Chemico-Biological Interactions xxx (2016) 1–6

Contents lists available at ScienceDirect

Chemico-Biological Interactions

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

Paraoxonases, mitochondrial dysfunction and non-communicable diseases

Jordi Camps*, Anabel García-Heredia, Anna Hernández-Aguilera, Jorge Joven

Unitat de Recerca Biomèdica, Hospital Universitari de Sant Joan, Institut d'Investigació Sanitària Pere Virgili, C. Sant Joan s/n, Reus 43201, Catalonia, Spain

ARTICLE INFO

Article history:
Received 23 November 2015
Received in revised form
23 February 2016
Accepted 4 April 2016
Available online xxx

Keywords:
Inflammation
Non-communicable diseases
Oxidative stress
Paraoxonase

ABSTRACT

The most common non-communicable diseases (NCD) are obesity, cardiovascular disease, diabetes, cancer, chronic respiratory diseases, and neurological diseases. Together, they constitute the commonest cause of death and disability worldwide. Mitochondrial alterations, oxidative stress and inflammation underpin NCD and are molecular mechanisms playing major roles in the disease onset and natural history. Interrelations between the mechanisms of oxidative stress, inflammation and metabolism are, in the broadest sense of energy transformations, being increasingly recognized as part of the problem in NCD. Whether or not oxidative stress and inflammation are the causes or the consequences of cellular disturbances, they do significantly contribute to NCD.

Paraoxonases are associated with mitochondria and mitochondria-associated membranes. They modulate mitochondria-dependent superoxide production, and prevent apoptosis. Their overexpression protects mitochondria from endoplasmic reticulum stress and subsequent mitochondrial dysfunction; highlighting that the anti-inflammatory effects of paraoxonases may be mediated, at least in part, by their protective role in mitochondria and associated organelle function. Since oxidative stress is implicated in the development of NCD (as a result of mitochondrial dysfunction), these data suggest that understanding the role and the molecular targets of paraoxonases may provide novel strategies of intervention in the treatment of these important diseases.

1. Mitochondrial dysfunction and non-communicable diseases

Non-communicable diseases (NCD) are, by definition, those chronic diseases that are non-infectious and non-transmissible. The most common NCD are obesity, diabetes, cancer, cardiovascular and neurological diseases. Obesity is one of the great epidemics of the XXI Century. In the European Union, approximately 35% of adults are overweight and 17% are obese; these numbers are being reflected in children [1,2]. The data are extremely relevant because obesity is key in the development of major diseases. Indeed, this disorder is often associated with comorbidities including several NCD such as diabetes mellitus, hypertension, metabolic syndrome, non-alcoholic fatty liver disease and cardiovascular disease. Furthermore, obesity is related to increased incidence of several classes of cancer including colorectal, liver, breast, pancreatic, endometrial, renal, prostate, lymphoma and myeloma [3]. Hence, investigating the molecular basis of obesity and its associated disorders can provide the tools to combat these alterations more effectively.

Mitochondrial dysfunction and impaired energy metabolism are central alterations in obesity. Cells can manage nutrient supply by increasing mitochondrial content. However, persistent nutrient surplus overwhelms the mitochondrial system and causes its dysfunction, leading to the accumulation of incompletely oxidized lipid products from the Krebs cycle. This causes fat accumulation and oxidative stress.

The intermediates also activate the endoplasmic reticulum stress cascade which disrupts the insulin signaling pathway leading to insulin resistance. In addition, accumulated free radicals cause mutations to the mitochondrial genome content, aberrant mitochondria and cell death by apoptosis [4,5].

Abbreviations: CCL2, chemokine ligand (C-C motif) ligand 2; CHOP, CCAAT-enhancer-binding protein homologous protein; NCD, non-communicable diseases; NF, nuclear factor; PERK, protein kinase RNA-like endoplasmic reticulum kinase; PON, paraoxonase.

* Corresponding author.
E-mail address: jcamps@grupsagessa.com (J. Camps).

http://dx.doi.org/10.1016/j.cbi.2016.04.005
0009-2797/

Mitochondrial architecture is regulated by the antagonistic processes of fission and fusion [5,6]. Mitochondrial fusion counterbalances functional defects and allows genetic compensation, while fission allows the segregation of damaged mitochondria and their recycling through a process termed mitophagy; a type of autophagy that eliminates damaged mitochondria (Fig. 1). Autophagy, or self-cannibalism, was first described in mammalian cells over 50 years ago, but the molecular bases for this process have not been satisfactorily elucidated. Macroautophagy is the main pathway, and involves the formation of a double membrane around aberrant cellular particles resulting in the organelle known as an autophagosome. Microautophagy, on the other hand, involves the direct engulfment of cytoplasmic material into the lysosome by invagination. Mitophagy plays a protective role in the response of the cell to pernicious stimuli and, particularly, in the response to inflammation or oxidative stress, thus acting as a defensive mechanism to alleviate inflammation, cell death and mitochondrial dysfunction [7]. A recent study reported that transgenic mice overexpressing the pro-inflammatory chemokine ligand (C–C motif) ligand 2 (CCL2) have morphological alterations in their mitochondria, with an increased fusion and an increased number of autophagosomes, compared to wild type and CCL2 deficient animals [8]. CCL2 is produced in cells as a consequence of oxidative stress, and its synthesis has been demonstrated to be inhibited by paraoxonase-1 (PON1) [9].

