

Intercellular Communication with Endothelial cells

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As a cellular interface between the blood and tissues, the endothelial cell (EC) monolayer is involved in the control of key functions including vascular tone, permeability and homeostasis, leucocyte trafficking and hemostasis. EC regulatory functions require long-distance communications between ECs, circulating hematopoietic cells and other vascular cells for efficient adjusting thrombosis, angiogenesis, inflammation, infection and immunity. This intercellular crosstalk operates through the extracellular space and is orchestrated in part by the secretory pathway and the exocytosis of Weibel Palade Bodies (WPBs), secretory granules and extracellular vesicles (EVs).

endothelial cells

intercellular communication

tunneling nanotubes

exosomes

extracellular vesicles

secretome

cytokines

chemokines

ectodomain shedding

secretory pathway

1. Introduction

Lining all blood vessels of the vascular tree, the endothelium represents a surface area of around 5000 m² composed of roughly 10¹⁴ endothelial cells (ECs) and can be perceived as an organ system [\[1\]](#). At the interface between the blood and tissues, the EC layer is involved in the control of key functions including vascular tone, permeability and homeostasis, leucocyte trafficking and hemostasis [\[2\]\[3\]](#).

Intercellular communication is a fundamental process in the development and functioning of multicellular organisms and to operate effective mobilization and recruitment of circulating cells at sites of inflammation, infection, or injury. An intensive crosstalk between ECs and circulating hematopoietic cells and other vascular cells is needed to maintain vessel structure, function and homeostasis. Major mechanisms governing EC interaction with adjacent cells in tissue or blood vessels include exocytosis and direct transfer of small cytoplasmic components via gap junction [\[4\]\[5\]](#). For communication with more distant cells, ECs must use additive mechanisms to counteract the diluting effect mediated by the constant flow of blood. To achieve long-distance communications, several strategies can be used, including the secretion of messengers such as cytokines, chemokines, complement proteins, coagulation or growth factors, the release of extracellular vesicles (EVs), or the formation of thin tubular membranous channels termed tunneling nanotubes (TNTs), which may contain and transfer different biomolecules (e.g., signaling mediators, proteins, lipids, and RNAs) or pathogens.

2. Endothelial Exocytosis

2.1. Secretory Pathway and Weibel–Palade Bodies

To provide a rapid answer to external stimulation or stress, ECs are equipped with specific rod-shaped organelles known as Weibel–Palade bodies (WPBs) in which several bioactive molecules are stored and rapidly released upon stimulation (**Figure 1**).

