Chapter 1

The Mesothelium

Embryology, Anatomy, and Biology

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Introduction

Using only dissection and gross inspection, Xavier Bichat first described the serous membranes of the coelomic body cavities in 1799 (1):

> Every serous membrane represents a sack without any opening, spread over the respective organs which it embraces, and which are sometimes very numerous, as in the peritoneum, sometimes single, as in the pericardium, covering these organs in such a manner that they are not contained in its cavity, and so that if it were possible to dissect out their surface, we should obtain this cavity entire. This sack exhibits, in this respect, the same disposition as those caps doubled in on themselves, which are worn at night; a trivial comparison, but which gives an exact idea of the conformation of these membranes.

Despite not using a microscope – because he felt they were of limited utility – Bichat described over 20 different tissue types and noted the resemblance of the serous membranes to the lining of the lymphatics; subsequent authors likened the serous membranes to epithelial surfaces (2). Then, in the late nineteenth century, Minot demonstrated that despite these characteristics, the cells lining the body cavities are mesodermal in derivation (3). For this reason, Minot proposed the term "mesothelium" to convey this apparent paradox of epithelial function stemming from mesodermal roots. It is fairly intuitive that the epithelium-like mesothelium can provide a barrier function, and when paired with a smooth, fluid-bathed surface, one can readily extrapolate that these sheets of cells are also capable of minimizing friction so as to protect their encased vital organs even further. However, while serving as a slippery surface may be the most conspicuous purpose of the mesothelium, ongoing studies continue to reveal myriad unexpected functions of these seemingly humble cells, many with notable pathophysiologic significance.

Gross Anatomy of the Body Cavities and Serous Membranes

Humans possess four serous membranes: the pleura, the pericardium, the peritoneum, and the tunica vaginalis, with the latter existing only in males. Each membrane is essentially continuous, covering both the outer aspect of the cavity and the components within it, as the parietal and visceral mesothelium, respectively (Figure 1.1). As such, each membrane can be viewed as a reflection of the other, but with a different underlayment, and can be likened to a fisted hand compressing the central aspect of an inflated balloon. In the case of the pleura, the distinction between parietal and visceral mesothelium occurs at the lung hilum, with the visceral pleura adherent to the lung and the parietal pleura coating the inner aspect of the chest wall (endothoracic fascia) and superior aspect of the diaphragm; the parietal pleura is frequently subdivided into the costal, mediastinal, diaphragmatic, and cervical (superior to first rib) regions, which demonstrate some distinguishing features. The parietal peritoneum coats the abdominal cavity as a whole, including the superior aspect of the retroperitoneal organs, such as the uterus and urinary bladder. The transition from parietal to visceral peritoneum occurs at many locations; for example, at the junction of the diaphragm with the superior aspect of the liver, or the reflection from the posterior abdominal wall onto the root of the small intestine mesentery (Figure 1.2). The human peritoneum is so expansive, with an estimated total surface area of approximately 1.8 m^2, that it is comparable to the skin in extent (4). The terminology relating to the pericardium can be inconsistent between sources and therefore somewhat

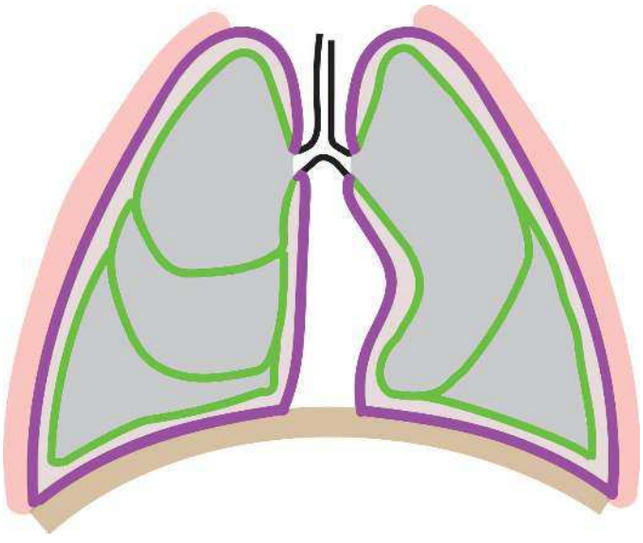

Figure 1.1 The parietal and visceral serous membranes consist of a continuous sheet of mesothelium. In the setting of the lung, the visceral pleura (green) is apposed directly to the lung parenchyma (gray) and reflects onto the chest wall (pink) and the diaphragm (brown) as the parietal pleura (purple); housed by these mesothelial cells is a true space, namely the pleural cavity (lavender).

