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Morphogenetic Mechanisms of Endothelial Cells During Lumen Formation in Sprouting Angiogenesis

Mohammad Salar Ghasemi Nasab[1], Hanieh Niroomand-Oscuii[1,*], Hossein Bazmara[2], Majid Soltani[3,4,5,6,7]

[1] Department of Biomedical Engineering, Sahand University of Technology, Tabriz, Iran
[2] Azad University, Pardis Branch, Tehran, Iran
[3] Department of Mechanical Engineering, K. N. Toosi University of Technology, Tehran, Iran
[4] Advanced Bioengineering Initiative Center, Computational Medicine Center, K. N. Toosi University of Technology, Tehran, Iran
[5] Cancer Biology Research Center, Cancer Institute of Iran, Tehran University of Medical Sciences, Tehran, Iran
[6] Department of Electrical and Computer Engineering, University of Waterloo, Waterloo, Ontario, Canada
[7] Centre for Biotechnology and Bioengineering (CBB), University of Waterloo, Waterloo, Ontario, Canada
**Corresponding author: Hanieh Niroomand-Oscuii, Department of Biomedical Engineering, Sahand University of Technology, Tabriz, Iran. Tel: +984133458456; Fax: +984133444360. E-mail: niroomand@sut.ac.ir*

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Different mechanisms such as cell migration, proliferation, branching, anastomosis, and lumen formation occur during the angiogenesis process. Lumen formation is one of the critical mechanisms which is not only necessary for the functional plexus but also for continuing of angiogenesis process. Although multiple studies investigated this mechanism during the angiogenesis process in both in vivo and in vitro conditions, it is not fully understood yet. Different studies have suggested distinctive mechanisms as the main mechanism for lumen formation. Recent studies, however, have shown the fundamental role of blood flow hemodynamics, especially during in vivo lumen formation. This newly introduced mechanism is called "inverse membrane blebbing"; suggesting that blood pressure causes the formation and expansion of lumen during the in vivo angiogenesis process. This paper reviews cell behavior during lumen formation in the angiogenesis process on a cellular scale.

INTRODUCTION

The vascular system has an important role in tissue survival, growth, and reproduction. This system has various functions such as metabolites delivery and recycling, exchange of gases, and transport of immune cells [1]. Abnormalities in the vascular system could cause different diseases and pathological problems [2, 3]. The vascular system of vertebrates is developed through complex and hierarchized mechanisms [4]. Due to its critical role, the vascular system is the first developed system during embryonic development [5]. Heart and primitive vascular plexus are formed and grown by vasculogenesis process [6].

Vasculogenesis refers to the formation of new vessels from the mesoderm which forms hemangioblasts. Remodeling and expansion of primitive vascular plexus occur through the second process known as angiogenesis, the process in which new blood vessels are formed from pre-existing vessels. Angiogenesis is performed after birth, but most of the endothelial cells are developed into quiescent the lifetime of which varies between different organs [7]. However, quiescent endothelial cells can respond to pro-angiogenic factors. For instance, lack of oxygen in the tumor cells disturb the balance between pro-angiogenic and anti-angiogenic factors in patients with cancer and a new vascular network is formed around the tumor through the angiogenesis process [8]. The angiogenesis process also occurs during wound healing [9], diabetes, multiple sclerosis, etc. During the angiogenesis process, the most important role is played by endothelial cells of the parent vessels. These cells respond to different signals (like chemical and mechanical signals) and show different behaviors. Migration, proliferation, elongation, and lumen formation mechanisms are the most important behaviors of endothelial cells during angiogenesis. Lumen formation is one of the important mechanisms during angiogenesis in which luminal space or tubal structure is formed in or between endothelial cells. Lumen formation is an essential mechanism that causes the perfusion of blood in newly formed vessels. Lumen formation has been investigated both in vitro and in vivo in different processes such as vasculogenesis and angiogenesis. Even though the main mechanisms of the lumen formation are well known, it is still obscure during angiogenesis; especially in in vivo conditions. In this paper, we will look at general mechanisms of lumen formation and review the studies on lumen formation during sprouting angiogenesis.

