Mesothelial cells and peritoneal homeostasis

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The mesothelium was traditionally thought to be a simple tissue with the sole function of providing a slippery, nonadhesive, and protective surface to allow easy movement of organs within their body cavities. However, our knowledge of mesothelial cell physiology is rapidly expanding, and the mesothelium is now recognized as a dynamic cellular membrane with many other important functions. When injured, mesothelial cells initiate a cascade of processes leading either to complete regeneration of the mesothelium or the development of pathologies such as adhesions. Normal mesothelial healing is unique in that, unlike with other epithelial-like surfaces, healing appears diffusely across the denuded surface, whereas for epithelium healing occurs solely at the wound edges. This is because of a free-floating population of mesothelial cells which attach to the injured serosa. Taking advantage of this phenomenon, intraperitoneal injections of mesothelial cells have been assessed for their ability to prevent adhesion formation. This review discusses some of the functions of mesothelial cells regarding maintenance of serosal integrity and outlines the mechanisms involved in mesothelial healing. In addition, the pathogenesis of adhesion formation is discussed with particular attention to the potential role of mesothelial cells in both preventing and inducing their development. (Fertil Steril® 2016;106:1018–24. ©2016 by American Society for Reproductive Medicine.)
Key Words: Mesothelial cell, tissue repair, inflammation, mesothelial-mesenchymal transition, postoperative adhesions, mesothelial cell transplantation

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Mesothelial cells form a monolayer of cobblestone-like cells that line the peritoneal, pleural, and pericardial cavities and most internal organs. This monolayer is termed the mesothelium and is a barrier and first line of defense against microorganisms and invading tumor cells. Following injury or exposure to foreign organisms or tumor cells, mesothelial cells initiate defense mechanisms, including inflammatory and immune responses. Mesothelial cells also provide a slippery nonadhesive surface to facilitate free movement of internal organs (1). When the integrity of the mesothelium is lost, a rapid healing response is initiated with complete repair within a few days. If this repair mechanism is impeded in any way, pathologic changes can occur to the serosal membrane, with potentially severe clinical manifestations such as adhesion formation, fibrosis, endometriosis, cancer, and metastases.

Embryologically, mesothelial cells are derived from the mesoderm, with cells gradually differentiating from round or cuboidal cells to elongated cells that line the celomic cavities (2). However, they share many properties of epithelial cells, such as apical/basal polarity, basement membrane adherence, junctional complexes, and surface microvilli. Their dual phenotypic characteristics influence the function of these cells, determining how they respond to environmental changes. The present review discusses some of the functions of mesothelial cells, how they regenerate an intact lining after injury, and the role they play in serosal pathologies, particularly the development of adhesions. We also discuss the potential use of mesothelial cells in tissue engineering applications to improve serosal repair and prevent adhesion formation.

ROLE OF MESOTHELIAL CELLS

Mesothelial cells are metabolically active cells that play important roles in maintaining serosal homeostasis. They provide a nonadhesive protective surface through the production of phospholipids and a well developed surface glycocalyx (fuzzy coat on the external surface of their plasma membrane consisting of glycolipids and glycoproteins) to allow movement of

Received August 3, 2016; revised September 1, 2016; accepted September 2, 2016.
S.E.M. has nothing to disclose. C.M.-A.P. has nothing to disclose. S.P. has nothing to disclose. S.E.H. has nothing to disclose.
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Fertility and Sterility® Vol. 106, No. 5, October 2016 0015-0282/$36.00

http://dx.doi.org/10.1016/j.fertnstert.2016.09.005

organs within the serosal cavities. The mesothelium acts as a semipermeable membrane regulating transport of fluid and cells across the serosa and is in constant contact with serosal fluid containing immunoglobulin, complement, lysozyme, and other proteins that aid microorganism clearance. Mesothelial cells display multiple pattern-recognition receptors, including Toll-like receptors, nucleotide-binding oligomerization domain–like receptors, RIG-I–like receptors, and C-type lectin-like receptors, which recognize carbohydrates and lipopolysaccharides on the surface of microbial pathogens such as bacteria, fungi, and viruses and in response release inflammatory mediators to initiate inflammation and activate immunomodulatory pathways (3).

Initiation of an effective inflammatory response requires rapid recruitment of leukocytes from the bloodstream to the site of injury through the generation of a chemotactic gradient and interaction with integrins and adhesion molecules on the surface of the mesothelial cells (4–6). The differential expression of adhesion molecules on mesothelial cells is also likely to regulate the specific type of cells that migrate. For example, integrins $\alpha 6\beta 1$ and $\alpha 4\beta 1$ selectively mediate adhesion and migration of T_H1 and T_H2 T-cell subsets, respectively, across human mesothelial cell monolayers (7). Furthermore, secretion of arginase by mesothelial cells and subsequent depletion of arginine leads to a reduced maturation of CD4+ T lymphocytes in vitro (8). Clearance of macrophages from the peritoneum is also controlled through integrin-mediated regulation of macrophage-mesothelial cell interactions involving very-late antigens 4 and 5 (9). This suggests that differential integrin expression and selective cell recruitment may have significant effects on immune regulation and resolution of resolution. Mesothelial cells also express class II major histocompatibility complex molecules and can therefore modulate the immune response through antigen presentation (10–13). Mesothelial cells also participate in the inflammatory and tissue repair process through the secretion of a wide range of cytokines, growth factors, and extracellular matrix (ECM) molecules (4, 14–19).

