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OPA1 and mitochondrial solute carriers in bioenergetic metabolism

Marc Germain*

Groupe de Recherche en Neurosciences; Département de Biologie Médicale; Université du Québec à Trois-Rivières; Trois-Rivières, Canada

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The mitochondrial fusion protein optic atrophy 1 (OPA1) is required to maintain cristae structure and for ATP synthase assembly. Our recent work demonstrates that OPA1 dynamically regulates these processes by sensing changes in nutrient availability through mitochondrial solute carriers and adjusting the metabolic output of mitochondria accordingly. This is a critical survival process as its inhibition leads to cell death.

Mitochondria are not the simple ATP producing machines they were once thought to be. In fact, their dynamic nature allows rapid regulation of key cellular processes, and mitochondria actually control a wide range of cellular processes including calcium handling, apoptotic cell death, autophagy, and differentiation, with important implications for tumorigenesis and neurodegenerative diseases.

Mitochondria fuse and divide dynamically in response to changes in the cellular environment through the control of a family of large dynamin-related GTPases. Among these, dynamin-related protein-1 (DRP1) regulates mitochondrial fission whereas mitofusins (outer mitochondrial membrane) and optic atrophy 1 (OPA1) (inner mitochondrial membrane) regulate mitochondrial fusion.[1] In addition, OPA1 is required to maintain the structure of cristae, the invaginations of the mitochondrial inner membrane where ATP synthesis occurs.[1,2] The role of mitochondrial dynamics in the regulation of cell fate first became evident following the discovery that mitochondria fragment during apoptosis, and that this fission is required to open cristae structure and maximize cytochrome c release and caspase activation.[1,3] Although pioneering work from Hackenbrock in the 1960s demonstrated that cristae structure changes with mitochondrial activity (in the absence of cell death),[4] the underlying mechanisms and the role of such changes in a physiological context remained elusive.

Our recent work has now started to address these questions.[2] Although starvation promotes mitochondrial elongation,[1,5] it also triggers critical fusion-independent changes within the cristae structure that are required to maintain mitochondrial activity when low amounts of substrates are present.[2] In fact, cristae structure and function of the electron transport chain (ETC) are intimately linked. For example, OPA1 is required not only to maintain cristae structure, but also for assembly of the ATP synthase and assembly of ETC components into respiratory supercomplexes.[2,6] Importantly, we have recently demonstrated that OPA1 oligomerization regulates these processes in a dynamic fashion and is thus required for cells to adapt to changing nutrient availability.[2] This is shown by the inability of *OPA1* knockout (KO) cells to grow in galactose and their rapid death when grown in the absence of amino acids (in Earl's Balanced Salt Solution).[2,6] When nutrients are scarce (starvation), OPA1 oligomerizes and promotes tighter cristae and increased ATP synthase assembly and oxygen consumption, all of which promote mitochondrial ATP synthesis and cell survival (**Fig. 1**).[2] Importantly, a mutant OPA1 that maintains cristae structure but is fusion-incompetent rescued the defective nutrient response of *OPA1* KO cells, dissociating cristae-driven regulation of mitochondrial function from mitochondrial fusion.[2]

OPA1 has been postulated to regulate cristae structure directly through its oligomerization.[1] However, OPA1 also interacts with key protein complexes that can act both upstream and downstream of OPA1 to regulate cristae structure and function. For example, OPA1 interacts with ATP synthase subunits as well as several components of the MINOS/MitOS/MICOS complex, both of which are involved in the formation and maintenance of cristae structure.[1,2] OPA1 also interacts with members of the SLC25A family of mitochondrial solute carrier proteins.[2] These inner mitochondrial membrane transporters carry a wide range of metabolites across the inner membrane[7] and are therefore uniquely positioned to act as sensors detecting changes in metabolite concentration and relaying the information to OPA1, which then promotes cristae tightening and ATP synthase assembly.

As stated above, study of the role of OPA1 in the maintenance of cristae structure has focused on apoptotic cell death and the fine-tuning of ATP production in response to changing nutrient availability. However, cancer cells and other rapidly dividing cells may rely on their mitochondria less for ATP production than for the generation of amino acids and lipids required for

