

"Impaired Phenotype" of Endothelial Cell-Derived Microparticles: Causality Factor Contributed the "Vascular Competence" in Diabetes and Metabolic Syndrome?

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Abstract

The recognition of the importance of overweight / obesity and metabolic syndrome as leading risk factor for diabetes and cardiovascular (CV) complications has greatly increased within last decades. Endothelial dysfunction mediating the diabetic complications associates with several important mechanisms, one of which is secretion of extracellular microparticles (MPs) by activated or apoptotic endothelial cells. MPs coordinate wide spectrum biological processes, i.e. angiogenesis, neovascularization, cell growth / differentiation, proliferation, coagulation, and they are involved in the epigenetic regulation of post-processing that is essential for phenotype modification, tissue repair, cell death, malignancy, and immunity. The commentary is discussed the role of impaired balance between number of both immune subsets of endothelial MPs in CV events development among dysmetabolic subjects. It has revealed that increased numbers of apoptotic MPs, as well as decreased numbers of MPs derived from activated endothelial cells aggravate endothelial damage and contribute to the continuously deteriorating endothelial damage leading to diabetes-related complications.

Keywords: Diabetes Mellitus; Obesity; Metabolic Syndrome; Circulating Endothelial Cell-Derived Microparticles; Cardiovascular Risk Factors

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Introduction

The results of recent clinical studies have well established that overweight / obesity and metabolic syndrome are represented the leading risk factor for T2DM and diabetes-related

Cardiovascular (CV) complications [1-4]. However, the impact of the dysmetabolic states on molecular mechanisms regarding vasculature repair systems and "metabolic memory" is not fully investigated [5-7]. By now, Endothelial Dysfunction (ED) has found a key player in increasing CV risk in overweight / obese and T2DM subjects [8, 9]. Furthermore, ED interacting with worse glucose metabolism, lipotoxicity, over production of free radicals and other components of oxidative stress contributes to increase CV risk [9, 10]. Based on current available evidence cell-to-cell cooperation is crucial for various biological responses including thrombogenicity, coagulation, inflammation, immunity, cell growth and differentiation, vascular and plaque remodeling [11]. In this context, extracellular Microparticles (MPs) acting as detrimental regulator of cell-to-cell cooperation are discussed a have as a key marker of global vascular damage in dysmetabolic patients [12].

MPs (microvesicles with size < 1000 nm) are released from plasma membrane of wide variety of cells including red blood cells, mononuclears, platelets, endothelial cells, resulting in specific (cytokine and growth stimulation, apoptotic agents, coagulation, active molecules' effect) and non-specific (shear stress) stimuli [13]. MPs coordinate wide spectrum biological processes, i.e. angiogenesis, neovascularization, cell growth / differentiation, proliferation, coagulation, and they are involved in the epigenetic regulation of post-processing that is essential for phenotype modification, tissue repair, cell death, malignancy, and immunity [14-17].

Numbers of circulating Endothelial cell-derived Microparticles (EMPs) were found a marker of endothelial dysfunction and predictor of CV complications in dysmetabolic subjects including obesity and T2DM [18-22]. Interestingly, EMPs depending on their origin (apoptotic cells or shedding from

activated endothelial cell) might have a different structure and produce controversial effects. Apoptotic-derived EMPs are capable of transferring biological information (regulating peptides, active molecules, hormones) or even genetic materials (micro-RNA, mRNA, and DNA), as well as proteins, lipid components, from one cell to another without direct cell-to-cell contact to maintain cell homeostasis [23]. Interestingly, hyperglycemia may reduce the packaging of miRNA-126 and miRNA-26a into EMPs, subsequently altered their biological effect on target cells, worse intercellular signaling mechanisms that is associated with higher risk of CV disease [24]. However, the contribution of EMPs and also of their associated miRNAs to the development of CV complications in diabetes is largely unexplored.

It has suggested that origin of circulating EMPs might impact on their biological content and produce the dual behaviour of EMPs. Apoptotic EMPs may be immune mediators, generating powerful signaling by the simultaneous receptor interaction. Therefore, they are discussed a marker of endothelial cell injury and vascular aging [25]. Yet, apoptotic EMPs induce endothelial damage including increased EC apoptosis, enhanced reactive oxygen species while decreased nitric oxide production and impaired angiogenic activity. Contrary, EMPs derived from activated endothelial cells did not contain nuclear components and they may exhibit angiogenic properties, ameliorate endothelial inflammation, and contribute to tissue protection [26]. Thus, increased numbers of apoptotic EMPs, as well as decreased numbers of EMPs derived from activated endothelial cells aggravate endothelial damage and contribute to the continuously deteriorating endothelial damage leading to CV events and CV disease.

Recently it has reported that patients with obesity, metabolic syndrome and T2DM may have impaired ratio between number of apoptotic EMPs and EMPs derived from activated endothelial cells [19, 20], associated with increased number of apoptotic EMPs [27]. This phenomenon was recognized as "impaired phenotype" of EMPs and it has related to cellular injury, inflammation, coagulation / thrombosis that leads to and vascular dysfunction [27-29]. Finally, "impaired phenotype" of EMPs appearing as epigenetic reprogramming of cells plays a pivotal role in the development of CV complications in T2DM [30-32]. Although there was a skepticism regarding origin of

imbalance in several poles of EMP in patients with obesity and diabetes, it has supposed that inflammatory cytokine and probably lipid abnormalities may consider a possible cause of predominantly immune phenotype of EMPs [33, 34]. Obviously patients with various dysmetabolic disorders might have different EMP patterns contributing to the development of CV complications. Probably, incorporation of the EMP level into a conventional risk factor model is able to be useful tool for improving of risk stratification of the dysmetabolic patients with high probability of CV disease [35-37].

In conclusion, these evidence support hypothesis that "impaired phenotype" of EMPs might be one of causality factor contributed the "vascular competence" in obesity, metabolic syndrome and diabetes. The determination of predominantly immune phenotype of EMPs appears to be attractive for risk classification models, whereas "impaired phenotype" of EMP determination is not easy for practical use due to lack of standardized methods for the measurement. However, large clinical trials are required to explain the predictive role of "impaired phenotype" in dysmetabolic individuals at higher risk of CV complications.

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