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Extracellular vesicles in obesity and diabetes mellitus

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ABSTRACT

Cell-to-cell communication happens via diverse mechanisms including the synthesis, release and transfer to target cells of extracellular vesicles (EVs). EVs include nanovesicles (i.e., exosomes) and microvesicles, including apoptotic bodies. The amount and cargo of released EVs, which consist of microRNAs (miRNAs), mRNA, proteins, DNA, among other molecules, are altered in obesity and diabetes mellitus. EVs from these diseases show with altered cargo including several miRNAs and the enrichment with molecules involved in inflammation, immune efficiency, and cell activation. The role of EVs in obesity regards with adipocytes-released vesicles that may end in a systemic insulin resistance. In diabetes mellitus, the exosomes cargo may signal to transform a normal phenotype into a diabetic phenotype in endothelial cells. The evidence of EVs as modulators of cell function is increasing; however, it is still unclear whether exosomes or microvesicles are a trustable and useful marker for the diagnose or early detection of obesity or diabetes mellitus. In this review, we summarise the reported information regarding EVs involvement in obesity, T1 and T2 diabetes mellitus, and gestational diabetes mellitus. We emphasise the fact that studies addressing a potential effect of obesity or diabetes mellitus on cell function and the severity of the diseases are done in patients suffering simultaneously with both of these diseases, i.e., diabesity. Unfortunately, the lack of information regarding the biological effects and the potential involved mechanisms makes difficult to understand the role of the EVs as a marker of these and perhaps other diseases.

1. Introduction

The general term extracellular vesicles (EVs) has been defined as cell-derived microparticles in the extracellular medium containing proteins, lipids and nucleic acids that interact with a neighbour or distant target cells (Huang-Doran et al., 2017). EVs include nanovesicles, microvesicles, and apoptotic bodies released from several tissues, and that differentiate by their size and biogenesis (Huang-Doran et al., 2017; Raposo and Stoorvogel, 2013). Nanovesicles, also referred as exosomes, are formed by the inward budding of endosomal membranes to form large lipid aggregations seen as multivesicular bodies (Abels and Breakefield, 2016). When multivesicular bodies fuse with the plasma membrane, they release exosomes to the extracellular medium. Exosomes are 20–100 nm in diameter vesicles and carry different signalling molecules including soluble and membrane-bound proteins, bioactive metabolites, lipids, DNA, miRNA, mRNA, along with other regulatory RNAs (Huang-Doran et al., 2017; Keerthikumar et al., 2016; Raposo and Stoorvogel, 2013; Valadi et al., 2007). Another type of EVs are

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the microvesicles (100–1000 nm in diameter) and apoptotic bodies (1–5 μm in diameter), which are formed by direct outward budding and plasma membrane fission, respectively (Huang-Doran et al., 2017). Apoptotic bodies are released from cells that are ongoing through apoptosis, are phagocytosed by surrounding cells and degraded by phagolysosomes (Raposo and Stoorvogel, 2013).

EVs contain a variety of cytosolic proteins such as integrins, major histocompatibility complex, cytoskeleton, and others that have been used as EVs markers (Kalra et al., 2013; Raposo and Stoorvogel, 2013). Several studies addressing the role of EVs are limited by the lack of specific physical properties or unique markers that could differentiate one type of EVs from another (Kalra et al., 2013; Keerthikumar et al., 2016). EVs are also involved in the modulation of relevant pathophysiological processes involved in diabetes mellitus (Müller, 2012), cancer (Hoshino et al., 2015), neurodegenerative diseases (Soria et al., 2017), and placental dysfunction (Adam et al., 2017). Nevertheless, unveiling the modulation of EVs will increase the understanding of the pathophysiology of diseases and reveal a potential following-up treatment of patients.

Obesity is a worldwide epidemic non-communicable disease where patients show a body mass index (BMI) > 30 kg/m^2 (WHO, 2016). Obesity associates with systemic complications, such as hypertension, dyslipidaemia, insulin resistance, and diabetes mellitus (Fernández-Sánchez et al., 2011; Ouchi et al., 2011; Pardo et al., 2017). The role of EVs in the aetiology of obesity is not clear; however, EVs biological effects in patients with obesity depend on the cargo which is determined by the metabolic and nutritional state of source cells. Diabetes is a disease that affects ~420 million people worldwide with a word prevalence of ~8.5% (WHO, 2016). Type 1 (T1DM) and type 2 (T2DM) diabetes mellitus characterised by reduced insulin synthesis or sensitivity, and abnormal D-glucose metabolism. When diabetes mellitus is first recognised in the second trimester of pregnancy, it is referred as gestational diabetes mellitus (GDM) (WHO, 2016). T1DM, T2DM and GDM also associated with endothelial dysfunction due to, among other factors, reduced bioavailability or response to vasodilators, including nitric oxide (NO) and the endogenous nucleoside adenosine (Silva et al., 2017). This phenomenon is regarded as critical for the microvascular and macrovascular disorders seen in patients with these diseases, including the developing foetus (Sobrevia et al., 2017, 2015). One of the mechanisms potentially involved in diabetes mellitus-associated vascular disorders and an altered immune response is a rise in the release of endothelium-, platelets, and monocytes-derived EVs (including exosomes and microparticles). In fact, out of the several molecules described as EVs cargo, it is still uncertain whether cargo in these EVs in patients with T1DM, T2DM and GDM is independent of obesity since not a differential mechanism has been reported.

