Biochemical and Biophysical Research Communications xxx (2016) 1–11

Contents lists available at ScienceDirect

Biochemical and Biophysical Research Communications

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

Emerging (and converging) pathways in Parkinson's disease: keeping mitochondrial wellness

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ARTICLE INFO

Article history:
Received 8 July 2016
Received in revised form
25 August 2016
Accepted 27 August 2016
Available online xxx

Keywords:
Parkinson disease
Mitochondria
Calcium
Dopaminergic neurons
PD-related proteins

ABSTRACT

The selective cell loss in the ventral component of the substantia nigra pars compacta and the presence of alpha-synuclein (α-syn)-rich intraneuronal inclusions called Lewy bodies are the pathological hallmarks of Parkinson's disease (PD), the most common motor system disorder whose aetiology remains largely elusive. Although most cases of PD are idiopathic, there are rare familial forms of the disease that can be traced to single gene mutations that follow Mendelian inheritance pattern. The study of several nuclear encoded proteins whose mutations are linked to the development of autosomal recessive and dominant forms of familial PD enhanced our understanding of biochemical and cellular mechanisms contributing to the disease and suggested that many signs of neurodegeneration result from compromised mitochondrial function. Here we present an overview of the current understanding of PD-related mitochondrial dysfunction including defects in bioenergetics and Ca^{2+} homeostasis, mitochondrial DNA mutations, altered mitochondrial dynamics and autophagy. We emphasize, in particular, the convergence of many "apparently" different pathways towards a common route involving mitochondria. Understanding whether mitochondrial dysfunction in PD represents the cause or the consequence of the disease is challenging and will help to define the pathogenic processes at the basis of the PD onset and progression.

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1. Introduction

Mitochondria are the only structures within the cells that are

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http://dx.doi.org/10.1016/j.bbrc.2016.08.153
0006-291X/

surrounded by a double membrane. The two membranes differ in protein and lipid composition and in their functional roles. The outer mitochondrial membrane (OMM) is characterized by the presence of β-barrel pore-forming proteins (named porins) that make it permeable to solute up to 5 kDa, while the inner mitochondrial membrane (IMM) is highly selective, since it is impermeable to ions and to most hydrophilic molecules. However, its crossing by specific molecules is controlled by the presence of specific transporters. In term of composition, it is characterized by an elevated proteins content, since, in addition to carrier proteins, it is embedded with the proteins of the respiratory chain (RC) and the ATP synthase. The IMM surface is enormously enhanced by a process of membrane invagination that gives rise to the so-called cristae, that can host a large number of RC complexes and ATP synthases, thus expanding the capacity of the cells to generate ATP in a rather confined space. The RC is composed by five multisubunits protein complexes: three of them (complex I, III and IV) pump protons (H^+) across the inner membrane thus establishing an electrochemical gradient that account for a membrane potential negative inside. Along with RC complexes, electrons are transported from the reduced substrates (NADH and $FADH_2$) to the oxygen that is converted in H_2O. Complex V, the ATP synthase, uses the electrochemical gradient generated across the IMM to produce ATP, by coupling the entry of protons to ADP phosphorylation. The electron transport, especially at complex I and III level, also generates the free radical superoxide ($O_2^{-\bullet}$), which by the large majority is converted to hydrogen peroxide by manganese superoxide dismutase (MnSOD), that in turn is converted to water by glutathione peroxidase and catalase. However, it can also generate the highly reactive hydroxyl radical ($OH^\bullet$) by reacting with Fe^{2+} or Cu^{2+} and peroxynitrite ($ONOO^-$) by reacting with nitric oxide. Free radicals may be also generated by the activity of mitochondrial monoamine oxidase (MAOA and MAOB), enzymes involved in the metabolism of serotonin, norepinephrine and dopamine. All these reactive species are potentially dangerous because they could cause membrane lipid peroxidation and damage protein and DNA or nitration of proteins at tyrosine residues, respectively. However, it is worth to note that the free radical superoxide ($O_2^{-\bullet}$) and H_2O_2 also serve important signalling functions in physiological processes, thus their generation has not exclusively detrimental consequences [1].

In terms of signalling molecules, the OMM, the inter-membrane space and the outer surface of the IMM are exposed to the same concentrations existing in the cytoplasm, while the inner surface of the IMM and the matrix are believed to be totally insulated from cytoplasmic second messengers with the exception of Ca^{2+} ions, whose entry into the matrix is controlled by the mitochondrial Ca^{2+} uniporter complex [2].