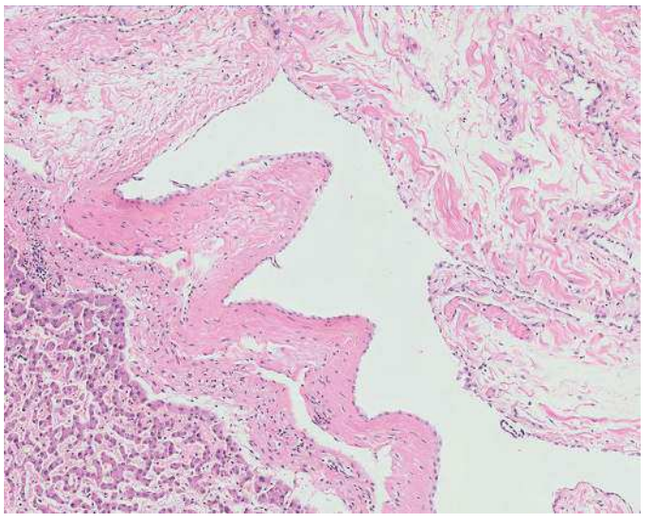

Figure 1.2 Peritoneal reflection from liver to diaphragmatic connective tissue. Visceral peritoneum lines the liver capsule (bottom left) and reflects onto the connective tissue lining the diaphragm (top right), where it is regarded as parietal peritoneum.

confusing; the visceral pericardium is more commonly known specifically as the "epicardium," and the seemingly general term "pericardium" is used by some in a more limited sense referring to the parietal pericardium. All of these cavities have in common that in the physiologic state there exists between the parietal and visceral membranes only enough fluid to prevent stress on the protected organs, making them true – as opposed to potential – spaces.

Basic Embryology of the Serous Membranes

The serous membranes develop in association with their underlying organs in an intimate manner that is highly conserved throughout vertebrates. Early in the third week of human gestation there is a division in the dorsal–ventral axis of the lateral plate mesoderm that carves out a space, i.e., the coelom, which will shortly thereafter be lined by mesothelium (Figure 1.3). The superficial layer produced by this separation forms the parietal (somatic) mesoderm, which combined with the immediately overlying ectoderm is known as the somatopleure and will form the body wall and parietal mesothelium; the deep layer constitutes the visceral (splanchnic) mesoderm, which can be viewed in combination with the underlying endoderm as the splanchnopleure and ultimately forms the organs of the coelomic cavities and the visceral mesothelium. It is exactly this emergence from a central division within a solid group of cells that results in the maintenance of physical continuity between the parietal and visceral mesothelium. The resulting coelom then exists as a single cavity until the fifth week of gestation, when septae begin laying the foundation that defines the future pleural, pericardial, and peritoneal cavities. The tunica vaginalis later forms from the processus vaginalis, which is a transiently patent extension of the peritoneum which is eventually obliterated in its central aspect to form a discrete cavity surrounding the testes.

The coelomic space is always bound by mesoderm throughout development, but mesothelium proper is not clearly established at the time the coelom is formed (5). Details of these processes stem from work done in model organisms, but it can be estimated that the mesothelium is established in the fifth to sixth weeks of human gestation. In vertebrates mesothelial development has been studied most thoroughly in the context of the epicardium, which is derived from the proepicardium (also known as the proepicardial serosa). The proepicardium is a transient, extracardiac primordium that contributes not only to the epicardium but also develops the coronary vasculature, cardiac fibroblasts, and smooth muscle of the cardiac vasculature (6). It begins as an epithelioid outgrowth from the sinus venosus and then courses through the pericardial coelom. In its earliest state the proepicardium demonstrates gene expression

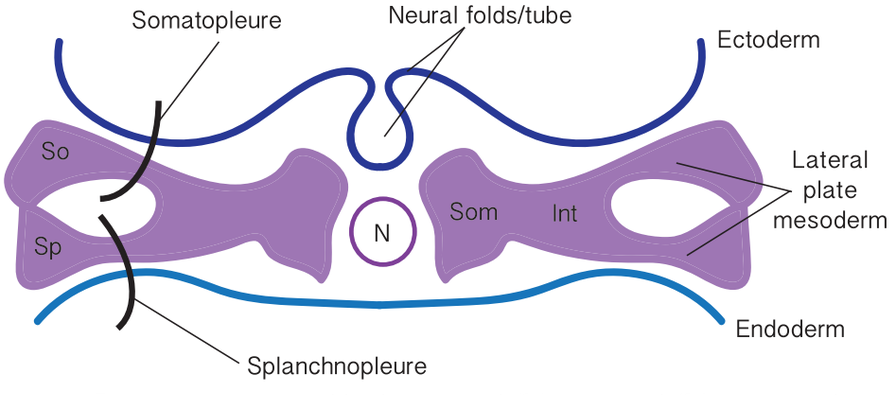

Figure 1.3 Mesothelial embryology. The lateral plate mesoderm divides into the somatic (So) and splanchnic (Sp) mesoderm, which partially comprise the somatopleure and splanchnopleure in combination with the ectoderm and endoderm, respectively (N, notochord; Som, somite; Int, intermediate mesoderm).

