peritoneal microcirculation is characterized by a relatively low vessel density [68], but this can be altered under pathological conditions. The density of peritoneal microvasculature under physiological conditions depends on age. The highest density is found in infants younger than 1 year, the lowest density is found in children 7–12 years of age, and density increases again in adults older than 18 years of age [58]. The thickness of the endothelial wall also varies with age. The endothelium is thickest in children 7–12 years of age, and thinnest in infants younger than 1 year and adults older than 18 years of age [58]. It is hypothesized that the reduced capillary density in childhood is caused by stretching of the growing peritoneal surface, in which angiogenesis cannot keep up with the rapid expansion of the peritoneal surface [58]. With regard to the mesenteric peritoneum, Culligan et al. have described that certain submesothelial areas of the mesocolon are highly vascularized [69].

3.3.2. *Lymphatic anatomy*

Different pathways of fluid drainage have been described by which fluid drains from the peritoneal cavity [70,71]. Fluid can be transported across the mesothelial lining of the peritoneum (i.e. through lymphatic stomata), into the celiac, superior mesenteric, and periportal lymph node groups. Subsequently, lymphatic fluid is transported to the thoracic duct by efferent visceral lymphatics [72,73]. Fluid in the abdominal cavity can also drain via diaphragmatic lymphatic channels towards the caudal and anterior mediastinal lymph nodes [1]. These channels may explain the occurrence of isolated mediastinal lymph node metastases in patients with ovarian cancer.

3.3.3. *Nerve anatomy*

Sensory nerve fibers arising from the abdominal wall and (partially) from the parietal peritoneum reach the central nervous system (CNS) via segmental spinal nerves. The most cranial part of the parietal peritoneum (covering the diaphragm) is innervated by the phrenic nerve and its fibers connect to corresponding cervical segments C4, C5 and C6. More caudally, parietal peritoneum derives its nerve supply from thoraco-abdominal nerves, segmental spinal nerves, subcostal and lumbosacral nerves. The obturator nerve innervates parietal peritoneum in the pelvis.

Sensory nerve fibers of the intestine (and the visceral peritoneum) have a more complex route to the CNS. Depending on the location, nerve fibers reach the CNS via the superior celiac and mesenteric plexus as well as via vagus and splanchnic nerves [74,75]. The sensory innervation of the viscera is derived from neural crest cells and consists mostly of small, thinly myelinated or unmyelinated afferents that appear in a mesh-like complex [76]. The majority of mesenteric afferents are located near or on blood vessels [77]. An important difference between parietal and visceral peritoneum is the amount and type of sensory nerve receptors. In the parietal peritoneum, pain receptors,

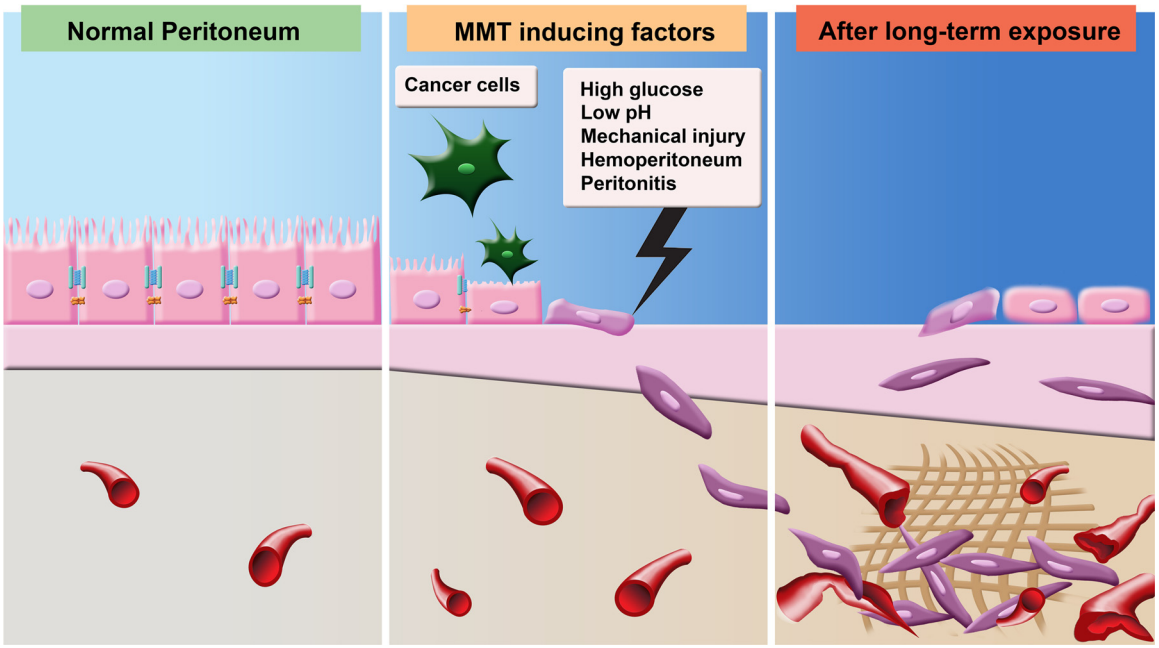

Fig. 5. Schematic representation of a cross-section of the peritoneum showing mesothelial-to-mesenchymal transition (MMT) as a consequence of cancer or, for example, long-term peritoneal dialysis.

stretch receptors and temperature receptors are found. These receptors have a relative low threshold and are therefore very sensitive to pressure, pain, temperature and laceration. In the visceral peritoneum only stretch receptors are present. The visceral peritoneum is insensitive to pain, but sensitive to stretch and chemical irritation [78]. These differences explain why movements in hollow organs (i.e. intestines) covered by visceral peritoneum do not cause pain, but are registered by stretch receptors.

