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Review article

Mitochondria in endothelial cells: Sensors and integrators of environmental cues

Sergio Caja[a], Jose Antonio Enríquez[a,b,*]

[a] Centro Nacional de Investigaciones Cardiovasculares Carlos III (CNIC), Melchor Fernández Almagro 3, 28029 Madrid, Spain
[b] Centro de Investigaciones en RED (CIBERFES), Melchor Fernández Almagro, 28029 Madrid, Spain

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ABSTRACT

The involvement of angiogenesis in disease and its potential as a therapeutic target have been firmly established over recent decades. Endothelial cells (ECs) are central elements in vessel homeostasis and regulate the passage of material and cells into and out of the bloodstream. EC proliferation and migration are modified by alterations to mitochondrial biogenesis and dynamics resulting from several signals and environmental cues, such as oxygen, hemodynamics, and nutrients. As intermediary signals, mitochondrial ROS are released as important downstream modulators of the expression of angiogenesis-related genes. In this review, we discuss the physiological actions of these signals and aberrant responses during vascular disorders.

1. Mitochondria in endothelial cells

The entire vascular system, from the heart to the smallest capillary, is lined by endothelial cells (EC). ECs are central elements in vessel homeostasis and regulate and passage of materials and cells into and out of the bloodstream. Every metabolically active tissue requires the development of an angiogenic network, and the development of this network is associated with metabolic changes and accompanying morphological and phenotypical variations in ECs. In most cell types, the key metabolic regulators are mitochondria, which are linked to a diversity of regulatory processes that allow cell proliferation [1] or trigger apoptosis [2], and also signals to nucleolus [3]. Mitochondrial content varies between endothelial beds; for example, brain ECs contain more mitochondria than ECs in other tissues. However, mitochondrial content in all ECs is low (2–6% of cytoplasm volume) compared with other cell types for example cardiomyocytes (about 32%) [4,5]. ECs have an absolute requirement for glucose and generate more than 80% of their ATP through glycolysis, and the low mitochondrial content in ECs is thus consistent with a role in regulating signaling responses to environmental cues rather than in energy production. Indeed, the activity of EC mitochondria is influenced by a variety of circulating factors, and these organelles provide important factors for ECs signaling (Fig. 1) [6–8].

1.1. Mitochondrial features: distribution, biogenesis and dynamics

The communication of EC mitochondria with other organelles is determined by their distribution, biogenesis, and dynamics [9]. For example, mitochondria are anchored to the cytoskeleton in coronary arterioles isolated from human myocardium; reactive oxygen species (ROS) released from these mitochondria in response to shear stress contribute to flow-mediated dilatation [10]. In pulmonary artery ECs, hypoxia triggers a perinuclear mitochondrial redistribution, with concomitant ROS accumulation in the nucleolus and induction of hypoxia-induced genes [3].

An increase in mitochondrial mass requires the coordinated replication and expression of mitochondrial DNA (mtDNA) with the parallel expression of nuclear-encoded mitochondrial genes. A key player in this coordination is proliferator-activated receptor-γ coactivator-1α (PGC-1α), which activates nuclear respiratory factors 1 and 2 and the nuclear expression of genes necessary for mitochondrial biogenesis [11]. In parallel, PGC-1α also activates mitochondrial transcription factors A and B (TFAM and TFBM), which regulate the expression of mtDNA genes. PGC-1α is expressed in ECs and regulates mitochondrial biogenesis and the expression of several mitochondrial antioxidant enzymes, playing a dual role in the protection against oxidative stress by supplying undamaged mitochondria and enhancing ROS defenses [12,13]. PGC-1α expression and mitochondrial biogenesis are affected by several factors, such as hypoxia and caloric restriction, in parallel with variations in vessel formation [14–16]. PGC-1α moreover regulates the expression of several genes related to lipid and glucose metabolism [14,15], induces VEGF expression [17], and decreases apoptosis [18], resulting in a coordinated acceleration of angiogenesis as ECs increase their metabolic demands during proliferation.

* Corresponding author at: Centro Nacional de Investigaciones Cardiovasculares Carlos III (CNIC), Melchor Fernández Almagro 3, 28029 Madrid, Spain.
E-mail address: jaenriquez@cnic.es (J.A. Enríquez).