In this review, we summarised the dynamics of the biological effects of EVs in obesity and diabetes mellitus and the different cargo which provides information related to their origin. We discussed the relationship between obesity and diabetes mellitus and the potential influence of EVs in these pathological conditions nowadays referred as diabesity (i.e., diabetes + obesity) (Astrup and Finer, 2000; Shafrir, 1996).

2. Obesity

Obesity occurs when there is an imbalance between the energy intake and the use of it, leading to an increase in the energy storage as fat in several organs, especially in adipose tissue (Shoelson et al., 2007). Normal weight is defined by a BMI in the range of 15–24.9 kg/m^2 and obesity >30 kg/m^2 (WHO, 2016). Obesity associates with the development of metabolic syndrome, predisposing the patients to develop hypertension, cardiovascular disease, dyslipidaemia, insulin resistance, and diabetes mellitus (Fernandez-Sanchez et al., 2011; Ouchi et al., 2011). Several studies involve EVs in obesity; however, their characteristics and a potential link with this disease are limited.

2.1. EVs plasma level

Obese patients show higher (~10 fold) level of plasma EVs compared with normal healthy weight (Eguchi et al., 2016; Murakami et al., 2007; Stepanian et al., 2013). The population of EVs from these patients include exosomes (~20%) and microvesicles (~80%). However, there is not clear whether the increase in plasma EVs in obese patients is due to an increase in exosomes, microvesicles, or both. The increased plasma level of EVs from obese patients is also seen in patients with excessive weight (BMI ≥25 kg/m^2), a phenomenon that correlated with the BMI, waist circumference, and fat tissue mass (Murakami et al., 2007). Interestingly, treatment of patients with a hypocaloric diet (Eguchi et al., 2016), diet plus exercise (Murakami et al., 2007), or weight loss after post-sleeve gastrectomy reduced their EVs plasma level, without reaching the level observed in healthy patients (Campello et al., 2016). Interestingly, the regulation of the number of plasma EVs

Table 1
Effect of obesity in the number of extracellular vesicles in peripheral blood.

	Type of EVs	Size (nm)	Markers	Source	EVs number	References
Studies in humans						
Obese	Microparticles	*nr*	CD41	Platelet	Increased	Murakami et al., 2007
Obese	Microparticles	<900	Annexin V, CD41	Platelet	Increased	Stepanian et al., 2013
Obese	Microparticles	<900	Annexin V, CD31	Endothelium	Increased	Stepanian et al., 2013
Obese	EVs	<1000	Annexin V, perilipin A	Adipocyte	Increased	Eguchi et al., 2016
Weight loss in obese	Microparticles	<900	Annexin V, CD41	Platelet	Reduced	Stepanian et al., 2013
Weight loss in obese	Microparticles	*nr*	Annexin V, CD61	Platelet	Reduced	Campello et al., 2016
Weight loss in obese	Microparticles	<900	Annexin V, CD31	Endothelium	Reduced	Stepanian et al., 2013
Weight loss in obese	Microparticles	*nr*	Annexin V, CD62	Endothelium	Reduced	Campello et al., 2016
Weight loss in obese	EVs	<1000	Annexin V, perilipin A	Adipocyte	Reduced	Eguchi et al., 2016
Studies in animals						
ob/ob mice	EVs	<1000	Annexin V, perilipin A	Adipocyte	Increased	Eguchi et al., 2015
HFD mice	EVs	<1000	Annexin V, perilipin A	Adipocyte	Increased	Eguchi et al., 2016
HFD rat	Microparticles	<1000	Annexin V, CD61	Platelet	Increased	Heinrich et al., 2015
HFD rat	Microparticles	<1000	Annexin V, CD31	Endothelium	Increased	Heinrich et al., 2015
HFD rat	Microparticles	<1000	Annexin V, CD45	Leukocyte	Increased	Heinrich et al., 2015
HFD-NAFLD mice[a]	EVs	<220	*nr*	*nr*	Increased	Povero et al., 2014

CD31, CD41, CD45, CD62, CD65, clusters of differentiation 31, 41, 45, 62, 65; HFD, high fat diet; NAFLD, non-alcohol fat liver disease; EVs, extracellular vesicles. *nr*, not reported.
[a] HFD induced.

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