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# SYMPOSIUM INTRODUCTION

# The Mitochondrial Contribution to Animal Performance, Adaptation, and Life-History Variation

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**Synopsis** Animals display tremendous variation in their rates of growth, reproductive output, and longevity. While the physiological and molecular mechanisms that underlie this variation remain poorly understood, the performance of the mitochondrion has emerged as a key player. Mitochondria not only impact the performance of eukaryotes via their capacity to produce ATP, but they also play a role in producing heat and reactive oxygen species and function as a major signaling hub for the cell. The papers included in this special issue emerged from a symposium titled "Inside the Black Box: The Mitochondrial Basis of Life-history Variation and Animal Performance." Based on studies of diverse animal taxa, three distinct themes emerged from these papers. (1) When linking mitochondrial function to components of fitness, it is crucial that mitochondrial assays are performed in conditions as close as the intracellular conditions experienced by the mitochondria *in vivo*. (2) Functional plasticity allows mitochondria to retain their performance, as well as that of their host, over a range of exogenous conditions, and selection on mitochondrial and nuclear-derived proteins can optimize the match between the environment and the bioenergetic capacity of the mitochondrion. Finally, (3) studies of wild and wild-derived animals suggest that mitochondria play a central role in animal performance and life history strategy. Taken as a whole, we hope that these papers will foster discussion and inspire new hypotheses and innovations that will further our understanding of the mitochondrial processes that underlie variation in life history traits and animal performance.

## Introduction

Animals display tremendous variation in their life histories and pace of life. A fruit fly dies of old age after a month and producing about 400 eggs (Ashburner et al. 2005). In contrast, a bowhead whale might live for two centuries producing fewer than 30 offspring (Würsig et al. 2017). Our understanding of the molecular and physiological

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mechanisms that contribute to the evolution of divergent patterns of aging and reproductive investment within and among species remains limited (Flatt and Heyland 2011; López-Otín et al. 2013). In the symposium of the Society for Integrative and Comparative Biology entitled "Inside the Black Box: The Mitochondrial Basis of Life-history Variation and Animal Performance" we highlighted that in animals, life-history traits depend on the critical function of a small, yet vital, intracellular organelle—the mitochondrion. As such, it is not surprising that the mitochondrion has emerged as a key player in shaping life-history evolution (Speakman et al. 2004; Balaban et al. 2005; Brand 2005; Monaghan et al. 2008; Salin et al. 2015).

Mitochondria are a hallmark of eukaryotic life and a vital signaling center of the cell (Bohovych and Khalimonchuk 2016; Vakifahmetoglu-Norberg et al. 2017). Mitochondria are best known for their role in producing the ATP molecules that fuel nearly all of the physiological processes supporting survival and performance of the animal. Mitochondria also are responsible for the production of heat, when respiration is uncoupled from the ATP synthase and protons flow from the intermembrane space back in the matrix. Mitochondria play a key role in the production of reactive oxygen species (ROS) that act as important cellular signals but can be damaging when produced in excess or left unmitigated. An imbalance between ROS production and the activity of antioxidants that quench them can lead to the accumulation of oxidative damage to proteins, lipids, and DNA (Halliwell and Gutteridge 2007). This oxidative stress has the potential to reduce animal performance, promote disease, and contribute to cellular senescence. Ecologists and evolutionary biologists have increasingly recognized the potential for oxidative stress to play a role in inter-individual and inter-populational variation in maintenance, growth, reproduction, and longevity (Dowling and Simmons 2009; Monaghan et al. 2009; Costantini et al. 2010; Speakman and Garratt 2014; Blount et al. 2016). Empirical tests of the prediction that elevated oxidative damage and higher costs of antioxidant defence directly translate into reduced fitness has produced equivocal results (Speakman and Selman 2011; Selman et al. 2012; Speakman and Garratt 2014; Blount et al. 2016). We argue that the lack of success of many efforts to link mitochondrial function to animal performance may be rooted in our overly simplistic theoretical and experimental approaches; a more comprehensive understanding of key functional traits of mitochondria (related to energy and redox balance, and cellular signaling) is likely necessary to understand the mitochondrial mechanisms underlying variation in the animal performance, life history, and fitness.