4. Physiology and pathophysiology

4.1. Tissue repair and adhesion formation

Peritoneal injury (for example due to surgery or peritonitis) activates the coagulation cascade, which generates fibrin that is deposited on the injured peritoneal surface [79]. Fibrin deposition is part of normal tissue repair, but complete degradation of fibrin (fibrinolysis) is necessary for adequate peritoneal healing. The balance between fibrin deposition and its degradation is crucial for normal peritoneal healing.

The conversion of plasminogen into plasmin is an important step in fibrinolysis, since plasmin is highly effective in the degradation of fibrin. Mesothelial cells produce tissue-type plasminogen activator (tPA) and urokinase-type plasminogen activator (uPA), which are both plasminogen activators [80]. However, mesothelial cells also produce plasminogen-activating inhibitor (PAI), which inhibits plasminogen activation and thus prevents fibrin degradation. When fibrin is not degraded completely, the fibrin matrix forms a scaffold for collagen-secreting fibroblasts and capillary ingrowth, contributing to peritoneal adhesion formation [81]. Peritoneal adhesions can cause pelvic pain, intestinal obstruction and female infertility, and complicate abdominal surgical interventions. Despite extensive research, peritoneal adhesions still represent an important clinical challenge and as yet there is no definitive strategy to prevent their formation [82].

There are considerable inter-individual differences in susceptibility to develop peritoneal adhesions. Various factors have been identified that increase the risk of post-operative adhesion development, such as genetic polymorphisms in PAI and the interleukin-1 receptor antagonist [83]. In addition, the formation of adhesions may be affected by the levels of hypoxia that occur during or after surgery.

4.2. The role of hypoxia and angiogenesis in adhesion formation

During laparoscopic surgery, carbon dioxide is used for insufflation of the peritoneal cavity in order to visualize intra-abdominal organs. In this way, a so-called pneumoperitoneum is established. Pneumoperitoneum may cause local tissue hypoxia due to the use of carbon dioxide and the increase in intra-abdominal pressure, compression of capillaries and decreased blood flow. Hypoxia, with attendant oxidative stress,free radical production and angiogenesis, may induce formation of peritoneal adhesions [84,85]. Free radicals are toxic to cells at higher concentrations and impair cellular functions. Free radicals can modify proteins, affect proper functioning of organelles and disturb intracellular signal transduction pathways. Induction of oxidative damage contributes to vascular dysfunction and remodelling, and can initiate and stimulate the development of adhesions [85]. Therapeutic strategies that target free radicals in preventing adhesion formation, are emerging. Pneumoperitoneum-induced adhesions were absent in mice that not expressing genes encoding for factors regulated by hypoxia, such as VEGF, hypoxia inducible factors and PAI-1 [86–90]. Moreover, *in vitro* studies demonstrate that exposure of peritoneal fibroblasts to hypoxia modulates expression of TGF-β, a major profibrotic factor [91–94]. These studies suggest that mesothelial hypoxia plays a key role in adhesion formation and that prevention of hypoxia or the use of antiangiogenic drugs may prevent or reduce peritoneal adhesion formation [95].

4.3. Peritoneal fibrosis and mesothelial-to-mesenchymal transition

Peritoneal fibrosis is often observed in patients undergoing peritoneal dialysis, and partially arises from dialysate with high glucose levels and low pH. Dialysis-induced fibrosis significantly decreases diffusion capacity, leading to failure of ultrafiltration. Peritoneal fibrosis is characterized by submesothelial thickening, vasculopathy, and autocrine proliferation [96,97].

Epithelial-to-mesenchymal transition of mesothelial cells can be triggered by factors affecting mesothelial cells, and plays a central role in peritoneal fibrosis (Fig. 5). During this so-called mesothelial-to-mesenchymal transition (MMT), mesothelial cells lose intercellular adhesions, microvilli and apical-basolateral polarity. Subsequently, they

