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ScienceDirect
Mitochondrion 7 (2007) 1–5
Mitochondrion
www.elsevier.com/locate/mito

Review

The essential requirement for superoxide radical and nitric oxide formation for normal physiological function and healthy aging

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Received 19 April 2006; accepted 22 September 2006
Available online 5 December 2006

Abstract

Contrary to the dogma that superoxide anion and hydrogen peroxide formation are highly deleterious to cell function and healthy aging, we suggest this premise is flawed. Superoxide anion and hydrogen peroxide formation are essential to normal cellular function; they constitute a second messenger system absolutely required for the regulation of the metabolome. Embraced within this regulation is the modulation of cellular redox poise, bioenergy output, gene expression and cell differentiation. A key component in the overall process is coenzyme Q_{10} whose prooxidant function through the formation of superoxide anion and hydrogen peroxide is a major factor in the overall processes. The free radical gas, nitric oxide (similarly to superoxide anion), functions in the regulation of a wide range of cell systems. As part of the normal physiological process, superoxide anion and NO function separately and interactively as second messengers. Superoxide anion and nitric oxide play an intrinsic role in the regulated ordered turnover of proteins, rather than randomly cause protein damage and their inactivation. The proposition that metabolic free radical formation is unequivocally deleterious to cell function is rebutted; their toxicity as primary effectors in the aging process has been overemphasized. The concept that a dietary supplement of high concentrations of small-molecule antioxidants is a prophylactic/amelioration therapy for the aging process and age-associated diseases is questioned as to its clinical validity.

Keywords: Coenzyme Q_{10}; Redox poise; Gene regulation; Metabolic regulation; Superoxide anion; Hydrogen peroxide; Nitric oxide; Peroxynitrite; Prooxidants; Antioxidants; Protein turnover; Aging

1. Introduction

It was first hypothesized by Harman (1956) that oxygen radical formation was a major deleterious contributor to the aging process and this suggestion hypothesized that oxygen radical formation by cells was a continuing toxic process which over time was a major causation of human aging (for review, Harman, 2003). This hypothesis apparently received strong experimental support from the studies of Boveris et al. (1972) and Boveris and Chance (1973), who demonstrated that large amounts of superoxide anion were generated by mitochondria during the process of complex I and II reduction of coenzyme Q_{10} and its oxidation by complex III. Chance et al. (1979) estimated that 1–3% of inspired oxygen was converted to superoxide anion; such large amounts of product would indeed be potentially highly toxic to cells. However, their interpretations in the light of more recent studies are not sustainable; their experiments demonstrating the formation of large amounts of superoxide anion involved treating isolated mitochondria with a series of respiratory inhibitors whose action was required to induce the formation of measurable amounts of superoxide anion and H_2O_2. More recent studies by Staniek and Nohl (2000) and St-Pierre et al. (2002) have demonstrated that intact normally respiring mitochondria do not produce high concentrations of reactive oxygen species. It is concluded that the earlier extrapolations of superoxide anion and H_2O_2 production by inhibited mitochondria were overestimated by several orders of magnitude radical formation by uninhibited mitochondria.

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1567-7249/$ - see front matter
doi:10.1016/j.mito.2006.11.009

We suggest that oxygen radical formation as a deleterious major contributor to the aging process is an oversimplified concept. Rather, superoxide anion and H_2O_2 constitute a second messenger, cell regulatory system, whose formation is essential for normal physiological function and healthy aging (Kopsidas et al., 2000; Linnane et al., 2002; Linnane and Eastwood, 2004, 2006). Further that both second messenger roles of superoxide anion and the free radical gas nitric oxide acting separately, and in concert, are essential for normal physiological function.

This short paper constitutes a very brief, perhaps overly simplified, outline of the essential physiological role played by prooxidants; an expanded more detailed manuscript is in preparation for publication elsewhere.