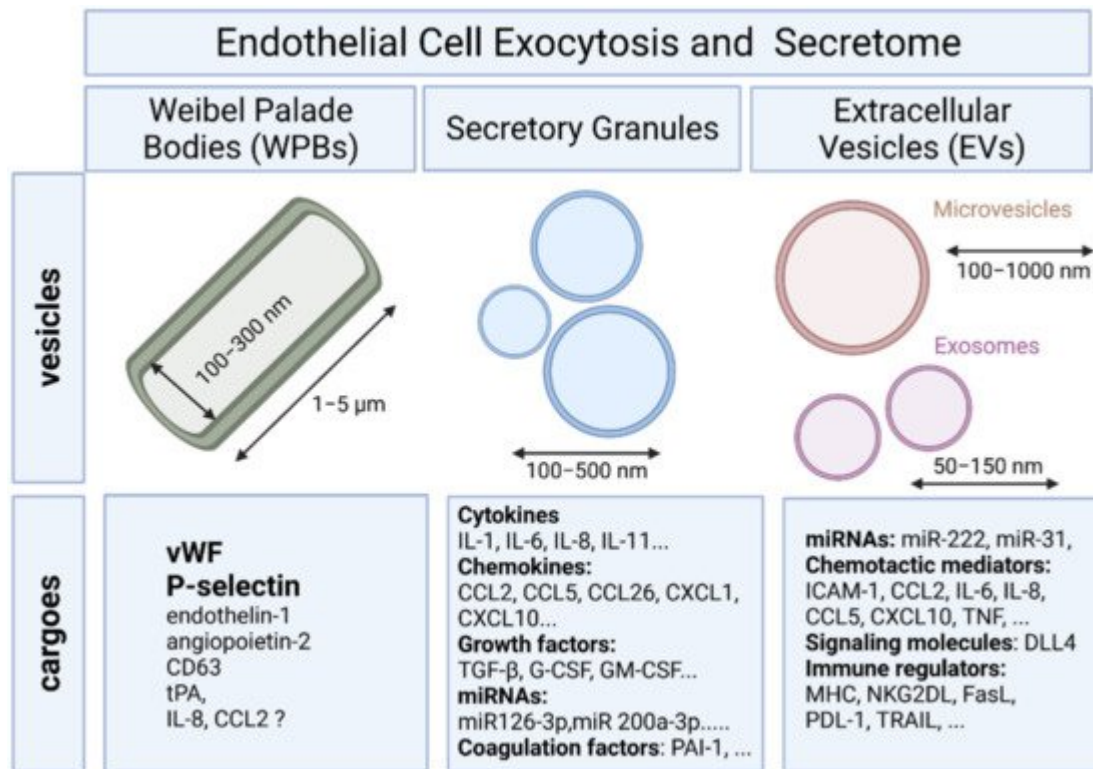


Figure 1. A schematic overview of secretory granules and extracellular vesicles and their cargoes in endothelial cells.

The most abundant cargo in WPBs is von Willebrand factor (VWF). VWF is a multimeric glycoprotein, which mediate platelet adhesion and aggregation at sites of endothelial damage and is a carrier for coagulation factor VIII and to the subendothelial matrix [6][7].

After their formation at the trans-Golgi network (TGN), WPBs accumulate in the cytoplasm and can remain within ECs for long periods of time (few days) [8]. These features of WPBs are consistent with a function as a storage organelle. Under resting conditions, WPBs undergo a very slow process of basal exocytosis. However, their rate of exocytosis is rapidly increased in response to external stimuli that elevate intracellular free calcium (Ca^{2+}) concentrations [9].

Several proteins have been found copackaged with VWF including P-selectin, Rab27a, endothelin 1, angiopoietin-2, or CD63 [10][11].

2.2. Endothelial Exocytosis of Secretory Granules

Differential release of various granule populations is a well-known feature of certain regulated secretory cells and it has been described for ECs. Stimulus-release coupling occurs via regulated exocytosis of secretory vesicles and Ca^{2+} was a key trigger of this process [12]. The N-ethylmaleimide-sensitive factor (NSF) protein is a key player in the multiple steps of both the constitutive secretory and endocytic pathways acting in ER to Golgi transport and in endocytic vesicle fusion [13]. Cytokines, chemokines, enzymes, growth factors, matrix proteins, and signaling molecules can all be secreted by fusion of the secretory granule with the plasma membrane and the subsequent release of the vesicular contents (Figure 1) [12].

Cytokines and other soluble mediators can be involved in distant as well as local communication. ECs secrete a range of paracrine, autocrine, and endocrine factors that mediate multiple aspects of EC function. An intensive crosstalk between cells via soluble factors, including cytokines, contributes to vessel structure, function, and maintenance, proliferation of ECs and vascular smooth muscle cells, EC-leukocyte interactions, platelet adhesion, coagulation, inflammation, and permeability [14].

ECs continuously communicate with other cells through a variety of mechanisms. A key mode of communication is the release of soluble cytokines and chemokines. These signals lead to the induction of biological processes, such as cell proliferation, differentiation, and migration that in turn influence the homeostasis of the tissues and organs by controlling the cell types and numbers that are produced [15]. The extracellular propagation of the signal is mediated by random molecular motion of the soluble cytokines- and chemokines. Although the cells cannot control diffusion, they can regulate their biological processes such as protein production and secretion rates.