Mitochondrial dysfunction and endoplasmic reticulum stress are strongly linked. The unfolded protein response (UPR) is a cellular stress response designed to restore the normal function of the cell by halting protein translation and activating protein repair. If this task is not achieved, the UPR induces apoptosis. A comprehensive review has been published by Ron and Walter [10]. Molecules participating in the UPR are shown in Fig. 2. The three pathways depicted in the figure link endoplasmic reticulum stress, inflammation and metabolism. The PERK arm of the UPR induces genes involved in antioxidant response, including PON1, as well as the transcription factor CCAAT/enhancer binding protein (C/EBP), homologous protein (CHOP), growth arrest, and DNA damage-inducible protein 34 (Gadd34) [11]. The activation of the IRE-1 arm regulates the expression of endoplasmic reticulum chaperones through the splicing of X-box binding protein-1 (XBP-1) mRNA, and may induce apoptosis and inflammation via the association with TNF receptor-associated factor 2 (TRAF2) activating the c-Jun N-terminal kinases (JNK). The third branch of the unfolded protein response is ATF6. The active N-terminal ATF6 regulates

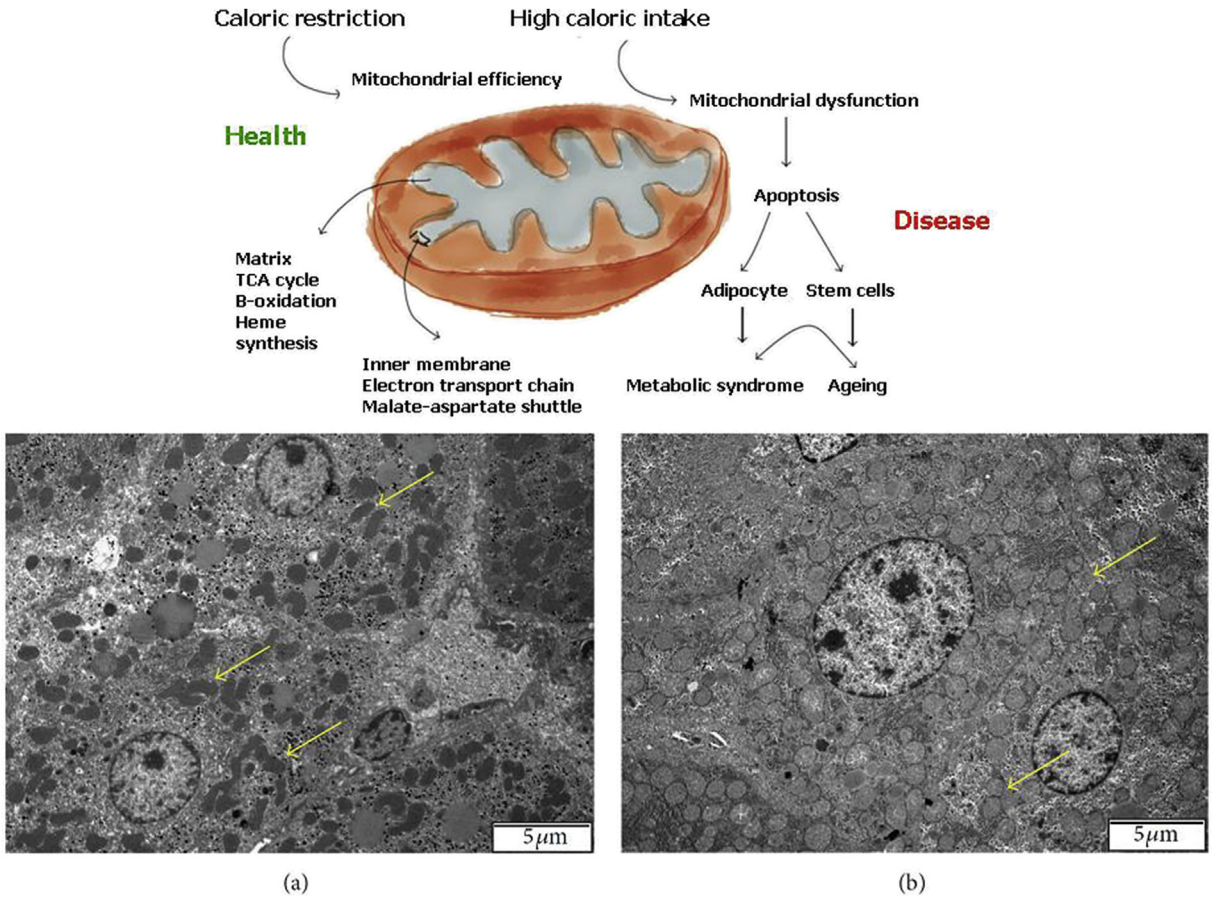

Fig. 1. Mitochondria are essential organelles since their most prominent role is to supply the cell with metabolic energy in the form of ATP through oxidative phosphorylation. In addition to their central role in various biochemical pathways, mitochondria are key regulators of apoptosis while participating in developmental processes, and aging. As part of these processes, mitochondria have a dynamic behavior which allows the cell to respond to its ever-changing physiological environment. The dynamics are determined by fusion and fission processes which regulate mitochondrial function. Mitochondrial morphology is controlled, essentially, by metabolism and inflammation. Each change in morphology is mediated by guanosine triphosphatases of the dynamin family; consistent with a model in which the capacity for oxidative phosphorylation is maximized under stressful conditions. Disruptions in these processes have been implicated in several human diseases. The arrows in panel (a) show mitochondrial fusion in the liver of a normal mouse. Mitochondria appear elongated, as bundles of two or three alongside each other, and without separation between them. The arrows in panel (b) show mitochondrial fission. In this case, mitochondria also appear bundled, but with a separating membrane. Figure reproduced with permission from ref. #4 copyrighted by the authors.

Please cite this article in press as: J. Camps, et al., Paraoxonases, mitochondrial dysfunction and non-communicable diseases, Chemico-Biological Interactions (2016), http://dx.doi.org/10.1016/j.cbi.2016.04.005