

Endothelium ^[1]

By: MacCord, Kate

The endothelium is the layer of cells lining the blood vessels in animals. It weighs more than one kilogram in adult humans ^[2], and it covers a surface area of 4000 to 7000 square meters. The endothelium is the cellular interface between the circulating blood and underlying tissue. As the medium between these two sets of tissues, endothelium is part of many normal and disease processes throughout the body. The endothelium responds to signals from its surrounding environment to help regulate functions like the resistance that blood vessels need to pump blood through the body (vasomotor tone), the policing of substances trying to enter or exit the blood vessel (blood vessel permeability), and the ability of blood to clot (hemostasis). In addition to diseases like atherosclerosis, endothelium has been indicated as a component in pathologies like cancer, asthma, diabetes, hepatitis, multiple sclerosis, and sepsis. The shape, size, and appearance of endothelial cells, called their phenotypes, vary depending upon which part of the body the cells are from, a property called phenotypic heterogeneity. The endothelium, its properties, and its responses to stimuli are governed largely by the local environment of the cells.

The phenotypic heterogeneity displayed by endothelial cells depends on two factors. First is the microenvironment of the individual cells. Endothelial cells respond to stimuli from their immediate surroundings and maintain a flexible and adaptive ability to respond to the needs of their local environment. For instance, endothelial cells in the blood-brain barrier are exposed to signals from cells in the brain, like astroglial cells, and they help to maintain the separation between circulating blood and cerebrospinal fluid. But endothelial cells in the capillaries surrounding the heart are exposed to signals from their neighboring heart muscle cells, cardiomyocytes, and they help perfusion of blood to the surrounding muscle. The second factor governing the phenotype of endothelial cells is the genetic basis of each cell. Research into the genes ^[3] expressed in endothelial cells from different parts of the vascular system indicates that endothelial cells may not be intrinsically identical—each endothelial cell varies from others in its ability to express genes ^[3] and proteins that may be different from its neighboring cell. Researchers hypothesize that these two factors, microenvironment and genetic make-up, partly determine the response of the individual endothelial cell to stimuli and creates a range of diversity within the endothelium as an organ system.

Wilhelm His ^[4] first introduced the term endothelium in 1865 by in an essay titled, *Die Häute und Höhlen des Körpers* (The Membranes and Cavities of the Body). His, a professor at the University of Basel ^[5] in Basel, Switzerland coined the term to distinguish between the cells lining the cavities of a body, especially blood vessels, and the epithelia, or layers of cells covering the outer surfaces of organs. Using microscopes, His detailed the developmental history of the membranes and cavities formed by the middle germ layer, or the mesoderm ^[6], during the early stages of development. From these observations, His determined that several factors distinguished the cells lining the interior of cavities from those lining the exterior of organs. To His, endothelial cells did not participate in growth processes, and they were passive or inert cells. The cells also did not produce secretions or act as an effective barrier for the vessels they lined. In addition to these factors, His noted that the structures of the cells appeared different from epithelial cells.

Many of His's contemporaries rejected both the term and the concept of endothelium on several grounds. First, they doubted that this tissue lacked fundamental differences, in either form or function, from the epithelium ^[7]. Anatomists expressed their dissent in numerous publications, including Carl Gegenbaur ^[8], a professor of anatomy at the University of Jena ^[9] in Jena, Germany, and Josef Hyrtl, a professor of anatomy at the University of Vienna in Vienna, Austria. Second, His classified the endothelium as a derivative of mesoderm ^[6]. Physiologist Michael Foster ^[10] at the University of Cambridge in Cambridge, England, and author of an 1874 textbook on physiology, objected to the classification because His's definition left out many epithelium ^[7]-like derivatives of the mesoderm ^[6], like the Wolffian ducts of the urogenital system.

Scientists' opposition to the category of endothelium on the basis of unsubstantiated differences in form and function from epithelium ^[7] subsided at the end of the nineteenth century with the advent of more powerful microscopes and new histology ^[11] techniques. Anatomists began to further study the endothelium, including Heinrich Wilhelm Gottfried von Waldeyer, at the University of Berlin ^[12] in Berlin, Germany, who consolidated the neuron ^[13] theory of nervous system organization ^[14] and coined the term chromosome. In the early twentieth century, as results from experimental embryology ^[15] eroded germ layer theory, a theory in which each of the germ layers ^[16], regardless of species, gave rise to a fixed set of organs, so too did scientists' objections to defining endothelium as a mesodermal derivative.

By the middle of the twentieth century, scientists had observed the distinct structure of the endothelium through the use of electron microscopes. In 1958, Richard Hibbs and colleagues at Tulane University in New Orleans, Louisiana, used electron microscopy ^[17] to investigate the structure of endothelial cells. To buttress previous research that indicated that endothelium tended to be specialized according to location and function, Hibbs and his co-workers investigated the appearance of endothelial cells of capillaries from the skin of the finger and the abdomen of humans ^[2]. This study showed that endothelial cells exhibit a degree of heterogeneity beyond what anyone had hypothesized. Six years later, George Palade and Ewald Weibel,

working at the [Rockefeller Institute](#)^[18] in New York, New York discovered what later researches called Weibel-Palade bodies, rod-shaped tubules in the cytoplasm that characterize all endothelial cells. These organelles store molecules like Von Willebrand factor, a clotting factor involved in hemostasis, and P-selectin, a cell adhesion molecule (CAM) that partly recruits white blood cells (leukocytes) to sites of injury during inflammation.

In the early 1970s, studies of endothelium revealed not only the structure of the cell, previously studied with electron microscopes, but also the function of endothelial cells. In 1973, Eric Jaffe and colleagues, working in [Cornell University](#)^[19] Medical College in New York, New York, and at the University of Connecticut School of Medicine in Farmington, Connecticut, isolated and cultured endothelial cells *in vitro*^[20], or outside of the body. With this result scientists could study the behavior of endothelial cells in controlled environments. While *in vitro*^[20] studies yielded insights into the heterogeneity of endothelial cell phenotypes, they did so under the assumption that endothelial cells maintain their site-specific phenotype in culture. According to many of the chapters in *Endothelial Biomedicine*, a textbook on the endothelium published in 2007 and edited by William Aird, this assumption is not always true.

In the 1980s, several research groups discovered that the phenotypic heterogeneity of endothelial cells extended into their molecular profiles—endothelial cells express site-specific genetic markers and molecules. Researchers in the 2000s used genomic and proteomic techniques to uncover diversity in site-specific expression of different [genes](#)^[3] and molecules by endothelial cells. Their work indicated that the endothelium exhibits a high degree of phenotypic heterogeneity, but it also responds to signals from its proximate environment. The ability of endothelium to react to its environment indicates that researchers may see such abilities only when they study endothelial cells as part of an integrated organ system.

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