General Mechanisms of Lumen Formation

Formation of luminal space or tubular structure is crucial in different tissues and organ development [10] and also during different mechanisms such as angiogenesis [11]. Different lumen formation mechanisms cause the formation of different luminal structures of various sizes and structures [12]. Lumen's diameter is regulated by blood flow and genetic information [13]. Some lumens transport the fluid, but some others transport and modify the fluied. Another distinction between different lumens is the number of cells in a cross-section view of the tissue. Lumens with large diameters could be composed of hundreds of cells in each cross-section; in the other way, some small diameter tubes are composed of only one cell [12]. The simplest lumens are just epithelial monolayers but most of the lumens contain additional cell layers. Most lumens contain a cell-cell junction as a cell attachment site; while some unicellular tubes have junctionless structures. Apical-basal polarity is one of the specific polarity behaviors in endothelial cells. In this process, the cell's apical membrane faces outside (or into the luminal space), and the basal membrane faces inside of the cell. Directed and controlled transmission of molecules can be seen between apical and basal membranes. Apical-basal polarity is necessary for lumen formation in some mechanisms. In a general view, lumen formation could be classified into six mechanisms [14]:

1. Wrapping: Neurulation or formation of the primary neural tube in vertebrates' embryos [15, 16] is the most common instance of these mechanisms. Differentiation of cell population within the ectoderm germ layer causes the formation of neural prosecutor's plate. This plate is polarized by its apical membrane. This polarized plate causes coordinated cell elongation through the apical-basal membrane axis [17]. Formation of wedge shape cells by cell division, contraction of actomyosin, the fusion of neural plate edge, and separation of these parallel tubes are some known cell behaviors during this mechanism [18].
2. Budding: branching of mammalian lung and Drosophila respiratory system are some morphogenesis examples of this mechanism [19, 20]. Elongation of cells population through their apical-basal membrane, gyration of buds, and formation of the lumen are the known cell behaviors during this mechanism [18]. In both wrapping and budding mechanisms of lumen formation, the epithelium is already polarized.
3. Cavitation: Formation of a central cavity in a thick cylindrical mass of cells by central cells apoptosis is the main process in cavitation [12]. Mouse salivary gland development [21, 22] and amniotic cavity formation [23] are some examples of lumen formation by cavitation. In the initial steps, the extracellular matrix

(ECM) transmits some polarization signal to the outermost cell layer which has a strong intracellular junction because of its attachment to the ECM; causing survival signal in these cells. However, the cell in the center express pro-angiogenic factors because of their lost attachment to ECM and neighbor cell; causing apoptosis cascade [23].

4. Cell hollowing: In this mechanism, the lumen is formed within a unique cell. The intracellular lumen or de novo lumens form in cell cytoplasm by cell ability of generation and fusion of vacuoles segment. Cell hollowing could be observed in some capillary endothelial cells [24].
5. Cord hollowing: In this mechanism, lumen forms in a thin cylindrical aggregation of endothelial cells, between neighbor cells, and at their contact without apoptosis. One of the popular instance of this mechanism is the Madin-Darby canine kidney that has been studied in both molecular and cellular scales [25-28]. Another example is the Drosophila heart [29] and Caenorhabditis elegans gut [30].
6. Membrane invagination: In this mechanism, lumen expands in neighbor cells that were already lumenized. Studies on the Drosophila trachea are an example of this mechanism; showing the difference between membrane invagination and cell hollowing [31].

Figure 1 shows the schematic of these six distinct mechanisms of lumen formation in general.