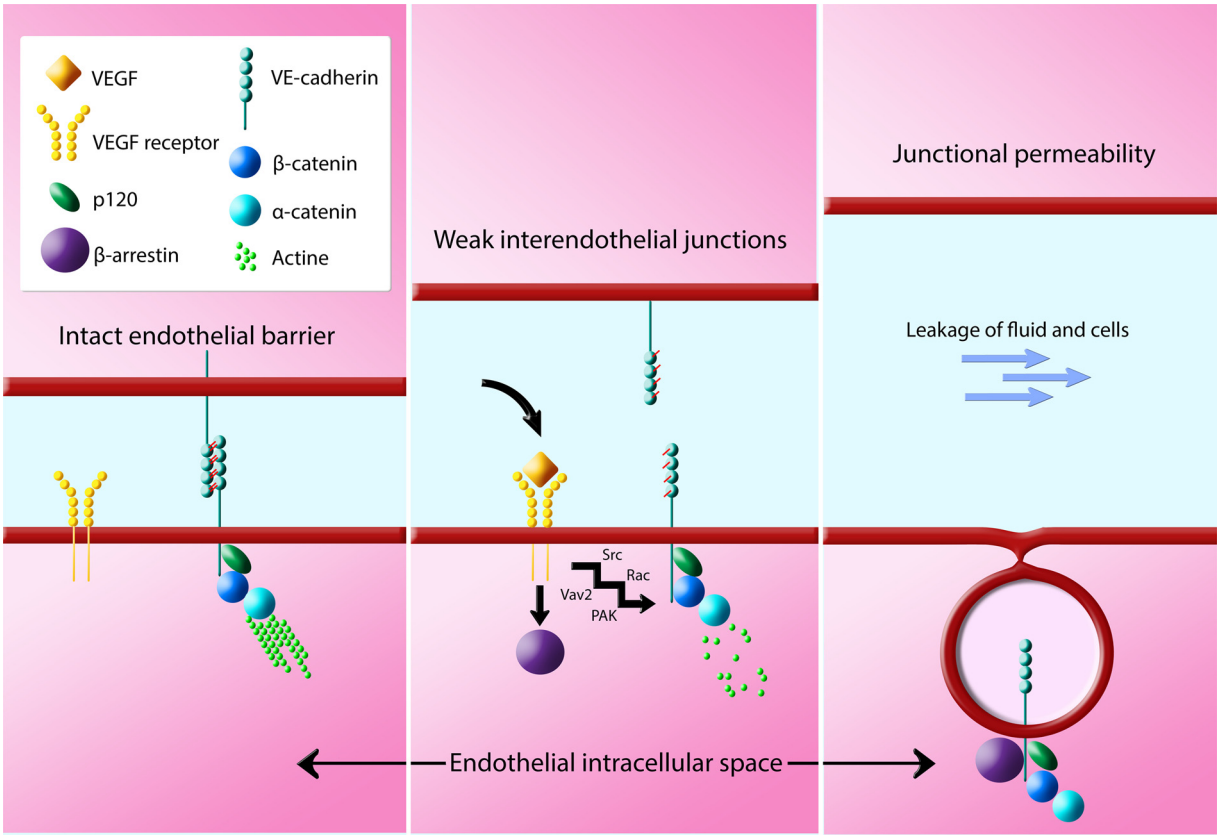

Fig. 6. Schematic representation of VEGF induced VE-cadherin endocytosis that increases vascular permeability in the peritoneum.

transform into migratory and invasive cells with a myofibroblastic phenotype [98] (Fig. 5). These express high levels of cyclooxygenase-2, connective tissue growth factor and VEGF, and induce angiogenesis. MMT is initiated by cytokines and growth factors such as TGF-β1, interleukin 1β and hepatocyte growth factor [99]. TGF-β1 has been suggested to be a key player in the induction of peritoneal fibrosis, whereas inhibition of TGF-β1 protects the peritoneum from dialysis-induced fibrosis [100].

4.4. Fluid transport across the peritoneal membrane and the formation of ascites

Under physiological conditions, the peritoneal cavity contains approximately 5–20 ml of peritoneal fluid. Peritoneal fluid is for the larger part produced by the peritoneal capillaries. From the peritoneal cavity, peritoneal fluid is transported through lymphatic stomata to the thoracic duct and back into the intravascular space. Renewal of the peritoneal fluid occurs every 1–2 hours [67]. Pathological disturbance of this equilibrium can lead to accumulation of peritoneal fluid, called ascites. Severe ascites causes abdominal distention and reduced quality of life as it impairs intestinal function, and leads to abdominal pain, anorexia and restrictive breathing. Ascites can be categorized based on the presence of high (exudate) or low levels of albumin (transudate). The amount of albumin present depends on the underlying pathophysiological process. Obstruction of the portal vein is a common cause of ascites. In this setting fluid with low levels of albumin (transudate) leaks directly from the liver surface and mesenteric vessels, through the peritoneum into the peritoneal cavity [101,102]. In addition, increased intra-abdominal pressure often decreases the absorptive capacity of the peritoneal surface and lymphatic system [102]. Other pathological conditions such as peritonitis and peritoneal carcinomatosis cause ascites without obstruction of the portal or hepatic vein. In these cases, ascites results from increased permeability of the capillary endothelium in the submesothelial layer of the peritoneum. In general, this fluid is an exudate, because albumin also leaks out of the capillaries and thus colloid osmotic pressure cannot counteract the formation of ascites [103].