profiles characteristic of mesothelium, including genes such as *WT1*, even before it has finished coating the outer surface of the heart, and it harbors distinct progenitor populations distinguished by marker gene expression such as the transcription factor Tbx18. The proepicardium forms a coat around the heart from a combination of direct migration and transpericardial seeding, i.e., shedding, from villous or bleb-like protrusions, with subsequent contributions to the tissues of the heart proper; these protrusions exist not only at the sinus venosus but also develop at the roof of the pericardial cavity near the cardiac outflow tract, where they likely also establish the epicardium surrounding the great vessels (6).

There has been speculation that a process similar to that forming the epicardium occurs in the context of the visceral peritoneum (serosa) covering the intestinal mesentery, because mesothelial features are first identified at the root of the dorsal mesentery of the intestine and can subsequently be observed more broadly; however, recent work suggests that the processes governing serosal development are very different from those of the epicardium (5,7,8). Elegant experiments using chick–quail chimeras have demonstrated that rather than originating from an exogenous migratory population, the intestinal serosa is established from mesothelial progenitors scattered throughout the splanchnic mesoderm that differentiate *in situ*. Moreover, although the pleura and pancreatic mesothelium develop in close proximity to the proepicardium, they both demonstrate "organ-intrinsic" mesothelial development like that seen in the intestinal serosa (9). Therefore, to date, the epicardium is the only known mesothelial membrane that develops from recruitment of exogenous migratory precursors, and organ-intrinsic mesothelial progenitors may be the common mechanism of mesothelium formation.

Functional Anatomy and Fluid Dynamics

Despite being in continuity, there are subtleties between the parietal and visceral mesothelium in the functional anatomy to justify that they be considered as separate structures; and while the serous membranes are essentially sacs that are impermeable to the outside world – with the exception of the fallopian tubes – they are not completely impervious but rather connected to the lymphatics. Von Recklinghausen first demonstrated openings between mesothelial cells in 1863 using silver stains, and multiple subsequent investigators questioned his findings (10,11). Over time, studies using electron microscopy confirmed the disruptions and it is agreed that "stomata" do exist between the mesothelium and the lymphatics, ranging from 2 to 11 μm in diameter (12). Stomata first appear late in ontogeny and increase postnatally. While it was initially thought that stomata only exist in the diaphragmatic peritoneum, there are reports of stomata in the majority of mesothelial sites, with some controversy as to whether they exist in the pelvis. It has also been demonstrated that there are stomata between the serous membranes themselves, thus joining the pleural cavity to the peritoneal and pericardial cavities. These connections may explain the phenomenon of asbestos fibers reaching beyond the pleural cavity to places they would not be expected to deposit due to inhalation (13).

More prominent openings of the mesothelium can also be found at "milky spots," which are much larger than stomata on average, ranging from 0.5 to 3.5 μm^2 (12). Milky spots are so named because of their white appearance stemming from their abundant lymphoid content. Not surprisingly, they have a direct connection to the underlying large lymphatic vessels – lymphatic lacunae as well as a rich capillary network. In place of a surface mesothelium, milky spots are lined by macrophages, which presumably facilitate immune function and uptake of any foreign particles. While milky spots are most prominent in the omentum, they are also present in numerous other locations, including the pleura and various peritoneal sites, such as the broad ligament.