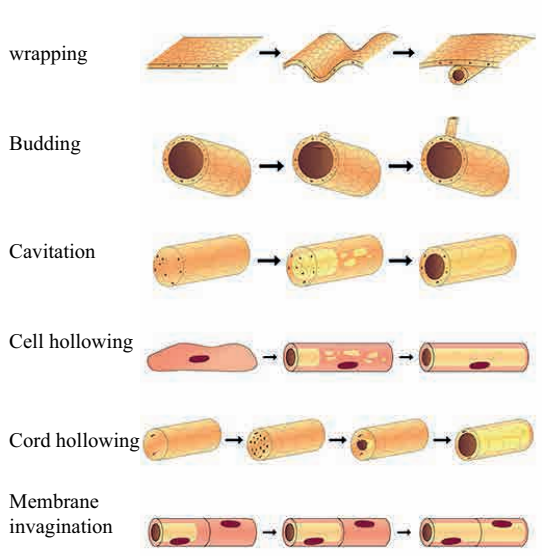

Figure 1: Different Mechanics of Lumen Formation.

Cellular Mechanisms of Lumen Formation During Sprouting Angiogenesis

Multiple studies were executed on the morphology of the lumen formation in the angiogenesis process in both in vivo and in Vitro conditions. Lumen formation is a critical step during the angiogenesis process that occurs on vascular sprouts during the invasion and growth of the cells [13]. Some of these studies are reviewed in the following paragraphs.

Cell Hollowing As the Main Mechanism of Lumen Formation

During sprouting angiogenesis, endothelial cells have different behaviors such as migration, elongation, mitosis, etc. This dynamical behavior of cells during angiogenesis and also difficulty in imaging make cell behavior studying challenging; especially in in vivo experiments. Until 1980, the angiogenesis process was studied in animal models [32, 33] and chick embryos [34]. In 1980, Folkman studied angiogenesis in vitro for the first time and paid attention to the mechanism of lumen formation during angiogenesis [35]. Accordingly, bovine capillary endothelial cells cultured in tumor condition medium were studied and electron microscopy was used for imagining. In this study, cylindrical vacuoles were observed in single cells at the first stage. After 48 hours, connected cells developed similar vacuoles, and a long lumen was formed. This study also suggested that 'Y' or 'T' shape vacuoles in single cells and the connection of these vacuoles with neighbor cells form branches. Therefore, Folkman's study for the first time suggested that lumens are formed by the formation of vacuoles that are converted to the lumen structure, and the connection of different tubes could result in branches formation. This mechanism is just like the cell hollowing mechanism without the requirement of blood pressure to form a lumen formation mechanism [35]. In 1996, human umbilical vein endothelial cells were cultured in 25 µL of type 1 collagen gel to allow the study of lumen formation [35]. In this study, basic fibroblast growth factor (bFGF) and vascular endothelial growth factor (VEGF) were also used in a serum-free culture medium as angiogenic factors. This culture medium was provided for direct observation of additives influence and allowed the distinction of different

steps such as lumen formation and capillary network formation. Vacuoles were observed with different sizes after several hours, and the luminal structure was observed after 12-16 hours. It was also observed that an ECM could influence cell behavior during angiogenesis. In this study, some blocking monoclonal antibodies have been used to investigate the role of integrin. Integrin links cells' cytoskeleton to the ECM. Their results showed that collagen-binding integrin α2β1 is required as a major regulator during the vacuoles and lumen formation process. The pinocytic mechanism was also suggested as a major mechanism for vacuoles formation during the angiogenesis process. This study also showed that intracellular vacuoles, their volume increase, and interconnection of them in endothelial cells; which are in connection with the ECM, results in lumen formation and vessel network [36].