3. Endothelial Cells and Extracellular Vesicles

3.1. Definition and Biogenesis of EVs

Intercellular connection by extracellular vesicles (EVs) is another way of cell to cell crosstalk that allows cells to deliver biological contents and messages to distant recipient cells. ECs constitutively secrete EVs into the blood in low concentrations under physiological conditions. It has been suggested that endothelial EVs account for approximately 5–15%, and constitute a large subclass of all circulating EVs in blood, albeit the majority of circulating plasma EVs are derived from platelets and erythrocytes [16]. However, the amount of EVs released by ECs remains difficult to estimate due in part to sampling artifacts and to a lack of standardization of the techniques for the isolation and characterization of EVs [17]. Plasma levels of endothelial EVs have been found to be elevated in various diseases involving EC injury or dysfunction [18].

MVs are large vesicles (100–1000 nm) that may display a diverse range of sizes and are released from the plasma membrane by budding. In contrast, exosomes are smaller vesicles (50–150 nm) that originate from the endosome [19].

All EVs bear surface molecules that allow them to be targeted to recipient cells. Once attached to a target cell, EVs can induce signaling via receptor–ligand interaction or can be internalized by endocytosis and/or phagocytosis or even fuse with the target cell's membrane to deliver their content into its cytosol, thereby modifying the physiological state of the recipient cell [19][20]. An integrin-associated protein, CD47, which protects cells from phagocytosis, is often found on the surface of EVs and was shown to increase the time of EV circulation in the blood by preventing their phagocytosis by macrophages and monocytes [21].

3.2. Mechanisms of EV Uptake and Cargo Delivery

In ECs, EV uptake has been shown to be mediated via the interaction of EV surface proteins such as tetraspanins with membrane receptors of the recipient cells [22]. Tumor-derived EVs bearing Tspan8-CD49d complexes have been shown to be internalized by vascular rat ECs, thereby enhancing EC migration, proliferation and sprouting [23]. EVs bearing Tspan8- α 4 complexes were also found incorporated by rat ECs after binding to intercellular adhesion molecule (ICAM)-1 [24]. EVs can also transmit information to recipient cells by EV/cell surface contact, without delivery of their content. As an example, during immune responses, EVs harboring major histocompatibility complex (MHC)–peptide complexes can activate cognate T cell receptors on T lymphocytes [25].

3.3. Endothelial Cell-Derived EVs

EC injury triggers the release of EC-derived EVs including both exosomes and MVs. Upon inflammation, the proinflammatory cytokine TNF leads to a dose-dependent increase in the release of endothelial EVs, which could be reversed by the use of blocking anti-TNF antibody [26]. Moreover, TNF promotes an induction of tissue factor (TF) on the surface of the endothelial EVs [26]. Stimulation of ECs with other inflammatory factors, including interleukin-1 (IL-1), interferon- γ (IFN- γ) and bacterial lipopolysaccharide have also been shown to induce the release of endothelial EVs containing higher levels of specific miRNAs than endothelial EVs derived from unstimulated ECs [27]. In addition to proinflammatory cytokines, coagulation factors such as thrombin [28], C-reactive protein (CRP) [29], and plasminogen activator inhibitor-1 (PAI-1) [30] are also capable of inducing the release of EVs from ECs [18].

3.4. EVs Trigger Endothelial Protection and Vascular Repair

Several studies have shown that EVs of endothelial origin can act to promote EC and vascular integrity in vitro and in vivo. Abid Hussein et al. have demonstrated that endothelial MV release is cell protective by exporting caspase-3, one of the effector enzymes of apoptosis, into MVs and thereby diminishing intracellular levels of proapoptotic caspase-3 [31]. In a similar way, Jansen et al. have demonstrated that incorporation of annexin I/phosphatidylserine receptor-dependent endothelial MVs by ECs protects ECs against apoptosis by inhibiting MAPkinase p38 activity [32].

