Review

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Diverse properties of the mesothelial cells in health and disease

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Abstract: Mesothelial cells (MCs) form the superficial anatomic layer of serosal membranes, including pleura, pericardium, peritoneum, and the tunica of the reproductive organs. MCs produce a protective, non-adhesive barrier against physical and biochemical damages. MCs express a wide range of phenotypic markers, including vimentin and cytokeratins. MCs play key roles in fluid transport and inflammation, as reflected by the modulation of biochemical markers such as transporters, adhesion molecules, cytokines, growth factors, reactive oxygen species and their scavengers. MCs synthesize extracellular matrix related molecules, and the surface of MC microvilli secretes a highly hydrophilic protective barrier, "glycocalyx", consisting mainly of glycosaminoglycans. MCs maintain a balance between procoagulant and fibrinolytic activation by producing a whole range of regulators, can synthetize fibrin and therefore form adhesions. Synthesis and recognition of hyaluronan and sialic acids might be a new insight to explain immunoactive and immunoregulatory properties of MCs. Epithelial to mesenchymal transition of MCs may involve serosal repair and remodeling. MCs might also play a role in the development and remodeling of visceral adipose tissue. Taken together, MCs play important roles in health and disease in serosal cavities of the body. The mesothelium is not just a membrane and should be considered as an organ.

Keywords: mesothelial cells, mesothelium, physiology and pathophysiology in serosa

Introduction

The pleura is the serous membrane which forms the lining of the pleural cavity and the peritoneum is the serous membrane covering the abdominal cavity. Further serosal membranes are the pericardium, the tunica vaginalis testis (covering the male reproductive organs in the scrotum) and the tunica serosa uteri (covering the internal female reproductive organs). The peritoneum is a large structure with a surface equivalent to the skin. However, relatively few is known about the functional anatomy of the serosal surfaces, in comparison with other organs of the body. Most data available in the literature have been generated by nephrologists interested in peritoneal dialysis, and focus on the peritoneum as a membrane. This short review gives an overview of the morphological anatomy of the mesothelial surfaces in the body and of the related, various functions of these organs.

Serosal surfaces are composed of mesothelial cells (MCs) attached on the basement membrane and subsequent connective tissue containing blood and lymph vessels, fibroblasts, mast cells, monocytes/macrophages, leukocytes, adipocytes, and nerve fibers (Figure 1A) [1, 2]. However, at the organ level, the structure of serosal membranes is not the same in all locations. For example, small lymph vessels are abundant in the submesothelial tissue of the intestines, rectum, uterus, urinary bladder and testis, while they are rare in other locations. Nerve fibers are more commonly observed in the organs of the lesser pelvis, where there are located in close contact to blood vessels in the submesothelial connective tissue [3].

The morphological characteristics of MC at the cellular level are also varying along their anatomical localization. For example, cubic MCs (tall and narrow-shaped cells with hollow reservoir function) are characteristic for the mediastinal pleura, the peritoneal side of the diaphragm, the parenchymal organs such as liver and spleen, lymphatic lacunae and milky spots, while the flat MCs are more uniform and widespread in the parietal mesothelium [3]. The parietal peritoneum can be easily detached from the retroperitoneal tissue, whereas the visceral peritoneum is tightly fixed to the bowel and to the parenchymatous organs. These morphological differences have been confirmed by gene profiling and protein expression analysis showing that peritoneal and pleural MCs have different phenotypic patterns [4]. Moreover,