Distinct Mechanism and Importance of Cell's Junction During Lumen Formation

Childs performed an in vivo study in zebrafish trunk by laser activation of a caged dye in 2002 [37]. He reported three different kinds of endothelial cells behavior: endothelial cell migrating until reaching the dorsal longitudinal anastomotic vessel (DLAV), aortic cells following the same path and stretching from the intersegmental vessel (ISV) to (DLAV), and endothelial cells forming T shape in DLAV. By their observation, they suggested that cell junction plays a critical role in lumen formation during sprouting angiogenesis [37]. Lumen formation in sprouting angiogenesis was firstly studied in vivo in 2006 [10]. In this study, lumen formation was observed in transgenic zebrafish by a high-resolution time-lapse two-photon imaging technique, and pictures were taken every 3-5 minutes. The results of this study also have been compared with in vitro models. In this study, the existence of vacuoles was reported, but they appear and disappear both in in vitro and in vivo investigations. Another interesting result of this study was the observation of membrane protrusions which causes extension and retraction of lumenal space. In this study, cytoplasmic mixing was not observed during multicellular lumen formation; indicating that exocytosis of vacuoles into cell-cell contact space causes multicellular lumen and blood vessel formation. The apoptosis of endothelial cells was not observed during this study; rejecting the cavitation mechanisms for lumen formation in sprouting angiogenesis. This in vivo study also emphasized on the fusion of intracellular vacuoles as the main mechanisms of lumen formation during the angiogenesis process. By injecting quantum dots into the circulation of embryos, lumenal space is suddenly connected to the main circulation of embryos; resulting in the formation of fully lumenal space and also loop formation [10]. Ying Wang and colleagues conducted another study on intersegmental vessels of living zebrafish embryos in 2010 to investigate the cord hollowing process during the initial stage of lumen formation [38]. This study showed that the initial stage of lumen formation is independent of blood flow and the intercellular junction. This study also emphasized on apical-basal polarity behavior of the endothelial cell. According to the results of this study, Moesin 1 is required for the stabilization of Ve-cadherin, and the formation of adherence junction between cells. Ve-cadherin causes apical-basal polarity in endothelial cells. This study suggested that the apical membrane is defined by adherent junctions between two endothelial cells that are in contact with each other. Then; this apical membrane is expanded, and vacuoles contribute to apical domain and primary lumens formation. Then, primary lumen or junctional contacts between cells are elongated along the vessel lengthwise during cell migration and the lumen formation process is completed [38]. However, in this study, large vacuoles were not observed in the dorsal aorta so the results suggested that the mechanism of lumen formation in sprouting angiogenesis is independent of vessel type [38].

In 2011, Herwig suggested two distinct mechanisms for lumen formation in the zebrafish embryo, cord hollowing, and cell membrane invagination [39]. Each mechanism causes the formation of different vascular tubes, and membrane invagination mechanisms are flow-dependent. This study used DLAV for analysis and observed unicellular, multicellular, and mixed cellular arrangements in DLAVs structure. In the membrane invagination mechanism, the cell junction was formed in the initial steps of anastomosis; resulting in expansion and

generation of the apical membrane compartment in the cell's interface. This study defined that although blood flow is not required for the generation of initial contact between cells, cell rearrangement and cell polarization are necessary for membrane invagination. The mechanism of cord hollowing was unique in other instances of this mechanism such as dorsal aorta lumen expansion but in DALVs, rearrangement of cells caused expansion of the lumen [39].

In 2013, another study was performed on zebrafish embryos to investigate morphogenetic mechanisms during anastomosis; using high-resolution time-lapse analysis [40]. Accordingly, the connection of two sprout cells caused an apically polarized and luminal pocket in the cell junction area. Figure 2 shows contact formation by tip cells during anastomosis.