The molecular identification of the different components of the MCU complex has revealed a complex system of regulation. Two pore channel components are present: MCU and MCUb, the latter being a dominant negative isoform. MCU and MCUb are assembled in a predicted tetrameric structure to form the active Ca^{2+} channel and their expression level ratio differs among the tissues, possibly representing a way to regulate MCU activity according to the different cells type demands [2,3]. The opening of the MCU is mediated by a regulatory dimer formed by the two EF-hand containing proteins MICU1 and MICU2 [4] and depends on the extra-mitochondrial Ca^{2+} concentration. At low Ca^{2+}, the prevailing inhibitory effect of MICU2 ensures minimal Ca^{2+} transfer in presence of a very large driving force for its accumulation, thus avoiding excessive (and potentially dangerous) Ca^{2+} cycling and overload into the matrix. As soon as extra-mitochondrial Ca^{2+} increases, Ca^{2+}-dependent MICU2 inhibition and MICU1 activation guarantee the prompt initiation of rapid mitochondrial Ca^{2+} accumulation, stimulating aerobic metabolism and increasing ATP production. In addition to MICU1 and 2, other components have been identified, among them MICU3, highly expressed in neuronal tissue, EMRE [5], an essential protein for the correct assembly of the complex and MCUR1 [6], whose role and inclusion in the MCU complex is still debated.

The RC, by generating the electrochemical gradient, and in turn a difference of membrane potential across the inner mitochondrial membrane, also sustains Ca^{2+} transfer inside the mitochondrial matrix which occurs downhill the gradient through the low affinity MCU. Two antiporters, the Na^+/Ca^{2+} exchanger [7] and the H^+/Ca^{2+} exchanger move Ca^{2+} out of the matrix, preventing the attainment of thermodynamic equilibrium and allowing the return of mitochondrial Ca^{2+} concentration to basal values after cell stimulation. Mitochondrial Ca^{2+} accumulation modulates mitochondrial function in a variety of ways, by activating Krebs cycle dehydrogenases and promoting the supply of oxidable substrate and the activity of the ATP synthase [8,9]. In addition, mitochondrial Ca^{2+} uptake and release control how much Ca^{2+} enters the cell, the Ca^{2+} concentration in cytoplasmic microdomains, the frequency of oscillatory cytosolic Ca^{2+} signals, the rate of propagation of a Ca^{2+} signal across cells: the role of mitochondria as buffering organelles is essential in the spatio-temporal tuning of cytosolic Ca^{2+} concentration and thus of the cellular responses. Thus, by assuring numerous physiological fundamental processes such as the cellular energy-metabolism equilibrium, the modulation of Ca^{2+} signalling, the cellular redox balance and significant biosynthetic pathways, mitochondria have pivotal role in a variety of cell types. Importantly, they govern also cell fate by controlling the apoptosis pathway [10]. In addition to the Ca^{2+} transporting systems on IMM, an important role is played by a large-conductance channel which controls the permeability of OMM. The molecular identity of this channels, known as the mitochondrial permeability transition pore (mPTP), has been recently established to be coincident with that of the ATP synthase, that under conditions of oxidative stress undergoes dimerization and assembly forming a pore structure. The exact composition of the mPTP complex is still debated, but general consensus has been reached on mPTP role. Its opening is activated by various pathophysiological conditions (e.g. Ca^{2+} increases in the mitochondrial matrix and oxidation of critical cysteines) is most likely involved in the swelling and fragmentation of the mitochondrial network that underlie the release of caspase cofactors from mitochondria [11].

Mitochondrial shape and movements within the cells are regulated and have an impact on mitochondrial function, especially in the central nervous system, where mitochondrial trafficking is critical to provide strategic intracellular distribution, presumably according to local energy request. Thus, the maintenance of a healthy mitochondrial network is fundamental to guarantee the integrity of numerous cell signalling pathways and, to this purpose, the cells developed a sophisticated system of quality control to renew mitochondria by the fusion/fission process and to eliminate them when damaged. It is now well accepted that defects in these processes impact on mitochondrial function and lead to disordered cell function, which manifests as disease.

Interestingly, despite of it might be expected that mitochondrial dysfunction would give rise to predictable defects in all tissues, a special relationship between impaired mitochondrial function and neurodegenerative diseases has been consistently observed, thus joining diseases which are different in aetiology, clinical symptoms and affected neuronal subpopulations. For instance, Alzheimer's, Parkinson's, Huntington's diseases and amyotrophic lateral sclerosis, etc. share common elements converging on mitochondria. For this reason, in recent years, mitochondria became the object of intensive studies with the aim to identify specific mitochondrial targets for therapeutic intervention.

Please cite this article in press as: D. Cieri, et al., Emerging (and converging) pathways in Parkinson's disease: keeping mitochondrial wellness, Biochemical and Biophysical Research Communications (2016), http://dx.doi.org/10.1016/j.bbrc.2016.08.153