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Could caveolae be acting as warnings of mitochondrial ageing?

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ABSTRACT

Ageing is a cellular process with many facets, some of which are currently undergoing a paradigm change. It is the case of "mitochondrial theory of ageing", which, interestingly, has been found lately to cross paths with another ageing dysfunctional process – intracellular signalling – in an unexpected point (or place) – caveolae. The latter represent membrane microdomains altered in senescent cells, scaffolded by proteins modified (posttranslational or as expression) with ageing. An important determinant of these alterations is oxidative stress, through increased production of reactive oxygen species that originate at mitochondrial site. Spanning from physical contact points, to shared structural proteins and similar function domains, caveolae and mitochondria might have more in common than originally thought. By reviewing recent data on oxidative stress impact on caveolae and caveolins, as well as possible interactions between caveolae and mitochondria, we propose a hypothesis for senescence-related involvement of caveolins.

Contents

1. Introduction

Cellular ageing is a process of many facets, some yet unknown, others that are just being unravelled, while some are well-known, but that are currently found under re-evaluation. Such a change of paradigm emerges in "mitochondrial theory of ageing" (Shokolenko et al., 2014), one of the hallmarks of ageing. Other milestones in ageing include changes in DNA repair and DNA damage response, shortening of telomeres (Cherif et al., 2003), changes in gene expression through epigenetic and posttranslational mechanisms, loss of protein homeostasis, desensitization to mitogens (Park et al.,

Abbreviations: ERK, extracellular signal-regulated kinases; FAK, focal adhesion kinase; Nrf2, nuclear erythroid 2 p45-related factor-2; Shp-2, SH2 domain-containing phosphatase-2; CSK, c-Src tyrosine kinase; HO-1, hemeoxigenase 1; HIF1, hypoxia induced factor 1; SHP-2, Src homology 2 domain-containing protein tyrosine phosphatase 2; PP2A, protein phosphatase 2A.

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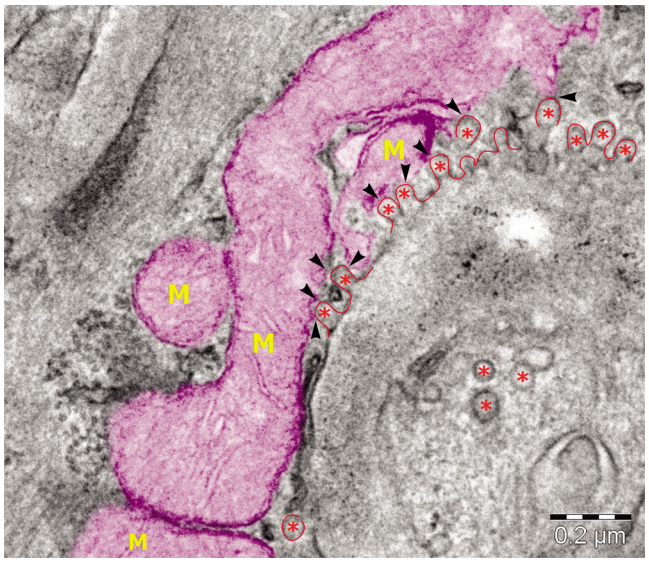

Fig. 1. Transmission electron microscopy of vascular smooth muscle cell from a brain arteriole (6 month-old CD-1mouse). Caveolae (*) establish contacts (arrow heads) with mitochondria (M).

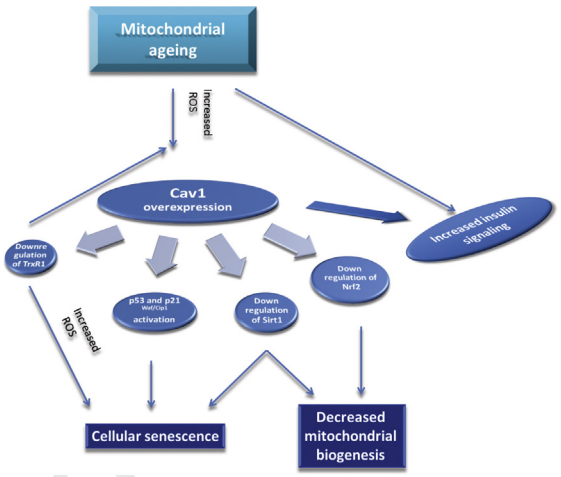

Fig. 2. Relationship between mitochondrial ageing and cav1 overexpression. Activation of cav1 gene expression by increased ROS production leads in turn to several caveolin-related events leading to cellular senescence.