*Correspondence to: Marc Germain; Email: marc.germain1@uqtr.ca
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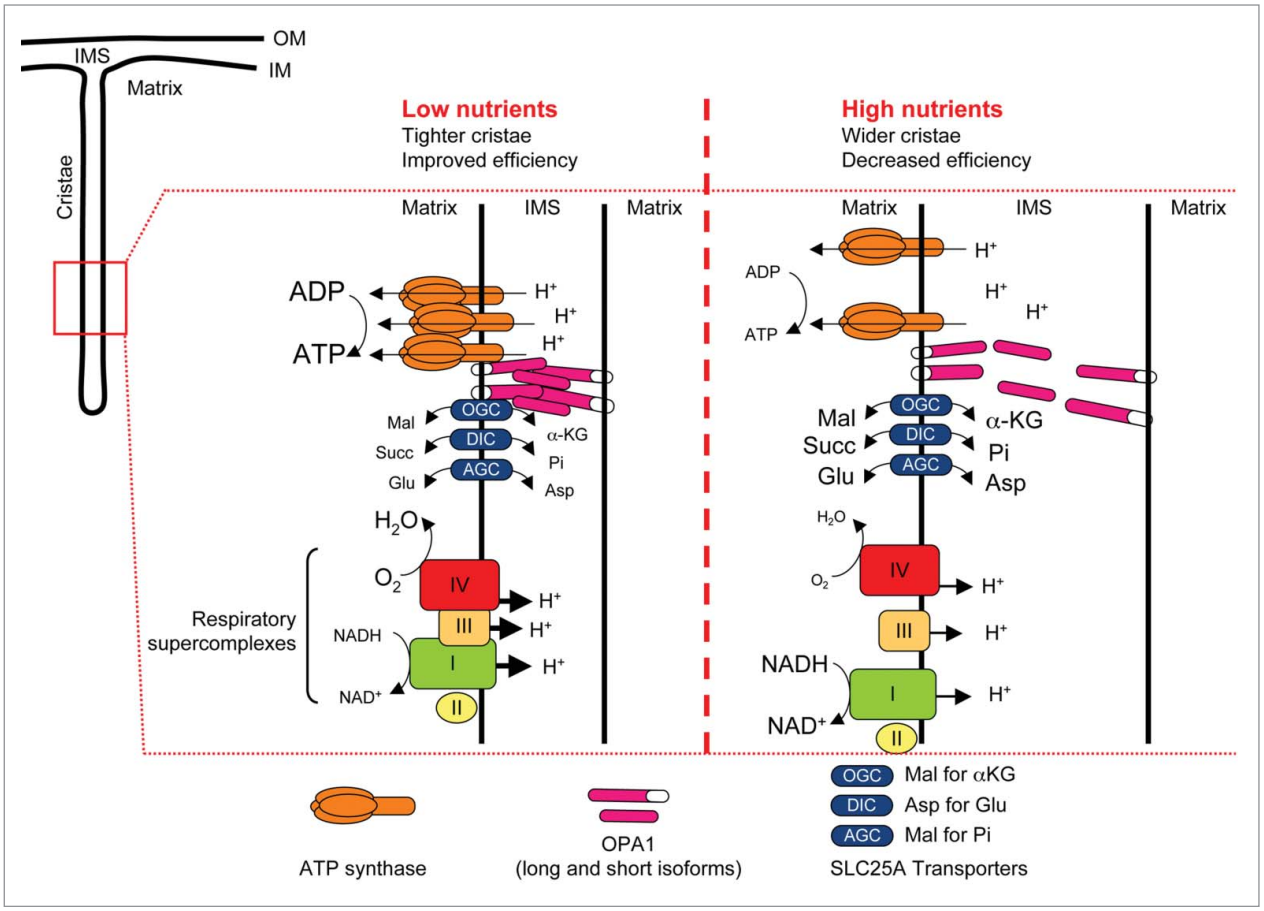

Figure 1. Regulation of mitochondrial ATP production by OPA1. Members of the SLC25A family of mitochondrial inner membrane transporters sense the levels of mitochondrial metabolites. Starvation leads to a decrease in metabolites, promoting interaction between the transporters and OPA1. This leads to OPA1 oligomerization, reduced cristae width, increased assembly of the ATP synthase, and formation of respiratory supercomplexes, all of which improve mitochondrial efficiency. Conversely, when nutrient levels are high, less OPA1 oligomerizes and mitochondrial ATP production is less efficient. Importantly, these changes occur in a fusion-independent fashion. α-KG, α-ketoglutarate; AGC, aspartate/glutamate carrier; DIC, dicarboxylate carrier; Glu, glutamate; IM, inner membrane; IMS, intermembrane space; Mal, malate; OGC, oxoglutarate carrier; OM, mitochondrial outer membrane; Pi, phosphate; Succ, succinate.

their growth.[8] In addition, several cancer cell lines are dependent on glutamine rather than glucose as a carbon source for energy production.[8] In that context, it is noteworthy that SLC25A transporters that interact with OPA1 are not only involved in the malate-aspartate shuttle required to transfer glycolysis-derived NADH to mitochondria (aspartate/glutamate carrier (AGC)/oxoglutarate carrier [OGC]) but also transport metabolic intermediates important for cancer biology.[7] It is therefore possible that OPA1-mediated metabolic regulation controls not only ATP production but also the distribution of mitochondrial metabolites to other pathways, either through fine-tuning of mitochondrial function or by restricting the diffusion of these intermediates within cristae. This latter possibility is suggested by modeling studies showing that a tight cristae structure prevents diffusion of metabolites between cristae and the intermembrane space where they can diffuse out to or in from the cytosol.[9]

In that context, a key question that remains to be addressed is the relationship between OPA1-mediated mitochondrial changes and the induction of autophagy, a catabolic process required to recycle nutrients and promote survival under starvation conditions.[10] Autophagy that is triggered by the decrease in nutrient availability at the tumor core where blood flow is restricted is thought to sustain the viability of cancer cells.[10] As reduced nutrient levels also trigger OPA1-dependent changes in the cristae to promote metabolic efficiency, the relative contribution of each to the survival of cancer cells needs to be addressed. In addition, it will be important to define the role of starvation-induced signaling pathways such as AMP-dependent protein kinase (AMPK)[10] in regulating mitochondrial function under these conditions as they may regulate the flow of metabolites to and from mitochondria.

Mitochondria lie at the interface between metabolic processes required for tumor growth and cell death

pathways that act as a safeguard against uncontrolled proliferation. Elucidation of the role of OPA1 as a central regulator of cristae structure that is required for both life and death will therefore provide important new insights into the regulation of these 2 opposite outcomes in cancer biology.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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