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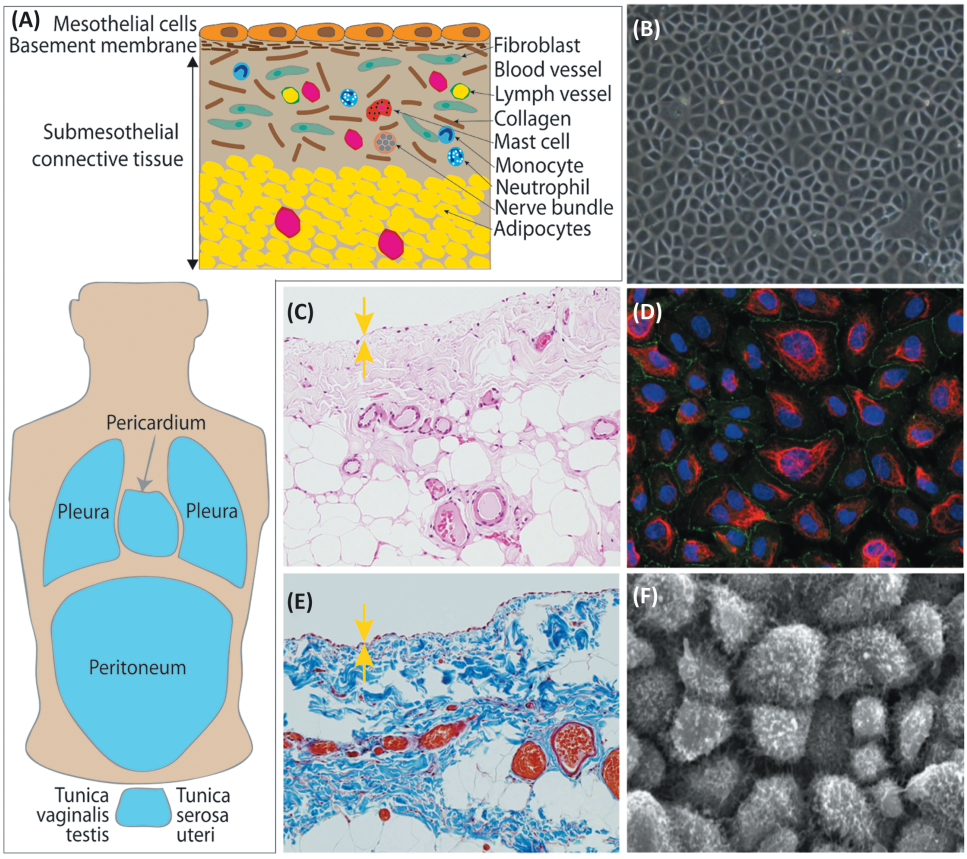

Figure 1: Morphology of the mesothelium.
(A) The mesothelium covers the surface of internal organs and cavities and forms the pleura, pericardium, peritoneum, the tunica vaginitis testis and the tunica serosa uteri (panel A, lower part). The fundamental structure of mesothelium is composed of a superficial monolayer of mesothelial cells (MCs), the basement membrane, submesothelial connective tissue containing fibroblasts, blood and lymph vessels, collagen tissue, inflammatory cells, nerve bundles and adipose tissue (panel A, upper part). Panel (B) shows a phase-contrast microscopic image of parietal peritoneal MCs from a rodent. Panel (C) shows a human peritoneal biopsy with a superficial monolayer of MC (yellow arrows) underpinned with submesothelial connective tissue (HE staining). Panel (D) shows MCs from the parietal peritoneum of a rodent. MCs express cytokeratin (red) and Zo-1 (green). (E) Masson Trichrome staining of the mesothelium showing keratin (red) and collagen (blue/green). Panel (F) shows a scanning electron microscopy image of parietal peritoneal MCs from a rodent. They show plenty of microvilli in the surface.

visceral and parietal MCs are also fundamentally different in their ability to adhere, migrate and invade [5] and are showing different properties in the process of fibrosis [6].

Besides being morphological components of serosal membranes, MC also plays several key functional roles (Figure 2). One of the basic functions of MC is to form a smooth surface allowing the internal organs to glide. In addition, MC plays a variety of physiological roles or biological functions in several processes such as tissue repair, fibrinolysis, regulation of inflammation, epithelial to mesenchymal transition (EMT) and mediation of the intraperitoneal dissemination of cancer cells. Clinical research has highlighted the role of MC in several pathological settings such as ageing, response to peritoneal dialysis, tissue injury and repair, and cancer progression [7, 8]. Moreover, recent genetic lineage tracing suggested that the mesothelium lining visceral adipose depots might be a potential contributor to tissue dysfunction in obesity, including the development of fibrosis and inflammation [9, 10].

