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Protein-mediated energy-dissipating pathways in mitochondria

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Abstract

Mitochondrial production of reactive oxygen species (ROS) is a well-established fact of fundamental importance to aging and etiology of many pathologies with serious public health implications. The ROS production is an innate property of mitochondrial biochemistry inseparable from the oxidative metabolism. Recent discoveries indicate that in addition to several ROS-detoxifying enzyme systems, which remove ROS, mitochondria may also be able to limit their ROS production by the mechanism comprising several protein-mediated energy-dissipating ("uncoupling") pathways. Although the physiological significance and in vivo modus operandi of these pathways remain to be elucidated, several proteins potentially capable of energy dissipation are known. This mini-review addresses the identity of mitochondrial protein-mediated energy-dissipating pathways and the experimental evidence to their role in controlling ROS production.

Keywords: Uncoupling; UCP; ANT; Membrane anion carriers; Reactive oxygen species; Proton leak

1. Introduction

Mitochondria are complex structures. In fact, mitochondria are very complex, topologically nightmarish, enigmatic, strangely attractive structures performing great variety of metabolic functions, most of which we are just beginning to understand (reviewed in [1]). They surely hold secrets of life and death, health and disease, physical fitness, and our origin. Mitochondria also are the "power plants" of aerobic cells; they produce ATP which fuels numerous cellular metabolic activities.

It is rather apparent that a malfunctioning power plant is a recipe for the disaster. It is unable to supply enough energy to other important processes; it can explode, burn, and emit dangerous radiation. Malfunctioning mitochondria do all that. They can consume cellular ATP instead of producing it, burn energy of nutrients as heat, "explode" upon Ca^{2+} overload, and emit dangerous "radiation" in the form of reactive oxygen species (ROS) that directly attack and damage other cellular structures.

However, even properly functioning mitochondria "habitually" produce some amount of ROS as an apparently unavoidable consequence of their oxidative metabolism. Endogenously produced ROS have no immediate lethal outcome to the cell and may in fact play a physiologically relevant and important role, by regulating gene expression or serving as messengers in various signaling pathways [1–4]. Mitochondria possess quite a powerful, multi-leveled ROS-defense system (reviewed in [5]); however, mitochondrial ROS production may vary significantly, depending on their metabolic state and other factors, and no defense system is perfect. It is believed that a recurrent over-production of ROS by mitochondria imposes a low-level "destructive pressure" on sensitive cellular structures and on mitochondria per se. Modern view on aging reserves a central role for mitochondrial ROS production (reviewed in [6,7]). A general idea is that reducing the over-

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production of ROS by mitochondria should increase individual's lifespan, reduce the probability of cancer and neurodegenerative diseases, and allow us living longer while staying healthier. No surprise that a drug that could do all that is much sought after. Developing such a drug requires deeper understanding of mechanisms and regulatory signals controlling mitochondrial ROS production that we currently have, but the research in this field is progressing very rapidly. Recent discoveries indicate that the best way to reduce mitochondrial ROS might be targeting their innate ROS-control mechanism, protein-mediated energy-dissipating pathways. This mini-review addresses the identity of these pathways and experimental evidence to their role in controlling mitochondrial ROS production.

2. Energy-dissipative pathways

"Energy-dissipative pathways" is a generalized expression to describe a number of mechanisms increasing non-productive energy expenditure in mitochondria. According to the chemiosmotic theory of mitochondrial energy transduction [8–10], free energy released upon oxidation of substrates in mitochondria is conserved by transforming it into the electrochemical gradient of protons across their membrane, $\Delta\mu_{H^+}$. The latter is spent to drive the metabolically useful endergonic reactions such as, e.g. synthesis of ATP or accumulation of ions against the gradient of their concentration. These reactions are catalyzed by various proteins which therefore serve as the "reverse transducers", converting free energy of the $\Delta\mu_{H^+}$ into a form other than heat. On the opposite, an energy-dissipating pathway uses the $\Delta\mu_{H^+}$ to drive a futile reaction producing heat as the only outcome, thereby reducing the amount of energy stored in the $\Delta\mu_{H^+}$. Although such a mechanism reduces the amount of energy available for other reactions utilizing the $\Delta\mu_{H^+}$ and decreases the efficiency of mitochondrial energy transduction, it may be metabolically useful to a cell in many cases, exactly because it reduces the $\Delta\mu_{H^+}$ or generates heat. A well-known example of the latter is the protein-catalyzed $\Delta\mu_{H^+}$ dissipation in brown fat mitochondria which produces large amount of heat for the purpose of thermoregulation. The regulation of mitochondrial ROS production may be another important example of a useful energy-dissipative pathway.

3. Summary of mitochondrial ROS production

Before reviewing the role and mechanisms of the mitochondrial energy-dissipating pathways, we would like to provide some background on the mitochondrial ROS production. Its physiological role and known mechanistic details have been extensively reviewed elsewhere [5,11–14]. For the purpose of this review, current state of affair in this field can be summarized as follows:

1. Mitochondrial ROS production is a well-established fact of fundamental importance to aging and etiology of most known pathologies with serious public health implications. All mitochondria in every tissue of any organism examined so far generate ROS. This is a price all eukaryotic organisms pay for the benefits of their oxygen-dependent metabolism.
2. In "healthy" mitochondria, ROS production is "a disease of excess", meaning that mitochondrial ROS production depends on the degree of their energization. With everything else equal, ROS production is maximal when the mitochondrial $\Delta\mu_{H^+}$ is maximal.
3. In pathologically altered mitochondria, ROS production may increase or decrease with no immediate dependence on their $\Delta\mu_{H^+}$.
4. Mitochondria possess a very powerful ROS-detoxifying system that also partially depends on their energy producing capacity. This system is crucial for protecting both the cell and mitochondria from exogenously produced ROS but not so efficient in scavenging ROS generated in mitochondria per se, due to the immediate vicinity of the ROS-generating sites to the ROS-sensitive targets in mitochondria.

As a consequence of (1), (2), and (4), any treatment perceived to diminish the mitochondrial ROS production without compromising their ability to detoxify ROS is very much sought after. Owing to (2) and (4), decreasing the mitochondrial $\Delta\mu_{H^+}$ without significantly compromising their energy-producing capacity is thought to be the best and only way to decrease the mitochondrial ROS production. This idea was expressed in the form of "mild uncoupling" concept introduced in 1996 by Skulachev [15–17]. The "mild uncoupling" concept presumes that a small decrease in the $\Delta\mu_{H^+}$ should significantly decrease the ROS production with practically no impact on energy production in mitochondria. The ROS-defense system (4) represents a special case; it may or may not benefit from the "mild uncoupling", depending on the nature of pathological changes.

There are three types of the ROS-producing sites in mitochondria (reviewed in [5]). The first type is represented by the respiratory chain enzyme complexes I and III and by the substrate:coenzyme Q reductases