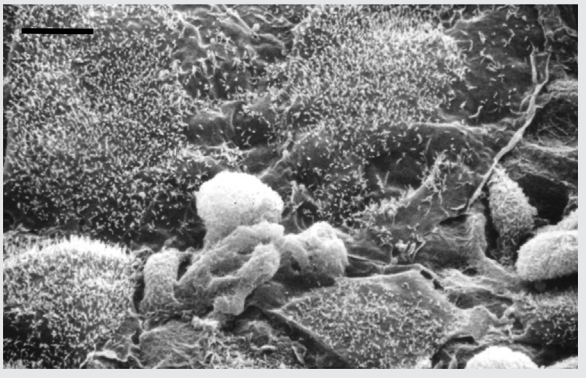
It is recognized that mesothelial cells release transforming growth factor (TGF) β, platelet-derived growth factor (PDGF), fibroblast growth factor, hepatocyte growth factor, keratinocyte growth factor, and members of the endothelial growth factor family (EGF, heparin-binding EGF, and vascular EGF) (20, 21) which initiate autocrine- and paracrine-induced cell proliferation, differentiation, and migration of mesothelial and other resident cells. They can be further stimulated when exposed to pathological situations such as peritonitis (22) and endometriosis (23) with the release of various cytokines and growth factors, such as interleukin (IL) 1β, tumor necrosis factor (TNF) α, EGF, PDGF, and TGF-β (24). Mesothelial cells also synthesize ECM molecules collagen types I, III, and IV, elastin, fibronectin, and laminin (24, 25) which are important for normal cell function. During tissue repair, they regulate ECM turnover by secreting proteases and antiproteases, including matrix metalloproteinases and tissue inhibitor of metalloproteinases, respectively, as well as regulatory factors, such as decorin and biglycan which inhibit TGF-β activity (26, 27). Furthermore, mesothelial cells control fibrin deposition and breakdown through production of tissue-type plasminogen activator (tPA), and its inhibitor plasminogen activator inhibitor (PAI) 1 and tissue factor (28–34).

MESOTHELIAL REPAIR

The mesothelium is a slowly renewing tissue, but if appropriately stimulated, its mitotic activity can be greatly increased. Within 48 hours of serosal injury, 30%–80% of mesothelial cells at the wound edge and on the opposing surface are stimulated to synthesize DNA, most likely by soluble mediators released from inflammatory and injured cells (35). Mesothelial repair differs from other epithelial-like surfaces because repair occurs diffusely across the injured surface, whereas for epithelium healing occurs solely from the wound edge. Furthermore, the integrity of the mesothelium is restored relatively quickly regardless of wound size. These observations suggest a unique mechanism for healing, where cells not only migrate onto the wound surface from the wound edge but also detach from opposing surfaces and distant sites and settle on the wound surface (Fig. 1). These free-floating mesothelial cells, detected in serosal fluid, subsequently proliferate and scatter to repopulate the injured area (36). Mesothelial cells are known to change phenotype in a process similar to epithelial-to-mesenchymal transition but termed mesothelial-mesenchymal transition (MMT) (37). TGF-β1, a key mediator of this process, induces the expression of the transcription factor SNAI1, with a dramatic down-regulation of epithelial markers, E-cadherin, and cytokeratins (38), resulting in a fibroblast-like and more motile phenotype. Mesothelial cells undergo MMT during continuous ambulatory peritoneal dialysis and up-regulate smooth muscle actin and type I collagen expression, which is consistent with a myofibroblast phenotype (38, 39). This suggests a fibrogenic role for mesothelial cells in conditions such as serosal fibrosis and adhesion formation.

There is also emerging evidence to support a blood-borne precursor, possibly originating from the bone marrow, that is released into the serosal fluid and subsequently attaches onto the denuded wound surface (40). The concept of a free-floating mesothelial cell has led researchers to investigate

FIGURE 1



Scanning electron micrograph 2 days after thermal serosal injury to a mouse testis. At the edge of the lesion, large flattened mesothelial cells, with variable numbers of short fine microvilli, have lamellopodia extended over fibrin and other cells. Scale bar = 12 μm.

Mutsaers. Mesothelial cells and peritoneal homeostasis. Fertil Steril 2016.