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REVIEW

Erythrocyte nanovesicles: Biogenesis, biological roles and therapeutic approach
Erythrocyte nanovesicles

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Abstract Nanovesicles (NVs) represent a novel transporter for cell signals to modify functions of target cells. Therefore, NVs play many roles in both physiological and pathological processes. This report highlights biogenesis, composition and biological roles of erythrocytes derived nanovesicles (EDNVs). Furthermore, we address utilization of EDNVs as novel drug delivery cargo as well as therapeutic target. EDNVs are lipid bilayer vesicles rich in phospholipids, proteins, lipid raft, and hemoglobin. In vivo EDNVs biogenesis is triggered by an increase of intracellular calcium levels, ATP depletion and under effect of oxidative stress conditions. However, in vitro production of EDNVs can be achieved via hypotonic treatment and extrusion of erythrocyte. NVs can be used as biomarkers for diagnosis, monitoring of therapy and drug delivery system. Many therapeutic agents are suggested to decrease NVs biogenesis.

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1. Introduction

Cells continuously secrete a large number of small molecules, macromolecules and nanovesicles into the extracellular space (Vlassov et al., 2012). Nanovesicles (NVs) are submicron membrane-coated vesicles of diameter up to 1000 nm, in which they are released from all cell types and contain cellular components of their parent's cell (Vlassov et al., 2012). Exosomes and microvesicles (MVs) are collectively known as extracellular vesicles (EVs), and they have an aqueous core surrounded by a lipid bilayer membrane (Kastelowitz and Yin, 2014). EVs are considered as a new class of signal mediators, which allow the transport of nucleic acids, proteins, lipids and second messengers (Vlassov et al., 2012; Kastelowitz and Yin, 2014). EVs play significant roles in genetic transfer, cytokine release, angiogenesis, transfer of cell receptors, and proteinase release (Kastelowitz and Yin, 2014). Under activation, growth, apoptosis, senescence, shearing stress, oxidative stress and injury, cells release excessive amount of EVs (Antwi-Baffour et al., 2013A,B).

Most of cells including endothelial cells, immune cells, cancer cells, hematopoietic cells, platelets, and erythrocytes are able to secret EVs (Fais et al., 2013). EVs are formed by budding of the plasma membrane through the dynamic redistribution of phospholipids (Lutz and Bogdanova, 2013). MVs and exosomes are differing in the biogenesis, size, surface markers, and biological roles (Fais et al., 2013). MVs are plasma membrane-derived vesicles with size range between 100 nm and 1000 nm. During their formation, MVs retain surface molecules from parent's cell as well as part of their cytosolic content (Loyer et al., 2014).

On the contrary, exosomes have size up to 150 nm and are derived from a cascade of the fusion between early and late endosomes, lysosomes, and others depending on their cellular source (Fais et al., 2013; Loyer et al., 2014). The fusion of multivesicular bodies with the plasma membrane allows the release of exosomes into the extracellular space. Exosomes are membranous structures with a lipid bilayer rich in phospholipids, proteins, cholesterol, ceramide, and sphingolipids (Vlassov et al., 2012). EVs can circulate in the vascular network, where they can evade phagocytosis as well as they can participate in autocrine, paracrine and endocrine signaling (Prati et al., 2010).

In healthy humans, circulating EVs are mainly derived from platelets and to a lesser extent leukocyte and endothelial cells. An increase of EVs biogenesis has been demonstrated in physiological and pathological conditions (Lovren and Verma, 2013). The vascular endothelium is one of the primary targets of circulating EVs; they contribute to the regulation of endothelial cell functions, coagulation and inflammation (Lovren and Verma, 2013). However, abnormal biogenesis of EVs leads to endothelial dysfunction and development of cardiovascular diseases (Lovren and Verma, 2013).

The biogenesis of EVs is an inherent property of the erythrocyte plasma membrane. In healthy individuals, erythrocytes derived nanovesicles (EDNVs) are present at basal levels (Jank and Salzer, 2011). However, aging, high intracellular calcium levels and oxidative stress are triggers of erythrocytes vesiculation and release of EVs. Oxidized erythrocytes (Oxi-Ery) released EVs rich in oxidized proteins, lipid peroxides, cholesterol and other oxidized substances. Oxi-Ery and EDNVs are engulfed by macrophages and smooth muscle cells resulted in foam cells formation, and this induced endothelial dysfunction and enhanced atherosclerotic process (Blum, 2009; Tziakas et al., 2010). An increase in EVs release was observed in hypertension, thrombocytopenia, multiple sclerosis, sickle cell anemia, diabetes, and atherosclerosis (Antwi-Baffour et al., 2013A,B).

Biogenesis, secretion mechanisms as well as biological roles of EVs have not been fully reported. Furthermore, their physiological and pathological roles are still a matter for research.