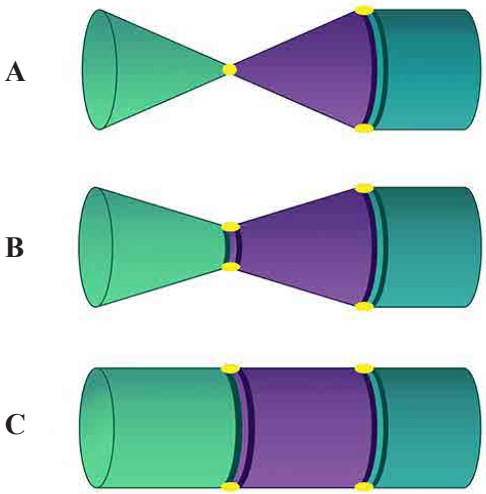

Figure 2: Contact of Tip Cells
A) Green and purple cells connect. Yellow shows cell connection; B) Cell junction area increases; C) New junction surface and apical membrane (dark green and dark purple) form

When cells' apical membrane is formed at the newly formed surface, two distinct mechanisms could cause multicellular and unicellular lumen. Figure 3 shows the cord hollowing mechanism; causing the formation of the multicellular lumen. In this mechanism, the rearrangement of cells forms a new junction and middle cell detachment. Whereas multicellular tubes are also formed by the converging of endothelial cells which are located in the seamless tube. In this situation, the intervening cell splits and also form longitude junctions [40].

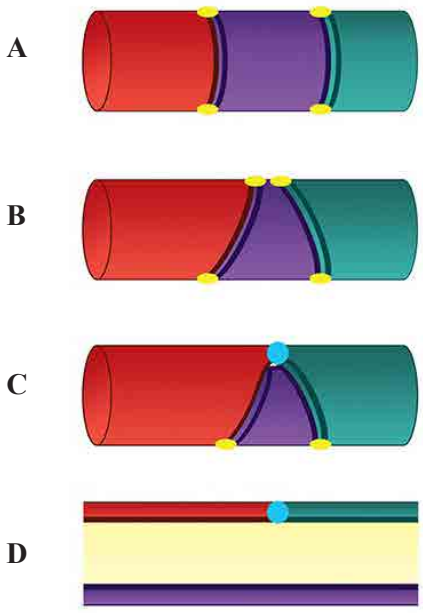

Figure 3: Formation of the Multicellular Lumen During Anastomosis
A and B) formation of the new junction; C) The detachment of the middle cell; D) Formation of the multicellular lumen

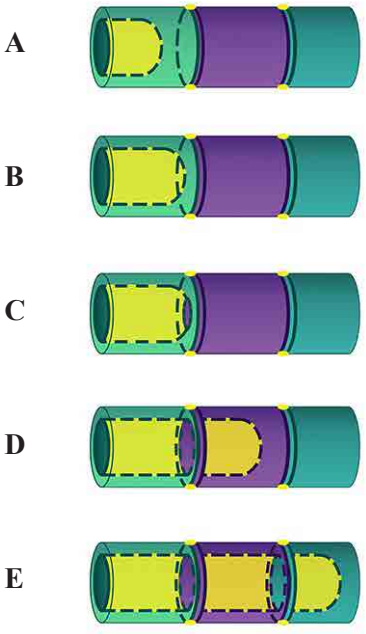

Figure 4: Formation of the Unicellular Lumen During Anastomosis
A and B) Invagination of the green cell's membrane into the purple cell; C) The fusion of the green cell membrane with its membrane; D) Invagination of purple's apical membrane (neighboring cell); E) Formation of the unicellular lumen

Membrane invagination is the second mechanism which causes unicellular lumen structure. Figure

4 shows this mechanism. When cell junction and membrane polarization occur, each of the fused tip cells will be between two lumenized spaces, proximal lumen at the base of sprout and distal sprout at cell junction. This study showed that blood pressure causes the invagination of the proximal membrane and extension of lumenized space in each of these tip cells. Cell membrane invagination was not observed in the absence of blood pressure [40].

In 2015, Yu observed single endothelial cells in zebrafish; using high-resolution imaging and endothelial-specific transgenes [41]. This study tried to definitively identify and study the cell's behavior and lumen formation; using mosaics with transgenes that mark the cell's nuclei and membrane simultaneously. By one frame imaging per minute, this study suggested that heterogeneous mechanisms can cause lumen formation including both cell hollowing and cord hollowing. By observation of small membrane vesicles and large vesicles, the study suggested that vacuoles are formed in a single cell [41].