3.5. Transfert of miRNAs via EVs

EVs are fully active membrane vesicles that contain and transfer functional intracellular contents. EVs convey cellular messages through their distinct cargoes consisting of proteins, cytokines, mRNA, or noncoding RNA such as microRNA (miRNA) or long noncoding RNA (lnc RNA) to target cells and influence their function and their phenotype [33]. Among the biological contents transferred by EVs into target cells, miRNAs play a key role by controlling mRNA and protein expression in recipient cells [16]. MiRNAs regulate the expression of mRNAs at post transcriptional level either via translational repression or mRNA degradation [34].

Numerous in vitro studies have demonstrated that extracellular miRNAs enwrapped with exosomes can alter gene expression in the recipient cells such as ECs. For instance, exosomes derived from hypoxic leukemia cells contain a subset of upregulated miRNAs including miR-210 which may enhance tube formation in ECs [35]. Like exosomes, MVs can also carry miRNAs. The presence of miRNAs in MVs has been reported from different cells including ECs [36].

3.6. EVs and Immune Responses

Evidence is emerging that extracellular vesicles can act as triggers and regulators of immune responses in particular in cancer [37]. Indeed, besides molecules commonly found in most exosomes (adhesion molecules, heat shock proteins, molecules involved in membrane trafficking and ESCRT, etc.), molecules with specialized function in immune responses like MHC class I and II, costimulatory molecules and several immune receptors and ligands (such as FasL, TRAIL, PD-L1, NKG2D ligands) have been identified in the cargo of various exosomes. ECs express not only MHC class I and class II and most of costimulatory molecules displayed on antigen presenting cells such as dendritic cells [38], but also a set of non-classical and MHC class-I-like molecules including HLA-E, MICA and other NKG2D ligands that may potentially activate cognate receptors on natural killer (NK) and T cells [39][40].

4. Shedding of Endothelial Protein Ectodomains

In addition to the proteins that undergo protein secretion via secretory pathways, several membrane proteins are known to be released into the extracellular space via ectodomain shedding [41]. Previous studies on membrane proteins revealed that about 2–4% of cell surface molecules undergo the shedding process [42][43]. Several membrane-bound EC adhesion molecules, growth factors, cytokines, and cell receptors can be proteolytically cleaved by sheddases that results in the release of soluble forms of fragments. The process of ectodomain shedding has been shown to regulate vascular pathologies and diseases such as degeneration, inflammation, cancer and physiological processes such as proliferation, differentiation, and migration.

A recent database for the identification of shed membrane proteins revealed that a largest portion of the shed membrane proteins (34%) were found to be related to immune response, blood, homeostasis and angiogenesis consistent with a major contribution of shedding in vascular biology [44]. Proteolytic removal of membrane protein ectodomains (ectodomain shedding) is a post-translational modification (PTM) that controls levels and function of numerous membrane proteins. The contributing proteases, referred to as sheddases, act as important molecular

switches in processes ranging from signaling to cell adhesion. The shedding process consists on the proteolytic removal of membrane protein ectodomains (ectodomain shedding) by a protease (referred to as sheddase) which cleaves a membrane protein substrate close to or within its transmembrane (TM) domain. This results in release of the soluble ectodomain from the membrane and a fragment that remain bound to the membrane.

5. Endothelial Cells and Tunneling Nanotubes

For long distance intercellular communications, ECs can also form «tunneling nanotubes» [45]. TNTs are thin (originally reported as ranging from 50 to 200 nm) membranous nanotubes, containing F-actin enclosed in a lipid bilayer, and able to transfer molecular information by forming a “tunnel” between distant cells (**Figure 2** and **Figure 3**) [46]. TNTs have been initially reported in *Drosophila* [47], and before described in a rat cell line (PC12 cells) in 2004 by Rustom and colleagues [46]. TNTs have been observed in multiple cell types in vitro [48] and in vivo [49]. In contrast to soluble factors or microvesicles that diffuse and decrease over distance, TNTs propagate signals through a network of cells that remain strong and robust despite the distance traveled [50][51]. TNT permit the direct exchange of various components or signals (e.g., ions, proteins and organelles) between non-adjacent cells at distances over 100 μm . TNTs allow connected cells to act in a synchronized manner over long distances, with some interactions on the scale of hundreds of microns away [52][53].