In a normal resting state, each of the coelomic cavities contains just enough fluid to maintain an essentially frictionless environment. In the pleural cavity, this fluid is estimated to be approximately 0.3 ml/kg and is hypo-oncotic in nature, consisting essentially of a plasma ultrafiltrate that is derived primarily from the systemic circulation supplying the parietal pleura (14). Using Starling forces, Neergard proposed in 1927 that pleural fluid dynamics are a function of the difference between hydraulic and colloidosmotic pressure. However, an increased understanding of the pleural anatomy in mammalian model systems over time has revealed the presence of interstitial spaces and lymphatics in the pleura, which undoubtedly contribute to the maintenance of fluid homeostasis (Figure 1.4). Consistent with this original hypothesis, it does appear that pleural liquid is derived from the vasculature of the parietal pleura as previously believed, but it travels through the extrapleural interstitium prior to entering the pleural space. Nearly all fluid drainage in turn proceeds through the lymphatics of the parietal pleura, which contain valves that ensure unidirectional flow and presumably contribute to volume control. These stomata to the pleural lymphatics are most prominent in the mediastinal and diaphragmatic regions, resulting in drainage of the pleura to the hilar, retroperitoneal, and lower mediastinal lymph nodes; given that pleural fluid is derived primarily from the apical aspects, it therefore seems that there is some degree of circulation within the pleural cavity (14,15).

Histology and Structural Biology

While mesothelial cells exhibit both epithelial and mesenchymal features – and it is this very ability to transition from one state to the other, i.e., to undergo epithelial–mesenchymal transition, that makes them such an interesting subject of study – mesothelial cells primarily demonstrate epithelioid morphology in their mature state forming the serous membranes. Normal resting mesothelial cells exist as a monolayer with apical–basolateral polarization overlying a basal lamina,

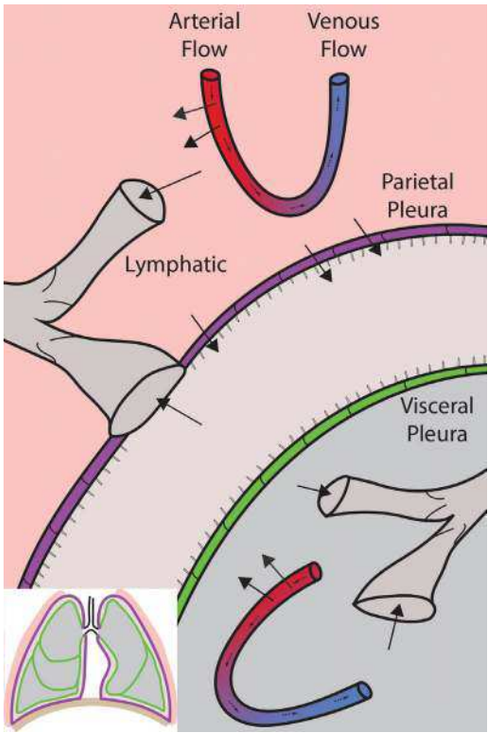

Figure 1.4 Pleural fluid dynamics. Pleural fluid is produced as an ultrafiltrate of the systemic circulation that first passes through the extrapleural interstitium. Drainage of the pleural cavity then occurs through lymphatics in the extrapleural tissues via stomata within the parietal pleura. The visceral pleura is not thought to contribute to the pleural fluid.

with the vast majority exhibiting the flat character of squamous cells (Figure 1.5a,b). These squamoid mesothelial cells are approximately 20–25 μm in diameter and characteristically have a centrally placed nucleus with a relative paucity of organelles that are primarily perinuclear in distribution or just overlie the nucleus (12). Interspersed among them to varying degrees, depending on location, are cuboidal mesothelial cells; there is a higher proportion of cuboidal cells in the mediastinal pleura, peritoneal diaphragm, liver, spleen, and "milky spots" of the omentum. These cuboidal cells have a diameter of only 8 μm on average and have markedly different features than squamoid mesothelial cells beyond their smaller footprint. They feature a larger nucleus with a prominent nucleolus, more numerous and complex microvilli, more developed organelles, increased mitochondrial content, and a different enzymatic profile that is more active than that of their squamoid counterparts. In addition to these two extremes of squamoid and distinctly cuboidal, cells with intermediate features exist and can even be the dominant cell type in some sites (12,16).

Like epithelium, mesothelial cells have a variety of specialized features, perhaps most notably microvilli (Figure 1.6). The microvilli of mesothelial cells were studied in great detail in the 1950s by Odor using the rat oviduct as a model system, and then in 1970, Stoebner declared that microvilli are perhaps the most useful defining feature of the mesothelium (17,18). Mesothelial microvilli are covered by a film of negatively charged, hyaluronic acid-rich glycoprotein – the glycocalyx – that is thought to aid in fluid adsorption, to provide a defense function against infection, and to protect against formation of adhesions; the hyaluronic acid can be demonstrated by Alcian blue staining (pH 2.5) and is sensitive to digestion with hyaluronidase (13). While the microvilli *per se* cannot be visualized by light microscopy alone under most circumstances, their abundance results in an apparent gap between cells, forming a sort of "window" that is readily visualized in cytologic preparations; in some preparations, e.g., Giemsa staining performed on an air-dried slide, metachromatic staining can highlight the microvilli as a unit (Figure 1.7). By electron microscopy, it is evident that the microvilli of mesothelial cells are diverse, but overall long and slender (up to 3 μm in length, compared to approximately 1 μm in the intestine), with the potential to increase the peritoneal surface area approximately 20-fold (12,19,20). Moreover, the mesothelial microvilli have known plasticity and can increase in concentration or alter their surface charge in response to changes in the environment. It is currently hypothesized that the main function of microvilli is to trap proteins from the serosal fluid to maintain mesothelial integrity (13).

