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Therapeutical Potential of Microvesicles in Cardiovascular Diseases

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Abstract

MicroRNAs (miRNAs) are small, highly conserved, non-coding RNA molecules that regulate hundreds of gene expression and thereby, affect global changes in the physiology of cells. Extracellular miRNAs are packaged with proteins or wrapped in microvesicles including microparticles, exosomes, and apoptotic bodies. These vesicles are potential candidates for therapeutical targets. Recent studies have indicated that microvesicles have the roles of deleterious information in blood vessel wall under pathological situations such as hypertension, myocardial infarction and metabolic syndrome, whose diseases are results of the endothelial dysfunction. However, the role of endothelial cells-derived microvesicles is unknown. Uncovering the difference and potential role of these microvesicles in endothelial cells is emerging.

Keywords: Apoptotic bodies; Endothelial cells; Exosomes; Microparticles; Microvesicles; Microrna

Introduction

MicroRNAs (miRNAs) are critical for normal cellular functions such as the regulation of the cell cycle, differentiation, and apoptosis, and their expression is disproportioned in various pathological states. Importantly, miRNAs are not only found intracellularly but also abundantly present in body fluids (i.e. blood, saliva, urine, and tears) [1]. Most of extracellular miRNAs are packaged with proteins (i.e. high-density lipoprotein and other RNA-binding proteins) and some are wrapped in microvesicles including microparticles (MPs), exosomes, and apoptotic bodies [2]. These vesicles, which were considered as cell dust, are now regarded as true biomarkers and vectors of biological information between cells. Depending on their origin, the composition of these microvesicles varies and the subsequent message transported by them, such as proteins or miRNA, can differ.

Like most cells, vascular endothelial cells release different types of membrane vesicles, including MPs and exosomes, in response to cellular activation or apoptosis. Additionally, apoptotic bodies might be generated during the final steps of programmed cell death [3]. These different vesicles are distinguished from one another on the basis of their subcellular origin, their size, their content, and the mechanisms leading to their formation. Studies of endothelial cells have shown that these vesicles, which contain miRNAs, can alter their gene expression and participate in various cardiovascular diseases.

Endothelial MPs

The diameter of MPs is approximately from 100 nm to 1 μm and endothelial MPs result from endothelial plasma membrane blebbing. A comparison of antigen expression on MPs from endothelial cells revealed that the endothelial markers platelet endothelial cell adhesion molecule-1 (PECAM-1/CD31) and E-selectin (CD62E) are more markedly expressed by MPs released from apoptotic cells, whereas α5 integrin (CD51) and intercellular cell adhesion molecule-1 (ICAM-1/CD54) are preferentially expressed by activation-induced MPs [4,5]. Although endothelial nitric oxide (NO) synthase (eNOS) and vascular endothelial growth factor receptor have also been identified on endothelial MPs [6], it is still unknown whether eNOS in MPs can generate NO. eNOS may also be present on platelet or erythrocyte-derived MPs. PECAM-1/CD31 is present on activated platelets, platelet MPs, and leukocytes. CD62E is expressed by activated endothelial cells but can equally be found on endothelial MPs generated following either tumor necrosis factor-α (TNF-α) activation or growth factor deprivation-induced apoptosis [5]. ICAM-1/CD54 is also expressed by leukocytes, and CD51 is present on monocytes/macrophages and platelets. Endoglin (CD105) and S-endo (CD146) are also expressed in MPs. The former is expressed by activated monocytes/macrophages and bone marrow cells and the latter has been found on pericytes, tumor cells, and activated T-cells [4].

The presence of endothelial MPs has been reported in human and murine plasma, vitreous fluid [7,8] and in inflammatory lesions such as the atherosclerotic plaque or ischemic tissues [6,9]. The protein composition of endothelial MPs highly depends on the stimulus triggering their release, and the identified proteins mostly originate from the plasma membrane, the cytosolic fraction, the cytoskeleton, or mitochondria. Interestingly, MPs contain nuclear materials such as DNAs, RNAs, and miRNAs, which they transfer to target cells [10,11]. Although most of the biological roles of nuclear materials in MPs remain to be determined, recent study has shown that mRNA horizontal transfer from endothelial MPs to endothelial cells promotes angiogenesis following eNOS expression [10,11].

Endothelial Exosomes and Apoptotic Bodies

The diameter of exosomes is less than 0.1 μm. They are produced in multivesicular bodies during endocytosis and play a role in antigen presentation. Unlike MPs, they abundantly express exosomal markers such as acetylcholine esterase, tetraspanins (e.g. CD9, CD63 and CD81), heat shock protein 72 (Hsp72), and proteins involved in multivesicular biogenesis (e.g. Tsg101) [12,13], although there are no exosome specific markers. Recent studies suggest that endothelial exosomes contain RNAs and microRNAs, and might be involved in vascular remodeling [14].

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Apoptotic bodies are larger than MPs or exosomes (up to 4 μm in diameter). Unlike MPs, a permeable membrane facilitates propidium iodide staining of the nuclear materials [15]. Previous reports indicate that apoptotic bodies are passive cargos delivering their nuclear contents to phagocytes by horizontal transfer, and they share this specific property with endothelial MPs [15,16]. Endothelial apoptotic bodies also circulate in human blood, and their content in miRNAs is altered in diabetic patients and possibly in patients with cardiovascular diseases [11].

Conclusion

There is a growing appreciation that secretory MPs, exosomes and possibly other types of cell-derived vesicles comprise a physiological channel for cell-cell communication, both among neighboring cells and within the bloodstream. Endothelial cells also appear to release vesicles. Secretory MPs, exosomes and/or apoptotic bodies have the potential to interact with endothelial cells during developmental stages. These vesicles as therapeutic tools could be useful and relevant for the prevention of cardiovascular remodeling such as subsequent neointima formation after vascular injury and for the regulation of angiogenesis in ischemic tissue after mycoardial or peripheral ischemic diseases. Furthermore, to clarify the signature of circulating these vesicles could lead to the development of novel diagnostic and therapeutic strategies.

Disclosures

The author declares no conflict of interest.

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