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The Endothelial Cell Secretome as a Factor of Endothelium Reparation: The Role of Microparticles

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Abstract

The secretome is considered a combination of factors produced by cells due to abundant spectrum of autocrine/paracrine triggers. All these actively synthetizing and secreting factors include proteins, adhesion and intercellular signal molecules, peptides, lipids, free DNAs, microRNAs, and microparticles (MPs). The components of secretome mutually may interact and thereby modify the MPs' structure and functionality. As a result, communicative ability of endothelial cell-derived MPs may sufficiently impaire. Subsequently, cross talk between some components of secretome might modulate delivering cargos of MPs and their regenerative and proliferative capabilities via intercellular signaling networks. The aim of the review is to discuss the effect of various components of secretome on MP-dependent effects on endothelium.

Keywords: Endothelium; Endothelial cells; Secretome; Reparation; Microparticles

Introduction

For last decade, elevated circulating level of microparticles (MPs) produced by various types of blood cells have been defined in the patients with established cardiovascular (CV) disease, as well as in individuals at higher risk of CV events and diseases [1-4]. There is suggestive evidence that a number of circulating endothelial cell-derived MPs might be a clinically useful biomarker that pretty accurate predicts CV complications in general populations and patients with known CV disease [5-7]. Although an origin of endothelial cell-derived MPs from activated or apoptotic cells is crucial for realizing tissue repair, degenerative processes modulation, immune mediation, and directly/indirectly vascular injury [8], there are several controversies regarding an involvement of MPs in pathogenesis of CV disease [9-11]. The first controversy affects the pathophysiological properties of MPs. Indeed, the MPs secreted by activated endothelial cells may contribute to tissue reparation, restore endothelial function, mediate progenitor cell mobbing and differentiation, whereas apoptotic MPs are able directly injury endothelial cells and via a transfer of several proteins, active molecules, chromatin compounds including microRNAs and DNAs, regulate inflammation, coagulation, and immune response [12]. The next controversy relates a different presentation of endothelial cell-derived MPs in plasma of healthy individuals and changing of their numbers in various CV diseases and CV risks. Interestingly, circulating number of MPs originated from apoptotic endothelial cells increases in patients with CV risk factors, after newly CV events and in individuals with established CV disease. However, the ability of activated endothelial cells to active secret MPs progressively decreases depending on CV risk presentation, i.e., diabetes mellitus, abdominal obesity, insulin resistance, renal disease, and is due co-existing endothelial disintegrity [13-15]. Unfortunately, although there is strong association between circulating number of activated endothelial cell-derived MPs and CV risk, elevated level of apoptotic endothelial cell-derived MPs appears to be much more accurate predictive biomarker relating to CV death and CV diseases progression [16]. Another controversy is that the endothelial cell-derived MPs are constitutive biomarker of endothelial dysfunction playing a pivotal role in inflammation, vascular injury, angiogenesis, and thrombosis. However, the circulating number of endothelial cell-derived MPs predicts CV manifestation and progression regardless a severity of endothelial dysfunction. In fact, the imbalance between number of circulating endothelial cell-derived MPs distinguished their origin (activated or apoptotic endothelial cells) can be applied as more promising routine tests to improve CV risk prediction [17,18]. Whether "impaired phenotype" of endothelial cell-derived MPs as a causality factor contributed the vascular "competence" in CV disease is a predominantly pre-existing phenomenon associated with genetic/epigenetic performances or is resulting in various metabolic and age-dependent factors is not clear. Probably, variable effect of endothelial cell-derived MPs might relate to particularities of the triggers, which induced cell mechanisms of synthesis and secretion of secretome. The aim of the review is to discuss the effect of various components of secretome on MP-dependent effects on endothelium.