Phenotypic or biochemical markers of MC

MC expresses a wide range of phenotypic markers observed in simple epithelial-like tissues such as the vascular endothelium or the corneal endothelium. These phenotypic markers include vimentin and cytokeratins (Figure 1D) [11, 12], E-cadherin [13–16], N-cadherin, Calretinin [17], Zo-1 [13, 15, 18] (Figure 1D), β-catenin [13, 19, 20], Wilms' tumor protein 1 (WT1) [21, 22], mesothelin [4, 23] and podoplanin [24, 25], etc. (Table 1).

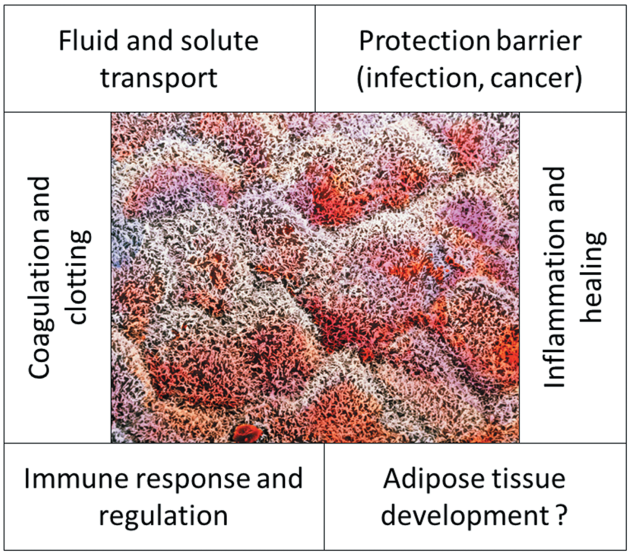

Figure 2: Functions and roles of methothelial cells.
MCs play decisive roles in health and disease. The mesothelium surfaces are not just a membrane and should be considered as polyvalent organs. Diseases of the serosal surfaces, such as peritonitis or peritoneal carcinomatosis, are often life-threatening. Further research is needed to better understand the various functions of MCs in order to develop effective therapies for these diseases.

Table 1: Molecules produced by mesothelial cells in pleura and peritoneum.