4.5. Cellular signaling inducing vascular leakage in peritoneum

Increased vascular permeability can be induced by various intercellular and intracellular signaling pathways that target the endothelial barrier [104]. One of the most potent inducers of such signaling pathways is VEGF. Once VEGF binds to VEGFR2 on endothelial cells, an intracellular signaling pathway triggers β-arrestin dependent endocytosis of VE-cadherin (Fig. 6). Since VE-cadherin is a key adhesion molecule, endocytosis of VE-cadherin reduces the adhesion capacity of endothelial cells, thus increasing permeability of the capillaries [104].

Blockade of VEGFR2 in patients with peritoneal carcinomatosis can restore the endothelial barrier and prevent production of ascites. Therefore, the VEGF receptor antagonist bevacizumab, currently used in the treatment of epithelial ovarian cancer, can affect the production of ascites [105]. Alternatively, inhibition of tyrosine kinase phosphorylation of VEGFR2 decreases receptor activity, thus inhibiting VEGF-induced processes such as angiogenesis and aforementioned endocytosis of VE-cadherin. When a tyrosine kinase inhibitor is administered to mice with peritoneal implants of ovarian cancer, peritoneal dissemination and ascites formation are inhibited [106,107]. Moreover, intraperitoneal administration of monoclonal antibodies directed against VEGF receptors in mice with peritoneal carcinomatosis prevents recurrence of malignant ascites [108].

4.6. The role of the peritoneal vasculature in peritoneal carcinomatosis

Gastro-intestinal or gynecologic cancer that metastasizes intra-abdominally can cause peritoneal carcinomatosis, a condition in which

the peritoneum is affected by numerous small-sized lesions. The role of the peritoneum in metastatic tumour spread has been studied extensively. Peristaltic bowel movements and respiratory movements contribute to dissemination of peritoneal fluid in the peritoneal cavity, enabling exfoliated cancer cells to adhere to peritoneal surfaces. Ovarian cancer cells express surface integrins which can bind efficiently to components of the ECM, such as collagen, laminin, fibronectin, fibrinogen and vitronectin. Once adhesion is established, the submesothelial stroma supplies mediators enabling metastatic cancer cells survive, proliferate and invade the peritoneum. Subsequently, a tumor-supportive microenvironment is created by attraction of inflammatory and stromal cells and chemokines. However, despite this tumor-supportive environment, peritoneal metastases remain small-sized with only superficial invasion of the submesothelial stroma. Mechanisms underlying this restrictive growth and invasion are still virtually unknown, but this phenomenon points to a complex interaction between cancer cells, peritoneal cells and the microenvironment. The process of peritoneal metastasis in epithelial ovarian cancer was recently summarized by van Baal et al [4]. Few studies investigated peritoneal vasculature in the presence of cancer deposits. Increased vascularization occurs in biopsies from peritoneum surrounding tumour depositions, a finding that can be explained by the fact that angiogenesis is initiated by cancer cells and 'cancer-associated mesothelial cells' [109]. Moreover, peritoneal deposits are more frequently observed at locations with immune cell aggregates, referred to as 'milky spots'. Milky spots contain mesothelial cells that secrete VEGF and they have a high capillary density. Studies in mice demonstrated improved survival of deposits in proximity with milky spots [110,111]. Hypothetically, increased vessel density in the peritoneum is important for attachment, survival and growth of peritoneal metastases [112].

5. Concluding remarks

The peritoneum is a complex structure with a variety of functions. This review provides an overview of current knowledge of embryonic development, anatomy, physiology and pathophysiology of the peritoneal membrane with special emphasis on microvasculature. The vascular response in pathological processes such as adhesion formation, inflammation and cancer is of considerable clinical importance and remodeling of peritoneal vasculature is involved in almost all associated diseases. The exact role of peritoneum in pathological conditions requires further elucidation. In order to develop new therapeutic strategies, it is imperative that the peritoneum, its physiology and pathophysiology are studied in detail.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial or not-for-profit sectors.

Acknowledgements

We like to express our gratitude to Yasin Ince, for his creative assistance in composing the figures in this article.