Microvilli are only one feature of mesothelial cells that is reminiscent of epithelium (12,13). Multiple mechanisms contribute to the epithelium-like barrier function of mesothelium, including tight junctions (zonula occludens), adhering junctions (zonula adherens), and desmosomes (macula adherens). The adhering junctions of mesothelial cells contain E, N, and P cadherins, but in contrast to the E-cadherin-predominant epithelium, N-cadherin is dominant in mesothelial junctions. Mesothelial cells also produce their own underlying basement membrane materials, communicate with one another via gap junctions, and actively engage in transport of both fluids and particulate matter using pinocytic transport. In some cases, namely the visceral peritoneum overlying the spleen and liver, there is a prominent layer of elastin beneath the basal lamina (12). Like microvilli, pinocytic vesicles can be demonstrated by electron microscopy in mesothelial cells, where they are seen primarily in association with the plasmalemma on the luminal surface; their functionality has been demonstrated by tracer studies. Multiple additional findings reflecting diverse function of normal mesothelial cells have been demonstrated, including lamellar bodies, lipid droplets, cytofilaments, glycogen accumulation, and occasionally primary cilia.

Postnatally, the inherent mesenchymal features of mesothelial cells are most apparent in reactive states; in the resting state their mesenchymal character is revealed primarily through special studies demonstrating expression of intermediate filaments that are characteristic of mesenchymal lineages (vimentin and desmin) in addition to those characteristic of epithelium (keratins), with the extent of coexpression varying according to context (Figure 1.5c,d). The mesenchymal features of mesothelial cells also become evident in culture, where they lose their polygonal character and take on a spindle appearance; *in vivo* these