Molecule	Site	Stimulus	References
Phenotypic or adhesion marker			
Cytokeratin	Pl, Pet		[11, 12]
Vimentin	Pl, Pet		[11, 12]
E-cadhelin	Pl, Pet		[13–16]
N-cadhelin	Pl, Pet		[17]
Zo-1	Pl, Pet		[13, 15, 18]
β-Catenin	Pl, Pet		[13, 19, 20]
WT1	Pl, Pet		[21, 22]
Mesothelin	Pl, Pet		[4, 23]
Podoplanin	Pl, Pet		[24, 25]
Aquaporin 1	Pet		[20]
Na + /K + –ATPase	Pet		[20]
SLC	Pet		[20]
CD40	Pet	IFN-γ, TNF-α	[29]
HCAM (CD44)	Pl, Pet	IL-1, EGF, PDGF	[30, 31]
ICAM-1 (CD54)	Pl, Pet	IL-1, TNF-α, IFN-γ	[26, 32–34]
VCAM-1 (CD106)	Pl, Pet	IL-1, TNF-α, IFN-γ	[26, 32–34]
ALCAM (CD166)	Pet		[25]
Cytokines or growth factors			
IL-1	Pl, Pet	EGF, TNF-α, LPS	[35, 36]
IL-6	Pl, Pet	TNF-α, IL-1	[36, 37]
IL-8	Pl, Pet	IL-1, TNF-α, LPS	[32, 37–39]
IL15	Per	IFN-γ, TNF-α	[29]
CSF (G, GM, M)	Pl, Pet	IL-1, TNF-α, EGF, LPS	[35, 36]
MCP-1	Pl, Pet	IL-1, TNF-α, IFN-γ	[35, 36]
RANTES	Pet	IL-1, TNF-α, LPS	[29, 40]
VEGF	Pl, Pet	IL-1, TNF-α, TGF-β	[41–46]
FGF	Pl, Pet	IL-1	[47]
TGF-β	Pl, Pet	IL-1, hypoxia	[48–51]
PDGF	Pl, Pet		[52, 53]
ET-1	Pl		[54]
IGF-1	Pl		[55]
KGF	Pl		[56]
HGF	Pl		[56]
HB-EGF	Pet		[31, 33]
HIF	Pl, Pet	hypoxia	[46]
MMP	Pl, Pet		[14, 46, 57–59]
Snail-1	Pl, Pet		[14, 46]
ECM related molecules			
Collagen I	Pl, Pet	IL-1, TNF-α, EGF, PDGF	[65–75]
Collagen III	Pl, Pet	TGF-β, EGF, PDGF, hypoxia	[65–75]
Collagen IV	Pl		
Elastin	Pl		[65]
Fibronectin	Pl, Pet	IL-1	[65]
Laminin	Pl		[65]
Hyalronan	Per		[79, 96]
Coagulation cascade proteins			
TF	Pl		[81–83]
tPA	Pl, Pet	TNF-α	[85–90]
uPA	Pet	TGF-β	[85, 87–92]
PAI-1	Pl, Pet	IL-1, TNF-α, TGF-β	[85–90, 92]

Pl, pleura; Pet, peritoneum; WT1, Wilms' tumor protein 1; Na + /K + –ATPase, sodium-potassium adenosine triphosphatase interleukin; SLC, sodium bicarbonate; HCAM, homing cell adhesion molecule; ICAM-1, intercellular cell adhesion molecule 1; VCAM-1, vascular cell adhesion molecule 1; ALCAM, activated leukocyte cell adhesion molecule; IL, interleukin; LPS, Lipopolysaccharides; G-, granulocyte, GM-, granulocyte monocyte, M-, monocyte, CSF, colony stimulating factor; MCP-1, monocyte chemoattractant protein-1; RANTES, regulated on activation normal T expressed and secreted chemokine; VEGF, vascular endothelial growth factor; bFGF, basic fibroblast growth factor; TGF-β, transforming growth factor β; PDGF, platelet-derived growth factor; ET-1, endothelin-1; IGF-1, insulin-like growth factor-1; KGF, keratinocyte growth factor; HGF, hepatocyte growth factor; HB-EGF, heparin-binding epidermal growth factor-like growth factor; HIF, hypoxia-inducible factor; MMP, metalloproteinase; ECM, extracellular matrix; TF, tissue factor; tPA, tissue plasminogen activator; uPA, urokinase plasminogen activator; PAI-1, plasminogen activator inhibitor (Created based on data from [1]).

MC expresses additional biochemical markers suggesting an active role of these cells in fluid transport, initiation and resolution of inflammation. These biochemical markers include aquaporin 1, sodium-potassium adenosine triphosphatase (Na^+/K^+-ATPase), sodium bicarbonate cotransporter (SLC) [20], integrin β1 (CD29) [26–28], CD40 as a member of the tumor necrosis factor (TNF)-receptor

superfamily [29], homing cell adhesion molecule (HCAM, CD44) [30, 31], intercellular cell adhesion molecule 1 (ICAM-1, CD54), vascular cell adhesion molecule 1 (VCAM-1, CD106) [26, 32–34] and activated leukocyte cell adhesion molecule (ALCAM, CD166) [25].