References

[1] J.O. van Baal, et al., The histophysiology and pathophysiology of the peritoneum, Tissue Cell 49 (1) (2017) 95–105.
[2] T.W. Sadler, J.L. Langmans, Medical Embryology, Wolters Kluwer Health/Lippincott Williams & Wilkins, Philadelphia, 2012.
[3] H. Hesseldahl, J.F. Larsen, Ultrastructure of human yolk sac: endoderm, mesenchyme, tubules and mesothelium, Am. J. Anat. 126 (3) (1969) 315–335.
[4] J. van Baal, et al., Development of peritoneal carcinomatosis in epithelial ovarian cancer: a review, J. Histochem. Cytochem. 66 (2) (2018) 67–83.
[5] B.S. de Bakker, et al., An interactive three-dimensional digital atlas and quantitative database of human development, Science 354 (6315) (2016).
[6] G.C. Schoenwolf, P.R. Brauer, P.H. Francis-West, Larsen's Human Embryology, 5th Edition, (2015).
[7] W. Risau, I. Flamme, Vasculogenesis, Annu. Rev. Cell Dev. Biol. 11 (1995) 73–91.
[8] K.L. Moore, The Developing Human, Clinically Oriented Embryology, 3rd edition, (1982).
[9] L.C. Goldie, M.K. Nix, K.K. Hirschi, Embryonic vasculogenesis and hematopoietic specification, Organogenesis 4 (4) (2008) 257–263.
[10] D.M. Noden, Embryonic origins and assembly of blood vessels, Am. Rev. Respir. Dis. 140 (4) (1989) 1097–1103.
[11] S.J. Mentzer, Intussusceptive angiogenesis, Expansion Remodel. Microvas. Networks 17 (3) (2014) 499–509.
[12] T.H. Adair, J.-P. Montani, Angiogenesis, San Rafael (CA): Morgan & Clapypool Life Sciences, (2010).
[13] S.J. Mentzer, M.A. Konerding, Intussusceptive angiogenesis: expansion and remodeling of microvascular networks, Angiogenesis 17 (3) (2014) 499–509.
[14] M.G. Dallinga, S.E.M. Boas, I. Klaassen, R.H.M. Merks, C.J.F. van Noorden, R.O. Schlingemann, Tip cells in angiogenesis, eLS. (2015).
[15] S. Patel-Hett, P.A. D'Amore, Signal transduction in vasculogenesis and developmental angiogenesis, Int. J. Dev. Biol. 55 (4-5) (2011) 353–363.
[16] M.S. Pepper, Transforming growth factor-beta: vasculogenesis, angiogenesis, and vessel wall integrity, Cytokine Growth Factor Rev. 8 (1) (1997) 21–43.
[17] J.R. Cooley, T.A. Yatskievych, P.B. Antin, Embryonic expression of the transforming growth factor beta ligand and receptor genes in chicken, Dev. Dyn. 243 (3) (2014) 497–508.
[18] M. Oshima, H. Oshima, M.M. Taketo, TGF-beta receptor type II deficiency results in defects of yolk sac hematopoiesis and vasculogenesis, Dev. Biol. (Basel) 179 (1) (1996) 297–302.
[19] S. Koch, L. Claesson-Welsh, Signal transduction by vascular endothelial growth factor receptors, Cold Spring Harb. Perspect. Med. 2 (7) (2012) a006502.
[20] P. Carmeliet, et al., Abnormal blood vessel development and lethality in embryos lacking a single VEGF allele, Nature 380 (6573) (1996) 435–439.
[21] S. Takashima, et al., Targeting of both mouse neuropilin-1 and neuropilin-2 genes severely impairs developmental yolk sac and embryonic angiogenesis, Proc Natl Acad Sci U S A 99 (6) (2002) 3657–3662.
[22] S. Koch, Neuropilin signalling in angiogenesis, Biochem. Soc. Trans. 40 (1) (2012) 20–25.
[23] J.C. Aster, In brief: notch signalling in health and disease, J. Pathol. 232 (1) (2014) 1–3.
[24] M. Teichert, et al., Pericyte-expressed Tie2 controls angiogenesis and vessel maturation, Nat. Commun. 8 (2017) 16106.
[25] A. Mahadevan, et al., The left-right Pitx2 pathway drives organ-specific arterial and lymphatic development in the intestine, Dev. Cell 31 (6) (2014) 690–706.
[26] J.O.A.M. van Baal, et al., The histophysiology and pathophysiology of the peritoneum, Tissue Cell 49 (1) (2017) 95–105.
[27] S.C. Blackburn, M.P. Stanton, Anatomy and physiology of the peritoneum, Semin. Pediatr. Surg. 23 (6) (2014) 326–330.
[28] Gray's Anatomy. 41st Edition S. Standring, 2015.
[29] A. Miller, M.K. Hong, J.M. Hutson, The broad ligament: a review of its anatomy and development in different species and hormonal environments, Clin. Anat. 17 (3) (2004) 244–251.
[30] J.C. Healy, R.H. Reznek, The peritoneum, mesenteries and omenta: normal anatomy and pathological processes, Eur. Radiol. 8 (6) (1998) 886–900.
[31] T. Tirkes, et al., Peritoneal and retroperitoneal anatomy and its relevance for cross-sectional imaging, Radiographics 32 (2) (2012) 437–451.
[32] J.C. Coffey, D.P. O'Leary, The mesentery: structure, function, and role in disease, Lancet Gastroenterol. Hepatol. 1 (3) (2016) 238–247.
[33] J.C. Coffey, et al., Mesenteric-based surgery exploits gastrointestinal, peritoneal, mesenteric and fascial continuity from duodenojejunal flexure to the anorectal junction–A review, Dig. Surg. 32 (4) (2015) 291–300.
[34] K.N. Michailova, K.G. Usunoff, Serosal membranes (pleura, pericardium, peritoneum). Normal structure, development and experimental pathology, Adv. Anat. Embryol. Cell Biol. 183 (2006) p. i-vii, 1-144, back cover.
[35] B. Melichar, R.S. Freedman, Immunology of the peritoneal cavity: relevance for host-tumor relation, Int. J. Gynecol. Cancer 12 (1) (2002) 3–17.
[36] F. Barberini, et al., Observations by scanning electron microscopy (SEM) on the surface of mesothelial cells of different peritoneal areas of rat (author's transl), Anat. Anz. 142 (5) (1977) 486–496.
[37] K.N. Michailova, A combined electron microscopic investigation of the peritoneal mesothelium in the rat, Eur. J. Morphol. 33 (3) (1995) 265–277.
[38] K.N. Michailova, Mesothelial lamellar bodies in norm and experimental conditions. Transmission and scanning electron microscopic observations on the peritoneum, pleura and pericardium, Anat Embryol (Berl) 208 (4) (2004) 301–309.
[39] S.E. Mutsaers, The mesothelial cell, Int. J. Biochem. Cell Biol. 36 (1) (2004) 9–16.
[40] K. Pelin, A. Hirvonen, K. Linnainmaa, Expression of cell adhesion molecules and connexins in gap junctional intercellular communication deficient human mesothelioma tumour cell lines and communication competent primary mesothelial cells, Carcinogenesis 15 (11) (1994) 2673–2675.
[41] T. Ito, et al., Effect of glucose on intercellular junctions of cultured human peritoneal mesothelial cells, J. Am. Soc. Nephrol. 11 (11) (2000) 1969–1979.
[42] M. Simionescu, N. Simionescu, Organization of cell junctions in the peritoneal mesothelium, J. Cell Biol. 74 (1) (1977) 98–110.
[43] Z.B. Wang, M. Li, J.C. Li, Recent advances in the research of lymphatic stomata, Anat. Rec. Hoboken (Hoboken) 293 (5) (2010) 754–761.
[44] Y.Y. Li, J.C. Li, Ultrastructure and three-dimensional study of the lymphatic stomata in the costal pleura of the rabbit, Microsc. Res. Tech. 62 (3) (2003) 240–246.
[45] J. Li, et al., A study of the three-dimensional organization of the human diaphragmatic lymphatic lacunae and lymphatic drainage units, Ann. Anat. - Anat.