Importance of Blood Pressure in Lumen Formation and Expansion

Gebala studied lumen formation; using zebrafish dorsal aorta and also mouse retina in 2016 [11]. This study showed that lumen formation occurs before anastomosis and focused on the effect of blood pressure on the lumen formation process. For this, the heart rate of the embryos has been reduced to reduce blood pressure, and also by using the laser, the connection between the aorta and the appendage ablated as well as blood flow was stopped. In both situations, the lumen formation process was not observed. This observation showed that lumen formation and expansion depend on blood flow's hemodynamics. In this study, it is observed that the formation of spherical membrane protrusions (like classical blebs) causes the formation of the lumen and its expansion during in vivo angiogenesis because of higher blood pressure compared with cytoplasmic pressure. This mechanism was named "inverse membrane blebbing" for the first time. Blood pressure causes a disturbance of the actomyosin cortex like a classic bleb; causing the detachment of the cortex from the plasma membrane and also the formation of a protrusion or bleb.

Unlike the classic blebs, the inverse blebs form towards the outside of the cell. This study suggested that the inverse membrane blebbing causes lumen formation, both unicellular and multicellular. The contraction of the actomyosin cortex causes a mechanism of retraction which controls the expansion of the lumen at the apical membrane. In this study, the formation of vacuoles was not observed so the study has suggested that the positive pressure difference between blood pressure and cell cytoplasm is the main reason for lumen formation and expansion during the in vivo angiogenesis process [11]. Figure 5 shows the inverse membrane blebbing mechanism during the sprouting angiogenesis process [11].

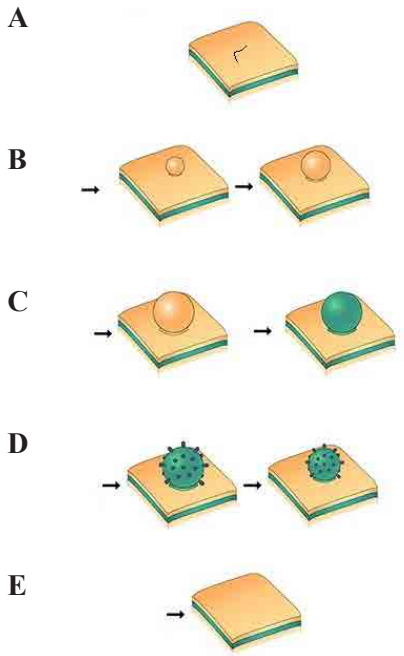

Figure 5: Inverse Membrane Blebbing Mechanism
A) Membrane local weakening because of blood pressure; B) Bleb formation and lumen expansion; C) F-actin polymerization on the bleb membrane; D) Bleb retraction: Myosin II recruitment, the formation of actomyosin fiber and its contraction

CONCLUSION

Lumen formation is an important mechanism during the angiogenesis process [39]. The blood flow also is important for the remodeling of the vascular plexus [42, 43]. This mechanism, however, is not fully understood. First studies on this mechanism put their attention on vacuoles, vacuoles size increase, and fusion of these vacuoles between cells. Further studies suggested distinct mechanisms

and also emphasized on anastomosis phenomenon and the importance of the cell-cell junction. Recent studies, however, indicate the critical role of blood flow in the formation and expansion of lumen during the angiogenesis process; especially in in vivo experiments. These studies have shown that the result of in vivo and in vitro experiments could be different. More studies are needed both in vitro and in vivo for a full understanding of this critical mechanism; especially during the angiogenesis process.

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CONFLICT OF INTEREST

The authors have no conflicts of interest to declare.

ETHICS APPROVAL

This is a review article and doesn't have any ethical dilemma.

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