

## Commentary

# Deficient mitochondrial biogenesis in critical illness: cause, effect, or epiphenomenon?

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See related research by Côté *et al.*, <http://ccforum.com/content/11/4/R88>

## Abstract

Recent studies indicate that mitochondrial dysfunction plays a role in the pathogenesis of a number of disease states. The importance of these organelles in shock and multiple organ dysfunction is of particular interest to those caring for the critically ill. Mitochondria have their own unique DNA (mtDNA) that encodes 13 essential subunits of electron transport chain enzymes, two ribosomal RNAs and 22 transfer RNAs. Importantly, mtDNA is especially susceptible to deletions, rearrangements and mutations because it is not bound by histones and lacks the extensive repair machinery present in the nucleus. The study by Côté *et al.* in this issue of *Critical Care* examines changes in mtDNA in critically ill patients. The results support further investigation into the role of mtDNA in the critically ill.

The role of mitochondria in systemic disease has been underappreciated, and in this issue of *Critical Care*, Côté *et al.* [1] examine changes in mitochondrial DNA (mtDNA) in critically ill patients. However, recent evidence has demonstrated impaired oxidative phosphorylation and defective mitochondrial homeostasis in a number of disorders [2,3]. Although the concept of mitochondrial dysfunction and bioenergetic failure during sepsis and shock is not new, recent experimental approaches have yielded novel and interesting findings [4-6]. These have led us and others to propose intriguing hypotheses regarding the pathogenesis of acquired mitochondrial dysfunction in a variety of disease states.

In this issue, Côté *et al.* examine changes in mtDNA in critically ill patients. Their data demonstrate a 30% reduction in the ratio of mtDNA to nuclear DNA (nDNA) in circulating cells of 28 critically ill patients when compared to healthy controls [1]. More importantly, this ratio increased by almost 30% at four days in survivors while non-survivors experienced a further reduction in the mtDNA/nDNA ratio. One might

conclude that loss or failed synthesis of mtDNA is a unifying cause of sepsis-induced mitochondrial dysfunction and that clinicians could use mtDNA copy number to predict mortality during critical illness. This requires a more detailed examination of mtDNA heterogeneity and mitochondrial regeneration.

Each mitochondrion has 2-10 copies of its own circular genome. These encode for 13 essential subunits of electron transport chain enzymes, two ribosomal RNAs and 22 transfer RNAs [7]. The structural subunits of the electron transport complexes and other mitochondrial proteins arise from nuclear genes [8]. Thus, expression of the genes encoding mitochondrial enzyme complexes is under dual control. mtDNA is particularly prone to deletions, rearrangements and mutations caused by oxidative stress because it is unbound by histones and because these organelles lack the extensive repair systems seen in the nucleus [9]. Therefore, reactive oxygen species produced during oxidative phosphorylation in a variety of disease states can damage mtDNA and mitochondrial proteins. This would lead to decreased ATP production and enhanced programmed cell death [7].

Heteroplasmy describes the coexistence of both mutant mtDNA and wild-type, non-mutant mtDNA within the same cell [8]. If the mitochondrial genome drift results in a significant amount of mutant mtDNA, cells exhibit reduced energy capacity and organs become dysfunctional [7]. The threshold for these processes is lower in highly oxidative tissue such as brain, heart, skeletal muscle, retina, kidney and endocrine organs [8]. This threshold effect explains tissue-related variability in the clinical presentation of both inherited and acquired mitochondrial diseases [8].

MtDNA = mitochondrial DNA; nDNA = nuclear DNA.

Impaired mitochondrial biogenesis represents an additional manner in which mitochondria may contribute to acquired disorders. Biogenesis includes all of the processes needed for mitochondrial homeostasis and division. It requires precise coordination between both mitochondrial and nuclear-encoded gene products as well as maintenance and replication of mtDNA [10,11]. Recent investigation demonstrates that experimental murine sepsis caused mitochondrial oxidative stress, a loss of mtDNA copy number and depressed basal metabolism in the septic liver [12]. In the recovery phase, mitochondrial biogenesis restored mtDNA copy number and oxidative metabolism.

Our understanding of bioenergetic failure in sepsis and shock has been largely limited by interpretation of early investigations. These studies assumed that preservation of cellular ATP indicated intact electron transport [13,14]. However, more recent data make it clear that cells can adapt and maintain viability by down-regulating oxygen consumption, energy requirements and ATP demand [15,16]. In the heart this response is called myocardial hibernation and results in cardiomyocyte hypocontractility with preserved cellular ATP [15]. Hibernating cells maintain ATP levels in the setting of defective oxidative phosphorylation by ceasing nonessential cellular functions to limit ATP utilization [15,16]. At the organ level, this down-regulated metabolic state may manifest as "organ dysfunction" or "organ failure". During hypoxia, ischemia and in early or non-fatal sepsis, such a response appears to be adaptive and often reversible as cells at risk maintain viability and recover after reoxygenation and reperfusion. Our data, however, indicate that during lethal sepsis a similar hibernation response, while initially adaptive, may become problematic as cells remain persistently down-regulated, enzyme complex content and activity decrease and organ failure becomes irreversible [3,4]. This may result from an acquired defect in gene expression and/or functional activity of any of the electron transport enzymes [17]. Our data suggest that persistently impaired mitochondrial gene expression may represent the irreversible defect that leads to organ failure and death.

The hypothesis that therapeutically enhancing mitochondrial biogenesis could improve survival is fascinating, especially if defects in mitochondrial replication and mtDNA synthesis also occur in cells of solid organs. Based on recent reports, it is conceivable that stem cells or fibroblasts may be able to restore defective mitochondria in neighboring cells with wild-type mtDNA [18]. Thus, future investigation should focus on increasing and restoring wild-type mtDNA to restore cellular oxidative capacity and organ function in sepsis and shock.

What is most exciting is that we are still gaining insight into this billion year old, complex organelle. However, it remains unclear if mitochondrial impairment causes organ dysfunction, is protective against impending organ injury or is an epiphenomenon. The data presented to date have not directly

addressed this issue. These questions demand a more exhaustive investigation of the fascinating processes of mitochondrial biogenesis and homeostasis during both health and disease.

## Competing interests

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