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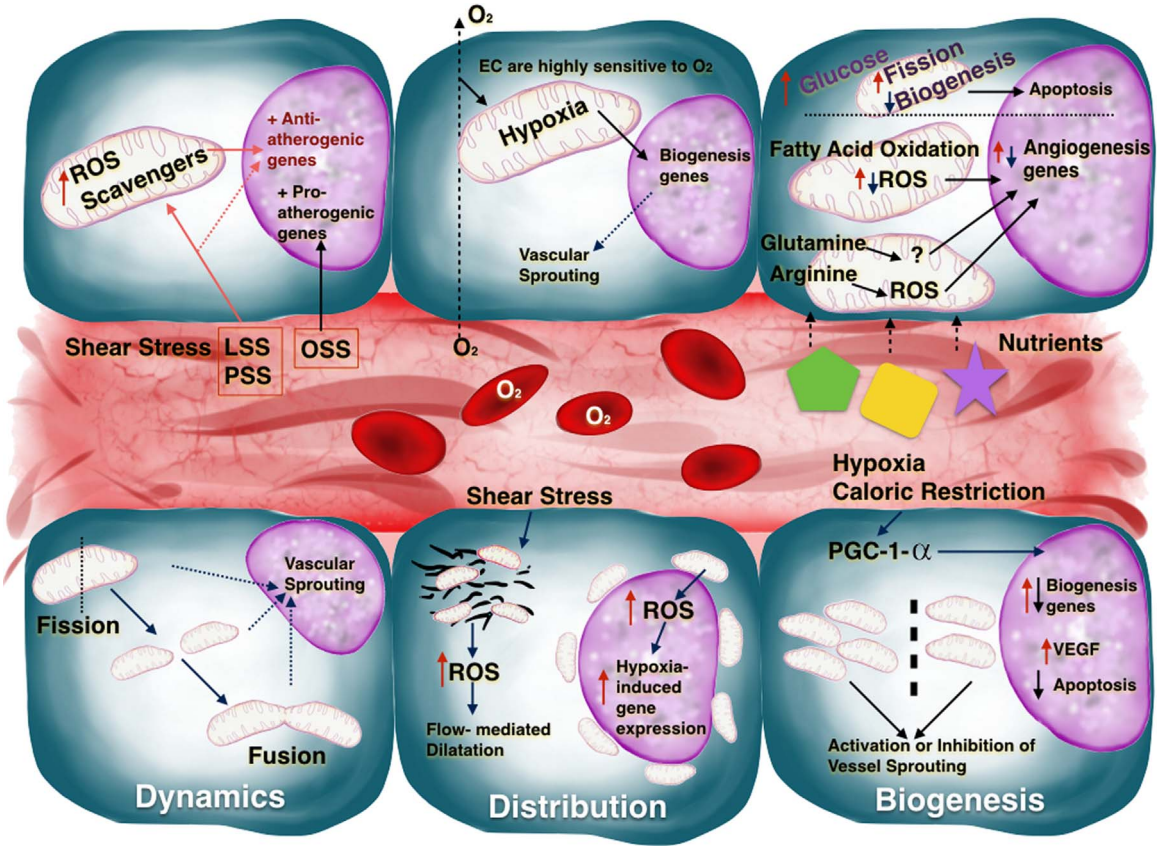

Fig. 1. A blood vessel delimited by ECs and some of the signals which affect angiogenic behavior via mitochondria. The cells at the top represent the effect on mitochondria of nutrients, oxygen, and shear stress (LSS, laminar shear stress; PSS, pulsatile shear stress; OSS, oscillatory shear stress) and how some of the signals released affect the expression of angiogenic genes. The cells at the bottom represent mitochondrial biogenesis, distribution, and dynamics and the consequences of these processes on EC proliferation and vessel sprouting.

Mitochondria are highly dynamic organelles that undergo cycles of fusion and fission that maintain mitochondrial integrity and intersect with apoptosis pathways [19]. Key regulators of this process include mitofusin-1 and 2 (MFN-1 and 2) and optic atrophy protein 1 (OPA-1). These proteins regulate fission-1 (FIS-1), which recruit DRP-1 (dynamin-related protein-1) to initiate the fission process. Fusion and fission are physiologically balanced processes. Fusion allows a better distribution of proteins, mtDNA, and metabolites to maintain electrical and biochemical connectivity [11]. Fusion is a determining factor in angiogenesis that can accelerate responses to VEGF and the activation of eNOS [20]. Fission, on the other hand, is a key factor in vascular sprouting. In pulmonary ECs, DRP-1 activation, which induces mitochondrial fission, stimulates angiogenesis by promoting proliferation, migration, and inhibition of apoptosis in a mitochondrial Ca^{2+}-dependent manner [19,21]. A defective mitochondrial network is observed in several pathological settings, such as high glucose and ischemia-reperfusion, and also during EC aging, highlighting the importance of the fusion/fission cycle during disease development [22–25]. Accumulated mitochondrial damage leads to a rearrangement of these networks, and organelles with normal membrane potential and functional components are reincorporated into mitochondrial networks after fission. In contrast, dysfunctional mitochondria cannot fuse with the network and become targets for elimination by mitophagy, the destruction of damaged mitochondria by autophagy degradation. Mitophagy enables ECs to purge defective organelles and thus avoid dysfunctional signaling to prevents apoptosis. In parallel with mitophagy, biogenetic mechanisms act during homeostasis to replace the loss of mitochondrial mass, providing a mechanism to control mitochondria quality [11,26,27]. Mitophagy during homeostasis is crucially regulated by mitochondrial membrane depolarization. The PTEN-induced putative kinase 1(PINK1) is normally recruited and degraded at the inner mitochondrial membrane. When mitochondria are damaged, membrane potential loss prevents PINK1 degradation, and its accumulation induce mitophagy. This process is led by the E3 ubiquitin ligase Parkin, that ubiquitinate mitochondrial proteins, promoting the organelle recognition and recruitment by the autophagosome [28–30]. Stimuli such as metabolic stress trigger mitophagy to protect EC mitochondria from damage [31]. Deregulation of mitophagy results in ROS production, inflammation, and cell death, ultimately leading to neurodegeneration [30], cardiovascular disease [32], and endothelial dysfunction during aging [33]. Mitophagy is activated in ECs by mitochondrial depolarization triggered by exposure to hydrogen peroxide, irradiation, or promoters of lipid peroxidation [27,34,35]. Recent reports demonstrate that PINK and Parkin are unregulated in diabetic and obese mice, and knock down of these proteins in the vascular wall resulted in deregulation of mitophagy, with a concomitant accumulation of damaged mitochondria and ROS, resulting in apoptosis. Administration of low doses of palmitic acid stimulates PINK-Parkin pathway to eliminate damaged EC mitochondria; however, under severe stress this mechanism of protection is shut down and the accumulated defective mitochondria trigger cell death [36]. Thus, the PINK-Parkin pathway, by promoting mitophagy, protects ECs from metabolic stress and has potential as a target for the prevention of cardiovascular disorders triggered by oxidative stress in the endothelium [11,36,37].

2. Mitochondria in endothelial cells: responses to environmental cues

2.1. The role of oxygen in EC mitochondrial behavior

Oxygen carried in from circulating blood transfers to perivascular