Production of cytokines and growth factors

MC produces several cytokines spontaneously or after stimulation, such as interleukin 1 (IL-1) [35, 36] IL-6 [36, 37], IL-8 [32, 37–39] and IL-15 [29] granulocyte colony stimulating factor (G-CSF), granulocyte monocyte CSF (GM-CSF), macrophage CSF (M-CSF), monocyte chemoattractant protein-1 (MCP-1) [35, 36] and regulated on activation normal T expressed and secreted chemokine (RANTES) [29, 40]. MC also synthesizes vascular endothelial growth factor (VEGF) [41–46], basic fibroblast growth factor (bFGF) [47], transforming growth factor β (TGF-β) [48–51], platelet-derived growth factor (PDGF) [52, 53], endothelin-1 [54], insulin-like growth factor (IGF) [55], keratinocyte growth factor (KGF) and hepatocyte growth factor (HGF) [56], heparin-binding epidermal growth factor-like growth factor (HB-EGF) [31, 33], Hypoxia-inducible factor (HIF) [46], metalloproteinase (MMP) [14, 46, 57–59] and Snail-1 (known as a zinc finger transcriptional repressor) [14, 46]. Finally, MCs are able to produce both reactive oxygen species (ROS) such as nitric oxide (NO) and ROS-scavengers, in particular under presence of stressors such as lipopolysaccharides (LPS), asbestos, methylglyoxal (MGO) and advanced glycation end products (AGEs) [45, 60–64].

Synthesis of extracellular matrix (ECM)

MC synthesizes extracellular matrix (ECM)-related molecules such as type I, III, and IV collagen, elastin, fibronectin, laminin and proteoglycans. The production level of ECM is increased by IL-1β, TNF-α, EGF, and TGF-β [65–75]. The renin-angiotensin system or AGEs also stimulates ECM production [76, 77]. MC provides a protective and non-adhesive surface for intracoelomic organs and tissues. The microvilli on the surface of MC (Figure 1F) secrete a protective barrier, “glycocalyx”, composed by glycosaminoglycans (GAGs) that may protect the body against infection and tumor dissemination [78], in particular hyaluronan, which has a high hydrophilicity by forming a hydrated gel polymer [1, 2, 79]. Meanwhile, MCs also produce fibronectin through a TGF-β receptor 1/RAC1/SMAD-dependent signaling pathway in the presence of TGF-β1 from ovarian cancer cells [80]. The activated MCs, “cancer-associated MCs” may promote metastasis by supporting tumor cell adhesion, invasion, and proliferation.

Procoagulant and fibrinolytic properties

MC maintains a balance between procoagulant and fibrinolytic activation by producing a whole range of corresponding regulators. MC expresses a powerful procoagulant, tissue factor (TF), which form fibrin by cleaving fibrinogen [81–83]. MC also expresses TF pathway inhibitor [84]. On the other hand, MC produces fibrinolytic activators such as tissue plasminogen activator (tPA) [85–90] urokinase plasminogen activator (uPA) and uPA receptor (uPA-R) [85, 87–92]. MC also secretes the corresponding inhibitor, plasminogen activator inhibitor 1 (PAI-1) and this secretion is regulated by TGF-β, thrombin and other inflammatory factors such as lipopolysaccharide (LPS), TNF-α, and IL-1 [85–90, 92]. MC defects and lesions cause an unbalance between procoagulant and fibrinotic properties and formation of fibrin bands between tissue and organs is observed. These bands eventually develop to fibrous adhesion that can be observed in postoperative intra-abdominal and pelvic adhesions [93], and similarly in pleural fibrosis [8].

Hyaluronan synthesis and recognition

Hyaluronan (HA) is a non-sulfated, linear GAG composed of repeating disaccharides of β-(1, 4) glucuronic acid (GlcUA) and β-(1, 3) N-acetyl glucosamine (GlcNAc). HA is synthesized by three synthase (HAS) proteins. HA play crucial roles in structuring tissue architecture, in cell motility, in cell adhesion, and in proliferation processes [94]. MC generates predominantly large HA (HMW-HA) with a high molecular weight between 200 and 2,000 kDa. HA catabolism is mediated by hyaluronidases, mechanical forces, and oxidative stress. The degradation generates HA polymers of smaller sizes, abbreviated low molecular weight-HA (LMW-HA; <200 kDa) and HA oligomers [95].