Secretome: definition and components

The variable spectrum of paracrine factors secreted by cells due to specific and non-specific triggers with exerted biological effects on target cells is determined by secretome. By now, the secretome is considered a collection of factors consisting of transmembrane proteins and other components actively secreted by cells into the extracellular space. All these synthetizing and secreting factors include proteins, adhesion and intercellular signal molecules, peptides, lipids, free DNAs, microRNAs, and extracellular vesicles (i.e., exosomes and MPs). A significant portion (roughly 20%) of the human secretome consists of secretory proteins incorporated into microvesicles.

Definition of microparticles

MPs are large and very variable on their shapes and dimensions (predominantly 100-1000 nm) heterogeneous sub-population of extracellular vesicles (EVs), which are shedding from plasma membranes of parent cells in response to cell' activation, injury, and/or apoptosis [19]. EVs contain cell-specific collections of proteins, glycoproteins, lipids, nucleic acids and other molecules, which are non-specific for EVs. Depending on their origin EVs are graduated to follow subsets, i.e., the exosomes (30-100 nm in diameter), the microvesicles (50-1000 nm in diameter), ectosomes (100-350 nm in diameter), small-size MPs (<50 nm in diameter) known as membrane particles and apoptotic bodies (1-5 μm in diameter). The exosomes are formed by inward budding of the endosomal membrane and are released on the exocytosis of multivesicular bodies known as late endosomes, whereas the microvesicles are attributed via budding from plasma membranes [20,21].

MPs are released by cellular vesiculation and fission of the membrane of cells. Under normal physiological condition a phospholipid bilayer of plasma membrane of cells represented phosphatidylserine and phosphatidylethanoalamine in inner leaflets, whereas phosphatidylcholine and sphingomyelin represent in the external leaflets. The asymmetrical distribution of phospholipids in the plasma membrane is supported by activity of three major intracellular ATP-dependent enzyme systems, i.e., flippase, floppase, and scramblase. Because aminophospholipids are negatively charged, but phospholipids exhibit neutral charge, the main role of intracellular enzyme systems is supporting electrochemical gradient. Both flippase and floppase belong to family of ATP-dependent phospholipid translocases [22].

The flippase translocates phosphatidylserine and phosphatidylethanoalamine from the external leaflets to the inner one. The floppase transports phospholipids in the opposite direction. Finally, scramblase being to Ca^{2+} dependent enzyme system exhibits unspecifically ability of moving of phospholipids between both leaflets of plasma membrane [23].

Importantly, disappearing of the asymmetrical phospholipid distribution in the bilayer of the cell membrane is considered a clue for vesiculation and forming of MPs. Indeed, both processes of apoptosis or cell activation are required asymmetry in phospholipid distribution that leads to cytoskeleton modifications, membrane budding and MPs release. The mechanisms of vesiculation affect genome and may mediate by some triggers including inflammation, while in some cases there is a spontaneous release of MPs from stable cells or due to injury from necrotic cells or from mechanically damaged cells. Particularly, the MPs are released in both constitutive and controlled manners, regulated by intercellular Ca^{2+} and Rab-GTP-ases and activation of μ-calpain. μ-Calpain is a Ca^{2+}-dependent cytosolic enzyme belong to protease, which cleaves talin and α-actin, leading to decreased binding of integrins to the cytoskeleton and a reduction in cell adhesion and integrity [24].

Recently MPs are considered a cargo for various molecules. Indeed, MPs carry proteins, RNA, micro-RNA, and DNA fragments from their cells of origin to other parts of the body via blood and other body fluids. Within last decade it has become to know that MPs would act as information transfer for target cells. However, the difference between innate mechanisms affected the release of MPs from stable cells, activated cells or apoptotic cells is yet not fully investigated and requires more studies.