Anzeiger 178 (6) (1996) 537–544.
[46] S.E. Mutsaers, Mesothelial cells: their structure, function and role in serosal repair, Respirology 7 (3) (2002) 171–191.
[47] A.F. Baradi, S.N. Rao, A scanning electron microscope study of mouse peritoneal mesothelium, Tissue Cell 8 (1) (1976) 159–162.
[48] S.P. Evanko, et al., Hyaluronan-dependent pericellular matrix, Adv. Drug Deliv. Rev. 59 (13) (2007) 1351–1365.
[49] J. Li, X. Chen, S. Yu, The ultrastructure of vesicle-containing cells and ER-cells of human peritoneum, Ann. Anat. 178 (4) (1996) 365–367.
[50] E. van der Pol, et al., Classification, functions, and clinical relevance of extracellular vesicles, Pharmacol. Rev. 64 (3) (2012) 676–705.
[51] G. Schmitz, G. Muller, Structure and function of lamellar bodies, lipid-protein complexes involved in storage and secretion of cellular lipids, J. Lipid Res. 32 (10) (1991) 1539–1570.
[52] J.W. Dobbie, Surfactant protein A and lamellar bodies: a homologous secretory function of peritoneum, synovium, and lung, Perit. Dial. Int. 16 (6) (1996) 574–581.
[53] J.W. Dobbie, New concepts in molecular biology and ultrastructural pathology of the peritoneum: their significance for peritoneal dialysis, Am. J. Kidney Dis. 15 (2) (1990) 97–109.
[54] Y.-Y. Chau, et al., Visceral and subcutaneous fat have different origins and evidence supports a mesothelial source, Nat. Cell Biol. 16 (2014) 367.
[55] P.D. Yurchenco, Basement membranes: cell scaffoldings and signaling platforms, Cold Spring Harb. Perspect. Biol. 3 (2) (2011).
[56] A.T. Raftery, Regeneration of parietal and visceral peritoneum: an electron microscopical study, J. Anat. 115 (Pt 3) (1973) 375–392.
[57] C.A. Witz, et al., Composition of the extracellular matrix of the peritoneum, J. Soc. Gynecol. Investig. 8 (5) (2001) 299–304.
[58] B. Schaefer, et al., Quantitative histomorphometry of the healthy peritoneum, Sci. Rep. 6 (2016) 21344.
[59] J.D. Williams, et al., Morphologic changes in the peritoneal membrane of patients with renal disease, J. Am. Soc. Nephrol. 13 (2) (2002) 470–479.
[60] P.J. Knudsen, The peritoneal elastic lamina, J. Anat. 177 (1991) 41–46.
[61] P.C. Benias, et al., Structure and distribution of an unrecognized interstitium in human tissues, Sci. Rep. 8 (1) (2018) 4947.
[62] R. Khanna, R.T. Krediet, The peritoneal microcirculation in peritoneal dialysis, Chapter 4, Nolph and Gokal's Textbook of Peritoneal Dialysis, 3rd edition, Springer, 2009.
[63] A. Kierszenbaum, Histology and Cell Biology: an Introduction to Pathology, Mosby, St. Louis, MI, 2002.
[64] V.V.V. Hira, D.A. Aderetti, C.J.F. van Noorden, Glioma stem cell niches in human glioblastoma are periarteriolar, J. Histochem. Cytochem. 66 (5) (2018) 349–358.
[65] K.K. Hirschi, P.A. D'Amore, Pericytes in the microvasculature, Cardiovasc. Res. 32 (4) (1996) 687–698.
[66] J. Peters, G.W. Mack, G. Lister, The importance of the peripheral circulation in critical illnesses, Intensive Care Med. 27 (9) (2001) 1446–1458.
[67] R.T. Krediet, B. Lindholm, B. Rippe, Pathophysiology of peritoneal membrane failure, Perit. Dial. Int. 20 (Suppl. 4) (2000) S22–42.
[68] Z. Uz, et al., Intraoperative incident dark field imaging of the human peritoneal microcirculation, J. Vasc. Res. 55 (3) (2018) 136–143.
[69] K. Culligan, et al., The mesocolon: a histological and electron microscopic characterization of the mesenteric attachment of the colon prior to and after surgical mobilization, Ann. Surg. 260 (6) (2014) 1048–1056.
[70] N.J. Abernethy, et al., Lymphatic drainage of the peritoneal cavity in sheep, Am. J. Physiol. 260 (3 Pt 2) (1991) F353–8.