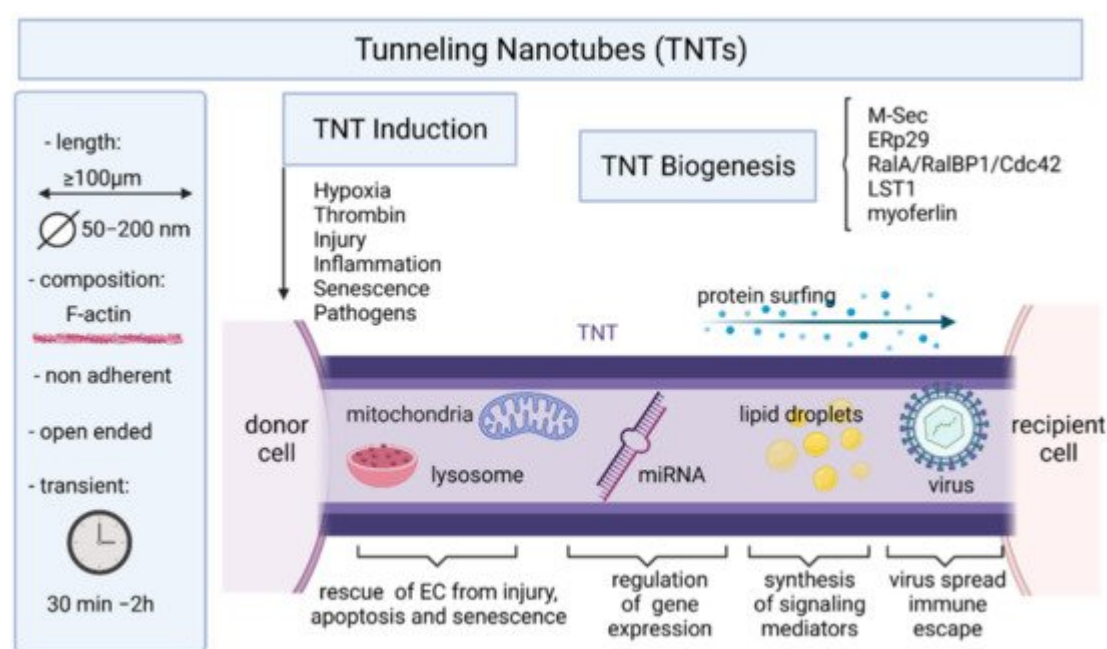


Figure 2. A schematic overview of TNT major characteristics and cargoes. Conditions inducing TNT formation and molecules implicated in TNT biogenesis are indicated.