Endothelial cell-derived microparticles

Endothelial cells release phenotypically and quantitatively distinct MP populations due to two main mechanisms, i.e., cell activation and apoptosis. As a result, MPs are sufficiently distinguished one another in their ability to present some antigens [19] and intravesicle components, i.e. matrix metalloproteinases (MMP)-2, MMP-9, MT1-MMP, chromatin, active molecules (heat shock proteins), some hormones (angiotensin II), growth factors (transforming factor-beta) [24-27]. It is suggested that the epigenetic modification of the parent cells might directly regulatory impact on functionality of secreted MPs and their ability to influence various biological effects [28]. Indeed, the endothelial cell-derived MPs isolated from the serum of patients with diabetes mellitus, chronic kidney disease, heart failure and atherosclerosis are defective in ability to induce vascular relaxation, maturation of progenitor cells and endothelium repair [29-32]. As factors contributing in the response of the target cells after stimulation MPs could be pointed inflammatory cytokines (tumor necrosis factor-alpha, interleukin: IL-4, IL-17), glucose, advanced glycation end-products, uremic toxins, free DNA, products of lipid peroxidation [33]. Nonetheless, hypoxia-modified endothelial cell-derived MPs are able to carry reactive oxygen species and thereby may impair target cells by promoting apoptosis and oxidative stress [34]. One cannot be excluded the role of metabolomics-regulated microenvironments of target cells as a causative factor modifying the response after MPs' cooperation [35,36]. It has been postulated that activation of p^{53} subunit, Akt/GSK-3beta and JAK2/STAT3 signaling pathways are involved in the regulation of MPs' synthesis and that these molecular targets are under close control of various metabolites and intermediates, as well as epigenetics' mechanisms [37-40]. Thus, secretome of endothelial cells including metabolites, proteins, intermediates, DNAs/reactive oxygen radicals, active molecules, may probably modify and even alter a communicative ability of MPs secreted by endothelial cells [41-44].

Relation between secretome and endothelial cell functionality

Endothelial cell-derived MPs are not only delivery of intra-vesicular cargo and information, but they may directly modulate vascular function via autocrine and paracrine effects through surface interaction of the target cells, and cellular fusion [45]. Subsequently, *in vitro* investigation has shown that the MPs and other fractions of secretome might mutually influence one another [9]. The final result of the interrelation may be shaping brand new biological components with irradiative abilities toward target cells [46,47]. Finally, it has been suggested that enhancing of the target cell mobility and differentiation through MP production could be impaired, inverted or even sufficiently changed [48]. Indeed, secretome of apoptotic peripheral blood cells may induce cytoprotection effect instead expected worsening tissue remodeling in animal model of acute myocardial infarction [49-51]. Additionally, this effect is probably due to the activation of pro-survival signalling cascades in the cardiomyocytes and the increase of homing of regenerative cells through stimulation of metabolically modified MPs. Additionally, in clinical settings angiogenic early outgrowth endothelial progenitor cells have been reported to contribute to endothelial regeneration and to limit neointima formation after vascular injury through cooperation with metabolically modified MPs [52].

Thus, there is a large body of evidence regarding being of modifying effect of secretome components on MPs' ability for tissue regeneration or injury. Moreover, regenerative potency of apoptotic cell secretome

was even higher than those in activated cells. However, new phenomenon opens serious perspective to clinical implementation of MPs as not just diagnostic tool with predictive possibilities, but as transfer system with therapeutic potencies [43,54].

Whether endothelial cell-derived MPs are capable to induce variable effects on target cells depending on proteomic of MPs or functional nature of secretome is not fully understood [55]. In fact, cross talk between some components of secretome including MPs might modulate delivering cargos of MPs through involving the intercellular signalling networks and thereby modify their regenerative and proliferative capabilities. Future investigations are requires to define the role of secretome in MPs' ability to produce different biological effects regarding endothelial repair, while recent studies have suggested the predominantly role of MPs' origin in this matter.

Conclusion

The endothelial cells secretome has most commonly investigated in pre-clinical settings as a source of regulating factors that influence target cells. However, the interaction between different components of secretome leads to modification of the MPs' structure and functionality. It has been hypothesized that endothelial regeneration is under tight control of autocrine and paracrine mechanisms affecting not just parent endothelial cells, but also secretome of them. The matter of metabolic modification of one is uncertain and requires more investigations in future.

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