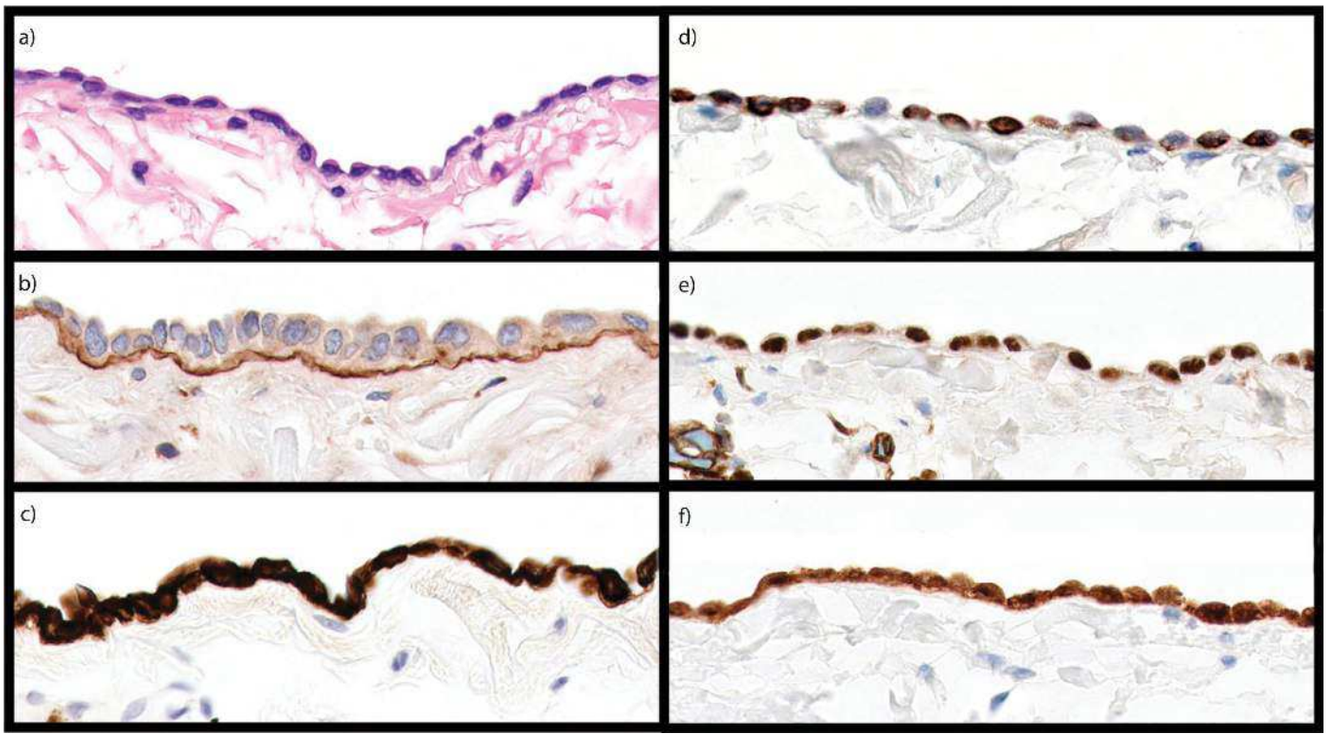

Figure 1.5 Basic mesothelial histology. Hematoxylin and eosin-stained section (a) demonstrates single-layer of mesothelial cells that rest on a basal lamina (b, laminin). Mesothelial cells express both keratins (c, CAM5.2) and intermediate filaments of mesenchymal cells (d, desmin) and can be identified by a variety of immunohistochemical markers with various localization (e, WT-1 in nucleus; f, calretinin in nucleus and cytoplasm).

features are most pronounced prenatally and in states of repair, which are discussed below. There are a variety of immunohistochemical markers that are characteristically expressed in mesothelial cells, both with epithelioid and spindle morphology; these include WT-1, calretinin, D2–40 (podoplanin), and keratins, with CK5/6 being the most frequently utilized clinically (Figure 1.5e,f).

Mesothelial Regeneration

Disrupted epithelial surfaces are known to heal from the edges of a wound, and it was thereby assumed for some time that mesothelium must undergo a similar process. Indeed, while normal mesothelium is not mitotically active (< 0.5 percent of cells dividing at rest), up to 80 percent of mesothelial cells can be demonstrated to be cycling at a wound edge (15). However, while cells at the wound edge develop spindle morphology and migrate into the wounded area and undoubtedly contribute to wound healing, as a whole, mesothelium regeneration appears to occur largely via an alternate mechanism. In the 1950s to 1970s, multiple investigators reported findings indicating that healing time for mesothelial wounds is not related to their size and rather that mesothelial wounds heal across the entire surface in such a manner that healing occurs within 7–10 days,

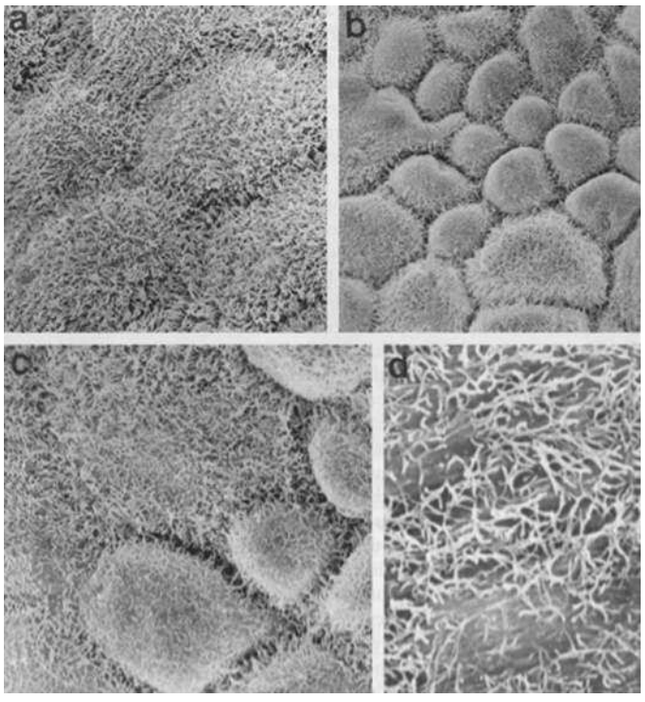

Figure 1.6 Scanning electron microscopy of microvilli. Microvilli can be so dense as to obscure cell boundaries (a, ×200), but can be variable in distribution (b, ×150; c, ×200). Panel (d) demonstrates a high-power view of microvilli (×3000). [With permission from Michailova & Usunoff, 2006, Springer.]

irrespective of size, thus arguing at a minimum that mechanisms other than healing from the wound edge must also be at play (21). Multiple theories have been proposed to explain this finding, including origination from residents beneath the mesothelium, settling of mesothelial cells having previously detached from another site, pre-existing free-floating serosal progenitors, and transformation from bone marrow-derived populations, including macrophages and pluripotent precursors (13,15,21).