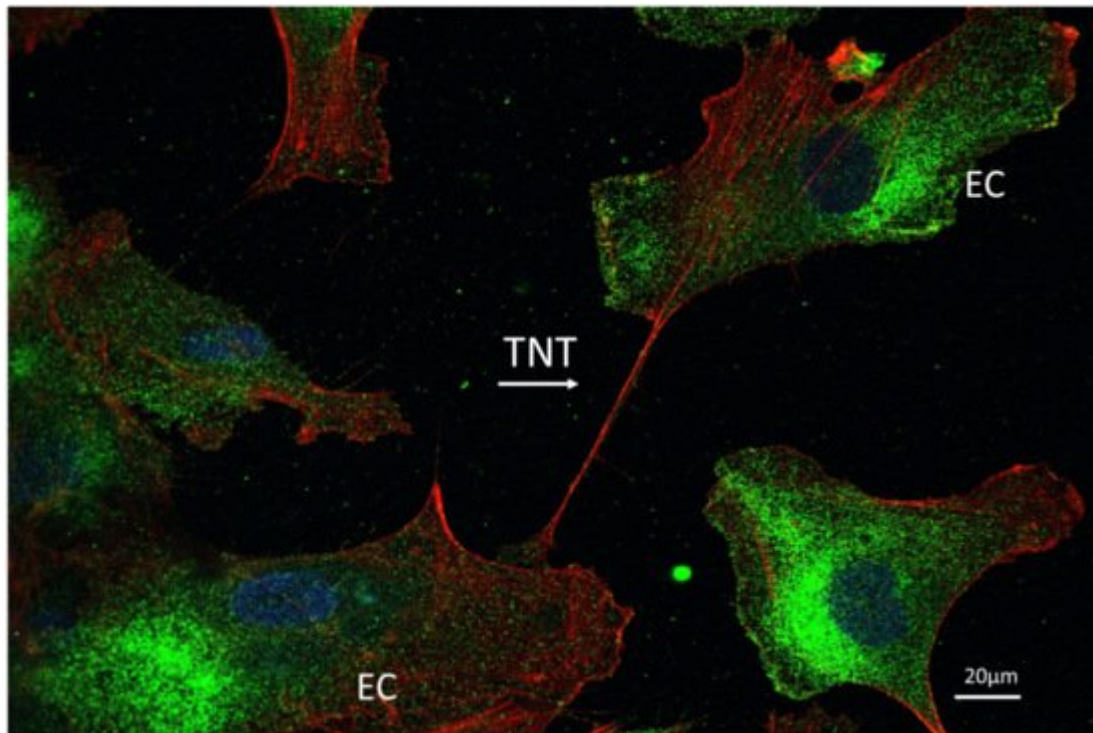


Figure 3. A representative confocal imaging of TNT between two endothelial cells. Colimmunostaining for F-actin (red) and MHC class I molecules (green) on human aortic EC culture. Nuclei are staining with DAPI (blue) and costainings are visualized as superimposition of images (magnification: 600×).

6. Conclusions

ECs possess a multilevel machinery to deliver messages to distant cells such as cells circulating in the blood vessel including platelets, leucocytes, other vascular cells, or normal and tumor cells in tissues. This intercellular crosstalk operates through the extracellular space and is orchestrated in part by the secretory pathway and the exocytosis of WPBs, secretory granules and EVs. WPBs and secretory granules allow both immediate release and regulated exocytosis of mediators implicated in the gatekeeper action of EC toward vascular homeostasis and permeability thrombosis, angiogenesis, inflammation, infection and immunity. The ectodomain shedding of transmembrane protein further provides the release of both receptor and ligands with key regulatory activities on target cells. EVs and in particular exosomes and TNT have emerged as an extensively studied mechanism of horizontal intercellular transfer of information [54]. EVs as well as most of molecules released by ECs might be useful, non-invasive biomarkers for the monitoring of EC and vascular function. Since endothelial EVs can efficiently deliver their cargo into target cells, they might be used as potential therapeutic agents to treat various diseases and injuries. Nevertheless, clinical applications will require further investigations to define with accuracy the uptake and targeting mechanisms as well as the content and functions of EVs in various contexts. Moreover, since ECs display specific phenotypes and functions that may vary according to the vascular bed and tissue [55][56], the impact of EC heterogeneity on secretome output, but also on TNTs, might require specific investigations.

Secreted mediators mediate a random pattern of intercellular communication that may not be predicted. In contrast, the communication via TNTs is more deterministic, by connecting a donor cell to a specific recipient cell. EVs and TNTs convey their messages via a large variety of cargoes, but also by direct receptor/ligand interactions initiating intracellular signaling in recipient cells or by external transport or molecular surfing on their surface. The potential role of TNTs on drug delivery has been proposed for cancer therapy [\[57\]](#). Alternatively, the inhibition of TNT formation might be another issue to impair TNT-mediated chemoresistance in tumors. Consequently, a deeper understanding of the complex role of the secretome and TNT in the communication from and with ECs in specific vascular beds and tissues in the next years is warranted, allowing the development of new clinical applications.

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