[71] S. Shibata, et al., The time course of lymphatic routes emanating from the peritoneal cavity in rats, Anat. Histol. Embryol. 36 (1) (2007) 78–82.
[72] G.B. Feldman, R.C. Knapp, Lymphatic drainage of the peritoneal cavity and its significance in ovarian cancer, Am. J. Obstet. Gynecol. 119 (7) (1974) 991–994.
[73] C.P. Parungo, et al., Lymphatic drainage of the peritoneal space: a pattern dependent on bowel lymphatics, Ann. Surg. Oncol. 14 (2) (2007) 286–298.
[74] K. Tanaka, T. Matsugami, T. Chiba, The origin of sensory innervation of the peritoneum in the rat, Anat Embryol (Berl) 205 (4) (2002) 307–313.
[75] F. Struller, P. Horvath, et al., Peritoneal innervation: embryology and functional anatomy, Pleura Peritoneum 2 (4) (2017) 153–161.
[76] J.A.D.B. Christianson, The role of visceral afferents in disease, in: L.A. Kruger (Ed.), Translational Pain Research: From Mouse to Man, CRC Press/Taylor & Francis, 2010.
[77] A.M. Brunsden, et al., Mesenteric afferent nerves are sensitive to vascular perfusion in a novel preparation of rat ileum in vitro, Am. J. Physiol. Gastrointest. Liver Physiol. 283 (3) (2002) G656–65.
[78] G. diZerega, Chapter 1: Peritoneum and Peritoneal Repair. Peritoneal Surgery, 1st ed., Springer-Verleg, New York, 2000.
[79] L. Holmdahl, The role of fibrinolysis in adhesion formation, Eur. J. Surg. Suppl. 577 (1997) 24–31.
[80] C.J.J.M. Sikkink, et al., Influence of monocyte-like cells on the fibrinolytic activity of peritoneal mesothelial cells and the effect of sodium hyaluronate, Fertil. Steril. 84 (Suppl. 2) (2005) 1072–1077.
[81] Y.C. Cheong, et al., Peritoneal healing and adhesion formation/reformation, Hum. Reprod. Update 7 (6) (2001) 556–566.
[82] W. Arung, M. Meurisse, O. Detry, Pathophysiology and prevention of post-operative peritoneal adhesions, World J. Gastroenterol. 17 (41) (2011) 4545–4553.
[83] C.N. Fortin, G.M. Saed, M.P. Diamond, Predisposing factors to post-operative adhesion development, Hum. Reprod. Update 21 (4) (2015) 536–551.
[84] P.R. Koninckx, et al., Role of the peritoneal cavity in the prevention of post-operative adhesions, pain, and fatigue, Fertil. Steril. 106 (5) (2016) 998–1010.
[85] A.O. Awonuga, et al., Advances in the pathogenesis of adhesion development: the role of oxidative stress, Reprod. Sci. 21 (7) (2014) 823–836.
[86] G. Bigatti, et al., Experimental model for neoangiogenesis in adhesion formation, Hum. Reprod. 10 (9) (1995) 2290–2294.
[87] C.R. Molinas, et al., Peritoneal mesothelial hypoxia during pneumoperitoneum is a cofactor in adhesion formation in a laparoscopic mouse model, Fertil. Steril. 76 (3) (2001) 560–567.
[88] C.R. Molinas, P.R. Koninckx, Hypoxaemia induced by CO(2) or helium pneumoperitoneum is a co-factor in adhesion formation in rabbits, Hum. Reprod. 15 (8) (2000) 1758–1763.
[89] C.R. Molinas, et al., Role of vascular endothelial growth factor and placental growth factor in basal adhesion formation and in carbon dioxide pneumoperitoneum-enhanced adhesion formation after laparoscopic surgery in transgenic mice, Fertil. Steril. 80 (Suppl. 2) (2003) 803–811.
[90] C.R. Molinas, et al., Role of the plasminogen system in basal adhesion formation and carbon dioxide pneumoperitoneum-enhanced adhesion formation after laparoscopic surgery in transgenic mice, Fertil. Steril. 80 (1) (2003) 184–192.
[91] G.M. Saed, et al., Hypoxia upregulates cyclooxygenase-2 and prostaglandin E(2) levels in human peritoneal fibroblasts, Fertil. Steril. 83 (Suppl. 1) (2005) 1216–1219.
[92] G.M. Saed, H.M. Abu-Soud, M.P. Diamond, Role of nitric oxide in apoptosis of human peritoneal and adhesion fibroblasts after hypoxia, Fertil. Steril. 82 (Suppl. 3) (2004) 1198–1205.