Generally, LMW-HA has a pro-inflammatory and carcinogenetic function, whereas HMW-HA has the opposite functions [94]. HA of MC increases the synthesis of by inflammation, including exposition to non-physiological solutions such as peritoneal dialysis. Increased HA levels can induce EMT in MC under physiological conditions, which is essential for cell migration during wound healing and re-mesothelialization [79, 96].

Meanwhile, CD44, the principal receptor for HA [97] is involved in binding gastric cancer [98, 99] and ovarian cancer cells [100] to the mesothelium. HA-CD44 interaction is required for the extravasation of activated T cells from circulating blood to inflammatory sites [101]. There is also evidence that the HA-binding ability of CD44 correlates with the suppressor activity of CD4 + /CD25 + regulatory T cells [102]. CD44 expression on MC has also been reported in tissue cultured MCs [103] or in the human hyperplastic mesothelium *in vivo* [104], although a recent in vivo study showed that intact mesothelium lacked CD44 expression [105]. High CD44 expression in cultured MCs could be explained by the isolation method, by the different composition of growth factors like HB-EGF in the culture medium [106] or by cells undergoing EMT [96]. Various post-translational modifications of CD44, including glycosylation, chondroitin sulfate addition, and sulfation could affect the HA-binding ability of this surface receptor. In spite of this extensive body of evidence, the membrane based regulation of CD44's hyaluronan-binding ability has not yet been clarified [107].

Sialic acid synthesis and recognition

Sialic acid (Sias) is a diverse family of molecules found at the outer edge of the glycan forest covering all vertebrate cells [108]. Given their high expression and ubiquitous location, Sias has many roles in biology, evolution and disease. The two most common mammalian Sias are N-acetylneuraminic acid (Neu5Ac) and N-glycolylneuraminic acid (Neu5Gc). Neu5Gc is hydroxylated from Neu5Ac by cytidine monophosphate-N-acetylneuraminic acid hydroxylase (CMAH). Humans cannot synthesize Neu5Gc due to inactivation of the CMAH gene during phylogenesis (about 2.8 million years ago) [109]. In spite of this inactivation, small amounts of Neu5Gc were detected using antibodies and high performance liquid chromatography and mass spectrometry analyses (HPLC-MS) in normal human epithelia and endothelia, and larger amounts are found in human carcinomas and inflamed tissues [110]. Notably, human cells express the Sias-binding immunoglobulin-like lectins (Siglecs), a family of immunomodulatory receptors whose functions are regulated by their glycan ligands. Siglecs are attractive therapeutic targets because of their cell type-specific expression pattern, endocytic properties, high expression on certain lymphoma/leukemia, and their ability to modulate receptor signaling [111]. Although only a few studies have been published on Sias in MCs, Neu5Gc were detected in malignant mesothelioma [112] and Sias-binding lectin (SBL) induced selective apoptosis in malignant mesothelioma cells in combination with tumor necrosis factor-related apoptosis inducing ligand (TRAIL) [113]. Otherwise, mucin 16 (MUC-16), a cell surface mucin expressed at high levels by epithelial ovarian tumors and its repeating domain is detected in the serum of cancer patients as the tumor marker, cancer antigen 125 (CA-125). Interestingly CA-125 is also well known as MC marker [114]. MUC16 binds to Siglec-9, which is an inhibitory receptor attenuating T cell and NK cell, and likely mediates inhibition of anti-tumor immune responses [115] or contribute to tolerance of the fetal allograft from maternal responses [116].