Variation in oxygen use (oxidation) and ATP production (phosphorylation), oxidative phosphorylation coupling, integrity and quality of the mitochondria, and the rate of ROS production, among others, contribute to variation in mitochondrial performance, and in turn, animal performance (Murphy 2009; Brand and Nicholls 2011; Salin et al. 2015). A comprehensive understanding of the role of variation in mitochondrial mechanisms in animal performance, life history, and fitness requires an integrative examination of these different aspects of mitochondrial function. Studies integrating measures of oxidative stress, energetic capacity, and mitonuclear interactions have already begun to provide interesting insights into the role that mitochondria play in animal life-histories (Hill 2015; Salin et al. 2015). The aim of the Society for Integrative and Comparative Biology Symposium and this issue of *Integrative and Comparative Biology* is to unify theories, identify improved approaches to quantifying mitochondrial performance, and introduce new and innovative empirical studies of the key links between properties of mitochondria and variation in animal performance and life history.

In this theme issue, we examine how mitochondrial variation may directly enhance or reduce animal performance and investigate the mitochondrial underpinnings of life history. Although mitochondria are traditionally viewed as the powerhouse of the cell, we argue that consideration of various facets of mitochondrial function (including bioenergetics, signaling, redox homeostasis, immune response, and interactions between mitochondrial and nuclear genomes) are needed to better understand the mechanisms that underlie both intra- and interspecific life-history traits. We also discuss the methodological approaches that are needed to measure mitochondrial function accurately and comprehensively. The papers in this issue span a range of animal taxa (from fruit flies to mice and fishes), life-history traits and performance, environmental contexts, and include both laboratory- and field animals. Themes that are addressed include (1) measurements of mitochondrial function, (2) mitochondrial responses to environmental variation, and (3) mitochondrial consequences for the animal performance and life history.

## Measurement of mitochondrial function

As mitochondria are the primary source of ATP and may be a substantial contributor of ROS to the cell,

our ability to accurately describe energy transformation and redox homeostasis in the cell is vital for understanding of the role of these organelles in animal performance. The results of two studies highlighted in this special issue quantify different functional variables and emphasize the importance of using caution when extending *in vitro* measurements to physiological conditions. Salin et al. (2018) contrasts two common methods of quantifying mitochondrial efficiency—ATP/O ratio and the respiratory control ratio (RCR). The results of this empirical study conducted in trout liver mitochondria suggest that these two indicators of mitochondrial respiratory performance can give contradictory messages about mitochondrial efficiency in fed versus fasted animals. Indeed, when quantifying the impact of fasting by the trout on liver Salin et al. (2018) found that the ATP/O ratio increased while RCR declined. Therefore, neither the ATP/O or RCR measures taken alone accurately reflect the performance of mitochondria *in vivo* (RCR because it contains no assessment of ATP production, and ATP/O because it contains no assessment of respiration to offset the proton leak). The authors emphasize the value of modifying the condition *in vitro* to provide a more realistic indication of mitochondrial performance in the cellular environment that mitochondria experienced in living animals.

In another study, Treberg et al. (2018) examine how to compare mitochondrial ROS metabolism across species, with a focus on hydrogen peroxide ($H_2O_2$) which has important roles in both signaling and oxidative damage. To compare across species the capacity of mitochondria to be both a source and a sink for $H_2O_2$ needs to be considered because $H_2O_2$ levels may be set by the interaction between formation and consumption processes within the mitochondrion (Munro and Treberg 2017). Moreover, comparative studies may require addressing the temperature dependency of mitochondrial processes to accommodate ectotherms and endotherms. The result of this comparison highlights the error associated with conducting ROS measurements at a common assay temperature.

Two important themes emerged from the mitochondrial measurements described above and other contributions herein. The first theme is that it is important to consider to what extent variation in the mitochondrial phenotype, often defined in a single tissue, affects individual fitness in an ecologically relevant manner. For example, Chung et al. (2018) demonstrate that mitochondrial properties differ among populations of Atlantic killifish (*Fundulus heteroclitus*) in the liver, but not in brain or heart, clearly indicating that mitochondrial properties are not necessarily equivalent among tissues. Similarly, mitochondrial properties and their relationship to fitness may differ between the sexes, perhaps due to sex- and tissue-specific energy demands, as shown in this issue by Buchanan et al. (2018) in Drosophilid fruit flies.

