The International Journal of Biochemistry & Cell Biology 77 (2016) 10–14

Contents lists available at ScienceDirect

The International Journal of Biochemistry & Cell Biology

journal homepage: www.elsevier.com/locate/biocel

Organelles in focus

Dialogue between endoplasmic reticulum and mitochondria as a key actor of vascular dysfunction associated to metabolic disorders

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ARTICLE INFO

Article history:
Received 2 March 2016
Accepted 9 May 2016
Available online 18 May 2016

Keywords:
Endothelium
Metabolic syndrome
Endoplasmic reticulum stress
Mitochondria
Mitochondria-associated membranes

ABSTRACT

Metabolic syndrome due to its association with increased risk of cardiovascular diseases and cardiac mortality, comprises a cluster of metabolic abnormalities such as central obesity, hyperglycemia, dyslipidemia, and hypertension. Recent studies have shown that metabolic syndrome patients exhibit impaired nitric oxide-mediated vasodilatation leading to endothelial dysfunction in addition to insulin resistance. Interestingly, development and maintenance of the unfolded protein response of the endoplasmic reticulum stress revealed a surprisingly direct link with metabolic syndrome and endothelial dysfunction. On the other hand, in metabolic disorders, interaction between endoplasmic reticulum and mitochondria is mandatory for the generation of mitochondrial oxidative stress and perturbation of mitochondrial function accounting, at least in part, for vascular dysfunction. Herein, we review the impact of the dialogue between endoplasmic reticulum and mitochondria in modulating the cellular signals governing vascular alterations associated to metabolic disorders.

1. Metabolic disorders as risk factors of cardiovascular diseases

Metabolic disorders including insulin resistance, diabetes, dyslipidemia and obesity are considered as risk factors involved in the increase to develop cardiovascular diseases (CVD) (Kaur, 2014). In particular, patients with metabolic disorders are more exposed to atherosclerosis, ischemic stroke (Ballantyne et al., 2008) and myocardial infarction (Deedwania, 2004) than healthy subjects. Among the changes at the vascular level affecting cardiovascular dysregulation, endothelial dysfunction is implicated in the initiation and progression of metabolic disorders (Ahirwar et al., 2015) and, on the other hand, it represents an early step for CV events (Totoson et al., 2014). Individuals with metabolic disorders exhibit higher degree of endothelial dysfunction (Kwaśniewska et al., 2015) probably due to the reduced plasmatic levels of nitric oxide (NO) in these patients (Ahirwar et al., 2015) as well as enhanced reactive oxygen species (ROS) generation, inflammation and changes of barrier function (Bakker et al., 2009). More precisely, the association of increased visceral obesity and other metabolic perturbations leading to oxidative stress and chronic inflammation impairs NO bioactivity, causing endothelial dysfunction (Kwaśniewska et al., 2015; Li et al., 2012). Furthermore, insulin resistance may impair NO bioavailability (Kwaśniewska et al., 2015) and decrease PI3 K/Akt signaling in the vascular wall, thus issuing endothelial damage.

2. Regulation of the endothelial function by the endoplasmic reticulum (ER) and mitochondria

Accumulating evidence suggests that dysregulation of ER and/or mitochondria actively participate in the development and maintenance of pathophysiological states, including metabolic diseases. In this part of the review, we will analyze the potential role of these organelles in the pathogenesis of vascular complications of metabolic disorders focusing particularly on their participation in the endothelial dysfunction. Endothelial cell layer is specially targeted in metabolic alterations due to its strategical localization. Indeed, endothelial cells are directly in contact with elevated concentration of glucose, insulin and triglycerides in blood suggesting that endothelial function alterations play an early stage in CVD. Endothelial dysfunction is related to decreased NO production in addition to endothelial-derived hyperpolarizing factor, increased

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http://dx.doi.org/10.1016/j.biocel.2016.05.011
1357-2725/

expression of adhesion and pro-inflammatory molecules and exacerbated ROS production.

2.1. ER and endothelial dysfunction

The ER is the organelle responsible for protein folding and maturation (Ron and Walter, 2007) and, among its main functions; ER participates to Ca^{2+} storage, lipid and glucose metabolism, and signal transduction (Tripathi and Pandey, 2012). The unfolded protein response (UPR) expresses the ER-to-nucleus signaling cascades, which supervises ER homeostasis (Qi et al., 2011). The UPR represents the imbalance between the amount of unfolded proteins entering the ER and the ability of the cellular machinery to deal with that amount (Ron and Walter, 2007). In metabolic disorders, this is mainly due to nutrient overload, along with increased demand for protein synthesis for its metabolism and local glucose deprivation due to insulin resistance (Achard and Laybutt, 2012). Besides, depending on tissues, UPR is triggered by a variety of pathological factors, such as nutrient deprivation, altered glycosylation, calcium depletion, oxidative stress, DNA damage and energy disturbance (for review see Liu et al., 2016). Three distinct classes of ER stress transducers that determine three different arms of the UPR have been determined: the inositol-requiring protein-1 (IRE1), the protein kinase RNA (PKR)-like ER kinase (PERK), and the activating transcription factor-6 (ATF6) (Ron and Walter, 2007). ER luminal chaperons, especially the binding immunoglobulin protein/glucose regulated protein 78 BIP/GRP78 of the HSP70 class, keep the former ER stress sensors inactive. Upon the accumulation of unfolded proteins, BIP is isolated from the ER stress sensors luminal domain, leading to their activation to reestablish homeostasis (Schröder and Sutcliffe, 2010). Interestingly, the link between ER stress and metabolic diseases is well established (for review see Tripathi and Pandey, 2012). Genetic overexpression of the ER chaperones in obese/diabetic mice has been shown to significantly improve insulin resistance and ameliorate glucose tolerance (Nakatani et al., 2005). Also, treatment with chemical ER chaperones like tauroursodeoxycholate (TUDCA), an ER stress inhibitor, improves metabolic disturbances reflected by improvement of insulin sensitivity in obese humans (Kars et al., 2010).