Immunoactive or regulatory properties

MCs also express toll-like receptors (TLRs) that can detect microbial components ubiquitous to most microbes and induce inflammation by activation of nuclear factor-κB (NF-κB) and signaling transduction pathways, and induction of chemokines [117, 118]. TLR-4 expression of human peritoneal cell is increased in murine after LPS stimulation [118]. Interestingly TLR-4 is also an important receptor of HA [95]. Meanwhile, recent studies of human malignant mesotheliomas showed that mesothelial tumorigenic cells escape from the control of the immune system through suppression of the proliferation and functions of T lymphocytes and increased recruitment of immunosuppressive regulatory T cells [119]. Furthermore, benign MCs also may suppress proliferation of pro-inflammatory $\gamma\delta$ T cells as well as of $CD4^+$ and $CD8^+$ T cells by secreting the immunosuppressor TGF-β [120]. Other researchers also indicated that $CD90^+/CD45^-$ MCs from human peritoneal fluid could immunosuppress $CD4^+$ T cells through expression of arginase [121]. These findings suggest that role of HA-CD44 or Sias-Siglecs interactions in the immunomodulatory mechanism of MCs should be researched more actively.

Epithelial to mesenchymal transition (EMT)

Epithelial to mesenchymal transition (EMT) occurs when MC loses their epithelial-like characteristics, including dissolution of cell-cell junctions, tight junctions, adherence junctions and desmosomes, and loss of apical-basolateral polarity, and acquire a mesenchymal phenotype, characterized by actin reorganization and stress fiber formation, migration, and invasion [122]. Several study associated with peritoneal dialysis therapy have shown that TGF-β1 signaling play a key role in EMT [123–125], following inducers, for example, integrins/integrin-linked kinase (ILK), Notch, NF-κB, phosphatidylinositol 3-kinase (PI3K)/Akt/mTOR pathway, extracellular-signal regulated kinases 1/2 (ERKs1/2), TGF-β activated kinase-1 (TAK1), c-jun-N terminal kinase (JNK) [126–130]. At the early stage EMT is a reversible process and the following factors promote mesenchymal to epithelial transition (MET) or modulate EMT; HGF, bone morphogenetic protein-7 (BMP-7) [131–133], Smad7 [134–136], and p38 mitogen-activated protein (MAP) kinase [137]. Meanwhile, recent genetic lineage analysis produced a new insight of the primary source of the myofibroblasts observed in peritoneal fibrosis; submesothelial fibroblasts were the major precursors of myofibroblasts during peritoneal fibrogenesis, and the surviving MCs serve as the principal cells for mesothelium repair, arguing against the transition of MCs to myofibroblasts via EMT [138]. Although a lot of works need to clarify the biological role of MCs during serosal inflammation and tissue repair, such as pleural and peritoneal fibrogenesis and adhesion formation, MCs may play a key role, contributing by balancing EMT/reversible EMT and procoagulant/fibrinolytic properties [8, 139].

Visceral adipose tissue development and remodeling

MCs might also play a role in the development and remodeling of visceral adipose tissue. MCs line visceral white adipose tissue (WAT), such as omental adipose tissue. Visceral adiposity is known to be a higher risk factor for chronic metabolic disease, such as type 2 diabetes or cardiovascular complications, than subcutaneous adipose tissue [140, 141]. Omental MCs show proinflammatory phenotype in obesity [142] and lineage tracing showed that intra-abdominal WAT has a different embryological origin that subcutaneous WAT [9, 143]. Beside WT1 and mesothelin, MCs also express adipose precursors markers such as CD29, CD34 and Sca1. Epicardium-derived cell cultures suggest that MCs differentiate into chondrocytes, osteocytes and adipocyte [10, 144]. MCs can respond to proinflammatory signals through TLR pathways and secrete cytokines as described above, so that a role of MCs in the development of a systemic inflammatory response in morbid adiposity can be postulated. Further research is required, however, to further explore the interaction of MCs with visceral adipocyte, in particular to determine how MCs are involved in the development and remodeling of visceral adipose tissue.

Conclusions

MC plays decisive roles in health and disease. The mesothelium surfaces are not just a membrane and should be considered as polyvalent organs. Diseases of the serosal surfaces, such as peritonitis or peritoneal carcinomatosis, are often life-threatening. Further research is needed to better understand the various functions of MCs in order to develop effective therapies for these diseases.

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