The second theme is that it is important to be mindful of what can be inferred from *in vitro* assays. For example, the rates of mitochondrial respiration to support ATP synthesis (state 3 respiration) and to offset proton leak (state 4 respiration) are measured when mitochondria are provided with unlimited availability of substrates, oxygen, and ADP (state 3) and are inhibited for ATP production (state 4) (Kadenbach 2003; Brand and Nicholls 2011). While measuring state 3 and state 4 respiration provides quantitative measures of performance, these states may rarely occur within the mitochondrion *in vivo* (Schulte 2015; Salin et al. 2018). One path forward may be to test how sensitive *in vitro* mitochondrial function is to change in physiologically or ecologically relevant abiotic factors, particularly variables such as temperature, ion concentrations, and both substrate and oxygen availability. These variables are expected to vary within an animal's environment and may fluctuate in the cytosol in cells of ectotherms and endotherms, osmoconformers, as well as animals at altitude or depth. Carefully considering the impact of these abiotic factors will provide important information about (i) how robust is the assay to changing conditions and (ii) how natural variation in mitochondrial capacity may be explained by ecologically relevant variation in abiotic factors.

## Mitochondrial adaptation to environmental variation

There is increasing evidence that mitochondria play a critical role in the survival and performance of animals via their capacity to adapt their function to meet the challenges imposed by environmental variation. Scott et al. (2018) examine how evolved and environmentally-induced variation in mitochondrial physiology supports aerobic performance in deer mice (*Peromyscus maniculatus*) native to the cold hypoxic environment at high altitude. Their analyses suggest that evolved increases in oxidative fiber density and mitochondrial abundance in the gastrocnemius muscle are associated with evolved increases in the aerobic capacity, a trait that is critical to exercise and thermogenesis and is known to improve fitness at high altitude. The observed increases in mitochondrial abundance arose

primarily from an enrichment of subsarcolemmal mitochondria, the subpopulation located closest to capillaries, which may be advantageous for mitochondrial $O_2$ supply. These mitochondrial phenotypes were unaffected by hypoxia acclimation, suggesting that adaptation may play a more important role than environmentally-induced plasticity in supporting mitochondrial performance at high altitude for this tissue. However, similar differences were not observed in the muscles of the diaphragm or heart, suggesting that adaptive variation in important mitochondrial phenotypes can be tissue specific.

Sokolova (2018) discusses the responses of mitochondria of intertidal animals to changes in temperature, salinity, pH, intermittent hypoxia, and pollutants. This review shows that the mitochondria of intertidal mollusks are adept at maintaining oxidative phosphorylation capacity in a broad range of temperature, osmolarity, and ion content and are resistant to the hypoxia-reoxygenation injury. This mitochondrial resilience to environmental shifts involves rapid modulation of the electron transport system capacity, upregulation of antioxidant defenses, and high activity of mitochondrial proteases involved in degradation of damaged mitochondrial proteins to match the cellular energy demand and maintain mitochondrial integrity. The work highlights the amazing plasticity in mitochondrial function that has evolved within Animalia and emphasizes the important role of mitochondrial plasticity in animals' tolerance of environmental change.

Bize et al. (2018) investigated the relative contribution of the mitochondrial and nuclear genomes in thermal adaption in two distinct evolutionary lineages of common voles (*Microtus arvalis*). Indeed, a major adaptation to cold of mammals is their ability to produce heat endogenously in the brown adipose tissue (BAT), known as nonshivering thermogenesis (NST) (Cannon and Nedergaard 2004). BAT is unique to mammals and contains a very high density of mitochondria that converts nutrients into heat, largely bypassing ATP production, during respiration. By comparing the two lineages in standardized conditions, Bize et al. showed evolved genetic differences in NST between the lineages. In addition, by swapping mitochondrial genomes between lineages, they also showed that between-lineage variation in NST and BAT size were significantly influenced by the mitochondrial and nuclear genomes, respectively. Their findings highlight that adaptation to thermal environment of mammals may be, at least partly, rooted in mitochondrial–nuclear interactions.