Overall studies favor that a free-floating serosal progenitor is responsible for much of the mesothelial healing process (13). Findings in favor of this theory include recovery of healing with the addition of peritoneal lavage cells, and conversely, impaired healing following peritoneal lavage that presumably removes said progenitors. Direct analysis of peritoneal fluid has also demonstrated an increase in the amount of free-floating mesothelial cells following injury, and tracing studies have directly demonstrated incorporation of mesothelial cells introduced by lavage. It is postulated that free-floating mesothelial cells are able to take hold of the components of the exposed extracellular matrix. It should also be noted that mesothelial cells secrete a variety of growth factors that facilitate healing, including transforming growth factor-beta, fibroblast growth factors, and platelet-derived growth factors among others, as well as extracellular matrix components, such as collagen types I, III, and IV, elastin, fibronectin, and laminin (13). Bone marrow-derived and submesothelial precursors are essentially excluded by rescue with lavage in the setting of irradiation to the bone marrow or wound, respectively.

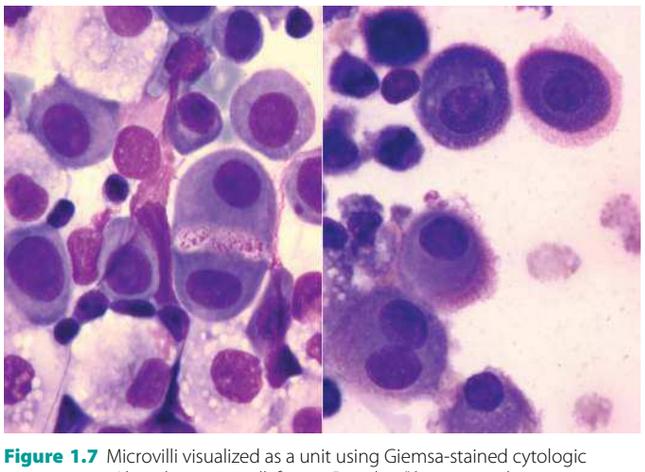

Figure 1.7 Microvilli visualized as a unit using Giemsa-stained cytologic preparations. Abundant microvilli form a "window" between adjacent mesothelial cells (left) that can in some preparations be recognized as a unit by metachromatic staining that rings the cell (right).

Manifestations of Mesothelial Cells in the Development of Other Mesenchymal Tissues

As mentioned previously, the mesenchymal features of mesothelial cells are evident in culture, as demonstrated by loss of their usual polygonal shape and acquisition of spindled morphology reminiscent of fibroblasts. Beyond this spindled appearance, for some time it has been known that true myofibroblastic differentiation, e.g., expression of smooth muscle actin, can be induced in mesothelial cells in culture (22). However, it has become increasingly clear that this function has biological relevance both embryologically and in the context of various states of injury, as mesothelial cells generate other cell lineages (23). One of the first observations of this phenomenon was identified using quail–chick chimeras, in which epicardial mesothelium was identified as differentiating into endothelium and smooth muscle through a process akin to the epithelial–mesenchymal transition (EMT) (24). Mesothelial cells are of course not truly epithelial despite their many shared features, and for this reason, the more specific term "mesothelial–mesenchymal transition (MMT)" also appears in the literature. Using lineage-tracing studies, such results of an EMT/MMT have since been observed in numerous contexts, including the myocardium, smooth muscle of the airways and vasculature, endothelium, hepatic stellate cells, fibroblasts, perivascular mesenchyme, gut tube anlage, and visceral adipocytes (23,25). Similarly, in the context of myocardial infarction, mesothelial cells are able to proliferate and migrate into the heart where

they differentiate into fibroblasts, vascular smooth muscle, endothelial cells, and potentially even cardiomyocytes (23).

Mesothelium in Immunity

Given that mesothelial cells are capable of uptake of particulate matter, it is not a huge leap to accept that they are also capable of phagocytosis. However, there are reports indicating that mesothelial cells can also perform antigen presentation and produce cytokines. For example, following phagocytosis of bacteria, mesothelial cells can release interleukin-8 (26). In fact, they can produce a variety of chemokines and cytokines, including IL-1, IL-6, IL-15, G-CSF, M-CSF, GM-CSF, IL-8, MCP-1, and RANTES, among others (13). In some cases these mediators are released as the result of phagocytosis of either foreign material or an organism by the mesothelial cell itself, and in others it is a response to other mediators in the cellular milieu that have been released by other cells with a more classic role in immunity, such as macrophages or T cells. Mesothelial cells also express a range of adhesion molecules that can be used to facilitate leukocyte migration. By serving as a dock for leukocytes and releasing various effectors of immune function in a polarized manner – i.e., into the body cavity – mesothelial cells are able to facilitate recruitment of leukocytes to the site of need.