2. Coenzyme Q_{10}: bioenergy, metabolic regulation, redox poise, and superoxide anion formation

Coenzyme Q_{10} oxido-reductase systems play a major role in the formation of superoxide anion (albeit not an exclusive one). Coenzyme Q_{10} is known to occur in all sub-cellular membranes and has a functional role in many known membrane oxido-reductase systems localized therein, notably in the mitochondria, plasmalemma, the Golgi apparatus (Crane, 2001) and lysosomes (Gille and Nohl, 2000). We have previously reported that coenzyme Q_{10} oxido-reductase systems play a major role in the regulation of sub-cellular metabolism through the agency of superoxide anion formation and metabolome modulation (Linnane and Eastwood, 2004, 2006). In Fig. 1, the global functions of coenzyme Q_{10} in relation to sub-cellular bioenergy systems, redox poise, metabolic flux modulation, gene regulation and oxygen radical formation are schematically outlined (refer Linnane and Eastwood, 2004, 2006 for further elaboration and explanation).

3. Cellular redox modulation and cell differentiation

Outside the field of aging studies there is a voluminous literature dating back some years on the essential role of oxygen radicals and redox signalling with H_2O_2 acting as a diffusible intracellular second messenger; it arises from the regulated functioning of various sub-cellular membrane oxido-reductase systems (for reviews, Finkel, 1998; Rhee, 1999; Werner, 2004).

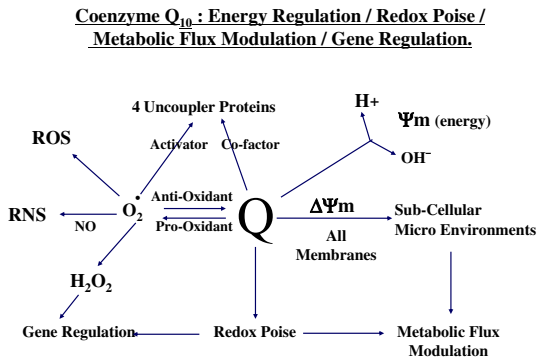

Fig. 1. This cartoon summarizes the wide-ranging roles played by coenzyme Q_{10} in the regulation of the metabolome (cf. Linnane and Eastwood, 2004, 2006).

There is also a growing literature on normally produced extracellular effectors determining the intracellular redox state of cells and consequently in some instances the course of cellular self-propagation or differentiation. As shown by Smith et al. (2000) extracellular effectors such as thyroid hormone, bone morphogenic protein 4, basic fibroblast growth factor, and platelet-derived growth factor regulate the cellular redox state of rat glial precursor cells. An intracellular redox environment induced to favour a more oxidized state by thyroid hormone or bone morphogenic protein 4 leads to a differentiation of the precursor cells into oligodendrocytes or astrocytes. On the other hand, an intracellular redox environment induced to favour a more reducing state by basic fibroblast growth factor or platelet-derived growth factor favours self-propagation of the precursor cells (Table 1). Superoxide anion and H_2O_2 play a major role in cellular redox modulation and as such are key components in the determination of cell-specific metabolomes.

4. Nitric oxide and peroxynitrite

NO is well recognised as an inter- and intracellular signalling molecule regulating blood vessel dilation, acting as a neurotransmitter and metabolic cell regulation, as well as an increasing number of other physiological systems.

Peroxynitrite radical arising from the reaction between superoxide anion and NO has long been described uncategorically as a highly toxic radical, but is this an oversimplification? We suggest such an interpretation should be accepted with caution. Thus, it has been reported that $ONOO^{\cdot}$ like NO and superoxide anion is an enzyme activator, one example of which is the activation of the Ca^{2+}-dependent ATPase of the endoplasmic reticulum, itself a major regulator of second messenger Ca^{2+} (Adachi et al., 2004). Fig. 2 summarizes some of the essential regulated separate, and interactive, roles played by superoxide anion and NO as second messengers contributing to the regulation of metabolism. As a caveat it may be added that large excessive overproduction of the free radicals NO and superoxide anion would most likely have toxic effects, such as for example, septic shock, brought about by excessive overproduction of nitric oxide. However, septic shock arises from an external trauma (bacterial infection), and in some but not all individuals there is an induction of an overactive immune system response; septic shock does not arise from an intrinsic systemic breakdown of NO formation.

5. Protein turnover regulation

The regulation of protein turnover is a huge topic and only part of the tip of this iceberg can be discussed here.