2000), altered nutrient signalling, stem cell pool depletion and premature cellular senescence (Harries, 2014).

Two of these main axes – mitochondrial dysfunction and altered intracellular communication – have been found lately to cross each other in an unexpected point (or place) – caveolae. These membrane microdomains with special biochemical composition own their particular architecture to scaffolding proteins (caveolins - 1, -2 and 3 and their regulatory proteins, cavins 1–4) (reviewed in (Chidlow and Sessa, 2010; Hansen and Nichols, 2010)). More than just scaffolds, caveolins bind to and inhibit signalling enzymes (heterotrimeric G proteins (Song et al., 1996), members of Ras superfamily, such as H-Ras (Song et al., 1996), RhoC (Lin et al., 2005); members of Src tyrosin kinases (Li et al., 1996), eNOS signalling (Bucci et al., 2000)). One exception from the rule "caveolae = signalling suppressors" is insulin signalling (Karlsson et al., 2004), repeatedly reported to be dependant of correct localization of insulin receptor and glucose transporter 4 to caveolae (Cohen et al., 2003; Fagerholm et al., 2009; Sekimoto et al., 2012). On an interesting note, insulin resistance was related quite recently, not only to caveolae biology alteration, but also to mitochondrial dysfunction (Raza et al., 2015; Crescenzo et al., 2014).

Independently, oxidative stress (Toussaint et al., 2000) and cav-1 overexpression (Volonte et al., 2002) were both shown to induce premature senescence in cell lines and were repeatedly reported to be increased in aged animal models (reviewed in (Liu and Xu, 2011; Zou et al., 2011)). More and more data relate cav-1 to oxidative stress and because inside the cell, oxidative stress and mitochondria are intimately related, in this review we shall attempt to outline connections between two major ageing process determinants.

2. Spatial and biochemical relationships between caveolae and mitochondria

Spatial relationship between mitochondria and caveolae has long been highlighted by confocal microscopy (Shiroto et al., 2014) and electron microscopy, showing close apposition between the two structures (Fig. 1).

In terms of biochemical structure, mitochondria and caveolae seem to share structural proteins, which could be explained by lateral diffusion through physical contact points. For example, cav1 immunoblotting and immunogold electron microscopy demonstrated its colocalization with mitochondrial membranes in liver and lung (Li et al., 2001). Certain mitochondrial proteins were, in turn, identified in purified caveolae through proteomic analysis (McMahon et al., 2006). According to Chatenay-Rivauday et al., ATP synthase beta subunit was purified from endothelial caveolae (Chatenay-Rivauday et al., 2004) and more recently, Kim et al. reported many mitochondrial oxidative phosphorylation complexes to be located in cell membrane lipid rafts (Kim et al., 2010).

Functional studies to investigate relationships between cav1 expression and oxidative stress were also performed, by either knocking out the protein in cell cultures (Pavlides et al., 2010) and laboratory animals (Shiroto et al., 2014) or overexpressing it in different experimental models (Fridolfsson et al., 2012; Asterholm et al., 2012). The outcome of these interventions varies, as indicated in Table 1 and discussed in detail later on.

Cooperation between caveolin and mitochondria seems to be a mechanism to enhance stress resistance and was proposed to be coordinated by signalling through receptors coupled with trimeric G inhibitory proteins (Wang et al., 2014). Surpassing the mitohormetic level of ROS production was reported to activate cav1 promoter (Bartholomew and Galbiati, 2010), leading to overexpressed proteins levels. In turn, increased cav1 will trigger "warnings" related to cellular senescence, as illustrated in Fig. 2

ROS- reactive oxygen species, Nrf2- nuclear factor (erythroid-derived 2)-like 2; sirt1–sirtuin1; TrxR1- thioredoxin reductase 1

In the following sections of the article, we shall attempt to elaborate on this diagram, providing some insights on mitochondrial ROS production, ROS relationship with caveolae and caveolin1 and how this relationship may lead to cellular senescence.

3. Mitochondria as a source of oxidative stress and a central player in cellular senescence

Mitochondria are in the centre of "mitochondrial theory of ageing", proposed by Harman (Harman, 1972), according to which reactive oxygen species (ROS) produced in these organelles are responsible for oxidative stress and premature ageing. Soon afterwards, positive correlation between ROS production and mitochondrial DNA mutagenesis were reported (Wei et al., 1998), although there are convincing reports that senescence induced by point mutations can also be ROS independent (Trifunovic et al., 2005). An impressive amount of data accumulated on increased mitochondrial damage and decrease in respiratory metabolism

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