Growing evidences support a critical role of ER stress in the development of the endothelial dysfunction. In a streptozotozin-induced hyperglycemic $ApoE^{-/-}$ mouse model, hyperglycemia promotes overexpression of endothelial ER stress markers in the aorta wall before any morphologic changes in vessel structure or cellular organization. Furthermore, the accelerated development of atherosclerotic lesions occurs before the onset of diabetes-associated dyslipidemia suggesting that ER stress takes place at an early stage of diabetes (Khan et al., 2009). Interestingly, oxidized LDLs through ROS production induce ER stress response in human endothelial cells (Sanson et al., 2009). Furthermore, at the tissue levels, these authors have also described the expression of ER stress markers in advanced atherosclerotic lesions (Sanson et al., 2009). Accordingly, endothelial XBP1 expression is found in areas of lesion severity, and atherosclerosis is quickened in lesions overexpressing XBP1, in Apoe-/- mice suggesting that high XBP1 levels damages the cells and therefore boosts atherosclerosis (Khan et al., 2009; Zeng et al., 2009). At the cellular level, treatment with tunicamycin, an ER stress inductor, of human aortic endothelial cells induces increased secretion of pro-inflammatory cytokines such as IL6, IL8, monocyte chemoattractant protein 1 (MCP-1), and the chemokine CXC motif ligand 3 (CXCL3), which play a role during atherogenesis (Gargalovic et al., 2006). Galán et al. (2014) have shown that *in vivo* treatment with tunicamycin leads to ER stress response which is associated with vascular endothelial dysfunction assessed by acetylcholine relaxation (Galán et al., 2014). Conversely, *in vivo* inhibition of ER stress with TUDCA not only improves ischemia-induced neovascularization by increasing pro-angiogenic pathways (endothelial NO-synthase (eNOS) and VEGFR2 signaling) but also normalized glucose, insulin and cholesterol levels in diabetic mice (Amin et al., 2012) suggesting that ER stress response contributes to metabolic complications in diabetes. Altogether, these data highlight the critical role of ER stress response in the development of endothelial dysfunction.

2.2. Mitochondria and endothelial dysfunction

Mitochondria are essential organelles involved in the pathophysiology of obesity and its vascular complications (for review see Duluc et al., 2012). These deleterious effects occur mainly through the mitochondrial biogenesis, dynamics and oxidative phosphorylation (OXPHOS) dysfunction leading to ROS production and apoptosis. These effects account for loss of endothelium integrity. Although mitochondrial content in endothelial cells is relatively low compared to cardiomyocytes and hepatocytes (Tang et al., 2014), mitochondria play a key role on endothelial function. Indeed, it has been shown that overexpression of PGC-1α, a factor regulating mitochondrial biogenesis, protects against oxidative stress and limits atherosclerotic lesion formation (Stein et al., 2010). Moreover, altered expression of components of the OXPHOS chain is related to impaired mitochondrial biogenesis that may contribute to endothelial senescence (Ungvari et al., 2008). Also, mitochondrial fragmentation and the subsequent loss of mitochondrial networks have been described in endothelial cells from diabetic patients as well as in cultured human aortic endothelial cells exposed to high glucose concentration (Shenouda et al., 2011). This was associated with the impairment of the eNOS activity and enhanced ROS production. Mitochondrial ROS can damage mitochondrial DNA, lipids and proteins as well as the complexes forming the OXPHOS chain that in turns can contribute to the self-perpetuating mitochondrial ROS production. Also, in a murine model of obesity, high-fat diet induces mitochondrial fragmentation along with decrease in mitofusin 2 (Mfn2) levels, a key component of mitochondrial fusion (Jheng et al., 2012; Schneeberger et al., 2013). Moreover, high levels of glucose lead to mitochondrial fragmentation associated with increased ROS production (Schneeberger et al., 2013). In addition, obese humans and type 2 diabetes patients display low Mfn2 transcript levels. Interestingly, upon acute weight loss these levels are increased, this raises the concept that nutrient status can adjust mitochondrial dynamics (Bach et al., 2005).

In summary, mitochondrial dysregulation at different levels is implicated in the pathogenesis of vascular complications observed during metabolic disorders.

3. ER stress and mitochondria dialogue: role on endothelial dysfunction

It is well established that ER and mitochondria collaborate between them through the physiological contact sites contributing for the exchange of metabolites such as lipids and Ca^{2+} between both organelles (Kornmann, 2013). These interconnections called mitochondria-associated membrane (MAMs) participate in the dialogue between ER and mitochondria (Vance, 1990) and play a major role in tethering and saving homeostasis and signaling pathways between the two organelles (Kornmann, 2013) (Fig. 1). For instance, an increase in the number of ER-mitochondria contact sites enhances Ca^{2+} transfer to the mitochondria allowing that cells adapt to stress conditions require enhanced metabolic output (Kopec et al., 2010). Interestingly, under pathophysiological conditions, emerging data show that contact sites between ER and mitochondria may play a key role in the pathogenesis of metabolic disorders. In this respect, mitochondrial Ca^{2+} overload favors apop-