[93] G.M. Saed, K.L. Collins, M.P. Diamond, Transforming growth factors beta1, beta2 and beta3 and their receptors are differentially expressed in human peritoneal fibroblasts in response to hypoxia, Am. J. Reprod. Immunol. 48 (6) (2002) 387–393.
[94] G.M. Saed, W. Zhang, M.P. Diamond, Effect of hypoxia on stimulatory effect of TGF-beta 1 on MMP-2 and MMP-9 activities in mouse fibroblasts, J. Soc. Gynecol. Investig. 7 (6) (2000) 348–354.
[95] C.R. Molinas, M.M. Binda, P.R. Koninckx, Angiogenic factors in peritoneal adhesion formation, Gynecol. Surg. 3 (3) (2006) 157–167.
[96] A. Aguilera, et al., Epithelial to mesenchymal transition as a triggering factor of peritoneal membrane fibrosis and angiogenesis in peritoneal dialysis patients, Curr. Opin. Investig. Drugs 6 (3) (2005) 262–268.
[97] P.J. Margetts, et al., Inflammatory cytokines, angiogenesis, and fibrosis in the rat peritoneum, Am. J. Pathol. 160 (6) (2002) 2285–2294.
[98] M. Yanez-Mo, et al., Peritoneal dialysis and epithelial-to-mesenchymal transition of mesothelial cells, N. Engl. J. Med. 348 (5) (2003) 403–413.
[99] J.P. Thiery, Epithelial-mesenchymal transitions in development and pathologies, Curr. Opin. Cell Biol. 15 (6) (2003) 740–746.
[100] J. Loureiro, et al., Blocking TGF-beta1 protects the peritoneal membrane from dialysate-induced damage, J. Am. Soc. Nephrol. 22 (9) (2011) 1682–1695.
[101] A. Cardenas, R. Bataller, V. Arroyo, Mechanisms of ascites formation, Clin. Liver Dis. 4 (2) (2000) 447–465.
[102] C.M. Moore, D.H. Van Thiel, Cirrhotic ascites review: pathophysiology, diagnosis and management, World J. Hepatol. 5 (5) (2013) 251–263.
[103] S.L. Sangisetty, T.J. Miner, Malignant ascites: a review of prognostic factors, pathophysiology and therapeutic measures, World J. Gastrointest. Surg. 4 (4) (2012) 87–95.
[104] J. Gavard, J.S. Gutkind, VEGF controls endothelial-cell permeability by promoting the beta-arrestin-dependent endocytosis of VE-cadherin, Nat. Cell Biol. 8 (11) (2006) 1223–1234.
[105] E. Pujade-Lauraine, et al., Bevacizumab combined with chemotherapy for platinum-resistant recurrent ovarian cancer: the AURELIA open-label randomized phase III trial, J. Clin. Oncol. 32 (13) (2014) 1302–1308.
[106] S. Machida, et al., Inhibition of peritoneal dissemination of ovarian cancer by tyrosine kinase receptor inhibitor SU6668 (TSU-68), Int. J. Cancer 114 (2) (2005) 224–229.
[107] L. Xu, et al., Inhibition of malignant ascites and growth of human ovarian carcinoma by oral administration of a potent inhibitor of the vascular endothelial growth factor receptor tyrosine kinases, Int. J. Oncol. 16 (3) (2000) 445–454.
[108] B. Stoelcker, et al., VEGF/Flk-1 interaction, a requirement for malignant ascites recurrence, J. Interferon Cytokine Res. 20 (5) (2000) 511–517.
[109] P. Sandoval, et al., Carcinoma-associated fibroblasts derive from mesothelial cells via mesothelial-to-mesenchymal transition in peritoneal metastasis, J. Pathol. 231 (4) (2013) 517–531.
[110] S.A. Gerber, et al., Preferential attachment of peritoneal tumor metastases to omental immune aggregates and possible role of a unique vascular microenvironment in metastatic survival and growth, Am. J. Pathol. 169 (5) (2006) 1739–1752.
[111] S. Masoumi Moghaddam, et al., Significance of vascular endothelial growth factor in growth and peritoneal dissemination of ovarian cancer, Cancer Metastasis Rev. 31 (2011) 143–162.
[112] J. Liu, X. Geng, Y. Li, Milky spots: omental functional units and hotbeds for peritoneal cancer metastasis, Tumour Biol. 37 (5) (2016) 5715–5726.