Mesothelium in Coagulation and Fibrinolysis

Mesothelial cells actively influence the steady state between coagulation and fibrinolysis. Procoagulant activity is facilitated by (1) release of tissue factor, which is the essential activator of the extrinsic pathway of the coagulation cascade, (2) physical assembly of the prothrombinase complex on the cell surface, and (3) secretion of plasminogen activator inhibitor (PAI-1 and PAI-2) (13). To counter this activity, fibrinolysis is facilitated primarily by release of tissue plasminogen activator (tPA) but also by urokinase plasminogen activator (uPA), both of which are capable of digesting fibrin. In the absence of tissue insult, these two processes exist in a delicate balance; following injury, it appears that the fibrinolytic activity of the mesothelium is increased (21). However, in many cases this may not be sufficient, and adhesions can result. There is work ongoing to address the possibility of harnessing these processes to reduce adhesions in the peritoneum.

Therapeutic Applications of Mesothelial Cells

Omental grafting has been used for many years in a variety of surgical settings as a means of facilitating wound healing, and additional applications are continually being developed (27–29). The cellular processes underlying the success of omental grafting are largely unclear, at least in part due to the variety of cell types that make up the omentum. Grafts obtained from cultures of isolated mesothelium have provided evidence that mesothelial cells are likely responsible for at least some of this success, with possible mechanisms including the generation of vasculogenic cells and/or paracrine secretion of growth factors that promote the process of neovascularization (16,30). Such potential for differentiating into a variety of lineages, both in the embryo and in the adult, makes the mesothelium an appealing target for tissue engineering. Potential applications include prevention and treatment of peritoneal adhesions, peritoneal restoration following dialysis, vascular grafting, and nerve regeneration (16,31). The vast majority of studies are preclinical at this stage, but there is abundant potential in this line of study that will be of interest in upcoming years.

Comparative Anatomy and Embryology

While the basic arrangement of somatopleure, the coelom, and splanchnopleure is conserved throughout true coelomates, as one may expect, there are some striking differences in the serous membranes between species (5). There is one notable and striking exception to the considerable similarity of the body cavities even within mammals, which is seen in the elephant. Embryologically, the pleural cavity of the fetal elephant is quite similar to that of the human, but it is obliterated late in gestation (32–35). This "congenital pleuridesis" completely obliterates the pleural space, thus raising the question as to the true necessity of having a pleural space in humans; this question also arises in the context of therapeutic pleuridesis, in which the pleural space is intentionally obliterated in order to prevent recurrent pleural effusion. It is thought that the elephant obliterates the pleural space as a means of handling the pressures associated with snorkeling at depth. Indeed, the obliteration cannot simply be a result of the size of the organism or the pressure of the water, as whales have normally developed pleural spaces.

In addition to structural differences between species, developmental processes can vary even when the resulting structure is essentially the same. The epicardium is structurally conserved among all vertebrates, but the manner in which it develops is fairly variable, despite the fact that the proepicardium can be demonstrated even in the fairly primitive dogfish (6,36). In dogfish, it appears that all of the epicardium is seeded in a transpericardial fashion, with patches eventually coalescing to form a complete membrane. In contrast, experiments in amphibian and avian embryos have demonstrated that most epicardium is formed by progenitors spreading across a tissue bridge between the villous protrusions of the proepicardium and the dorsal aspect of the ventricles, although transpericardial seeding also occurs. Perhaps surprisingly, transpericardial seeding is the predominant mechanism in mammals. It is hypothesized that this difference stems from the closed nature of the pericardial cavity in dogfish and mammals, whereas the pericardial cavity communicates with the extraembryonic coelom in avian embryos, which could result in loss of the seeded progenitors from their intended location.

The fallopian tubes are the only connection between the serous cavities and the outside world in humans. In contrast,

the peritoneum of fish has a well-established and large connection to the outside world that is used for the excretion of fluid and cells. Interestingly, while microvilli have been designated as a hallmark feature of mesothelial cells, they are not present in the peritoneum of fish. Various functions have been attributed to the microvilli that abundantly coat the human mesothelium, among them protection from frictional contact. Such a function is congruent with the absence of microvilli in the peritoneum of fish, where the membranes are not subject to abrasion, but float rather freely in a pool of water.

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