## Mitochondrial consequences for the animal performance and life history

Jimenez (2018) explores differences between birds and mammals in the relationship between oxidative damage, mitochondrial function, and life history within the context of the trade-off between growth rate and longevity. Jimenez found that birds display positive correlations between rate of growth and mitochondrial performance and longer-lived birds are more resistant to oxidative stress than shorter-lived birds. In contrast, mammals display positive correlations between mitochondrial performance and longevity, and long-lived dogs accumulate more DNA damage late in life than short-lived breeds. While data from both taxa imply both mitochondrial function and oxidative stress contribute to difference within species, these findings suggest that precise mechanisms that underlie this trade-off may not be consistent between species.

Austad (2018) provides a historical and comparative perspective on the theories that suggest energy expenditure, oxidative damage, and mitochondrial performance contribute to rates of aging. This review questions the significance of oxidative stress and mitochondria function in aging based on evidence that neither high ROS levels nor high antioxidant levels alter longevity and that induced mitochondrial changes can lengthen, rather than shorten, life span. While the inconsistency between investigators' predictions and results may lead some to suggest that the mitochondrial theory of aging is dead, Austad emphasizes that responses of animals that have been subject to artificial selection under the constant, benign conditions of the laboratory may bear little resemblance to those found under the natural conditions in which the animals evolved. Maintenance under laboratory conditions negate the expression of phenotypes or interactions between phenotypes that are vital for both reproduction and survival in the wild (Barbaric et al. 2007), and co-variation between antagonistic traits may be uncoupled. Thus, Austad emphasizes the importance of field studies in furthering research on mitochondria and aging.

While the interpretation of oxidative stress data presented by Jimenez and Austad may seem contradictory, Hood et al. (2018) emphasize that the cellular and animal response to an increase in relative ROS levels is not consistently negative. Under the theory of mitochondrial hormesis, the cellular response to ROS is hormetic, with modest levels of ROS benefiting mitochondrial respiratory performance and increasing longevity and high levels being damaging. Hood et al. highlight data that suggest

that reproduction may either be enhanced or inhibited by a change in ROS exposure and suggest that consideration of the additive effects of ROS induced by exogenous and endogenous stressors may be necessary to reveal reproductive-longevity trade-offs in some species.

Chung et al. (2018) characterized the relationship between life history and mitochondrial performance with a north–south gradient in Atlantic killifish. They showed that northern subspecies inhabiting colder waters display faster development and growth as well as increased respiratory capacity of liver mitochondria, and differences in mitochondrial membrane lipid composition, relative to their slow growing, less active southern counterparts. These data suggest that variation in mitochondrial properties could underlie variation in the pace of life in Atlantic killifish.

Finally, Buchanan et al. (2018) investigated the consequences of mitochondrial dysfunction due to a genetic mitochondrial–nuclear incompatibility in *Drosophila* for immunity and immunity–fecundity tradeoffs. An energetically-compromised genotype compromised immune function, but only in females. Furthermore, these compromised females also experienced immunity–fecundity tradeoffs that were not evident in wild-type control genotypes that have normal energy metabolism. These data suggest that mitochondrial and mitochondrial–nuclear genetic variance can have sex-specific effects on fitness and can reveal variation for life-history tradeoffs due to cellular resource limitation in a manner analogous to environmental–resource limitation. Condition-dependent effects of mitochondrial variation will be important in determining the efficacy of selection on mitochondrial function and an integrated, mechanistic approach to investigating the complex cellular roles of the mitochondria is expected to make significant advances on this front.

## Conclusions

A key theme that emerged from the symposium papers and discussions is the overwhelming importance of mitochondrial plasticity and adaptation in the energetic capacity and performance of an animal. Depending on the species and conditions, mitochondria can adjust their performance within seconds to days to respond to changes in food availability, temperature, or their redox environment. Likewise, over evolutionary time, mitochondrial performance may become intimately tuned to meet the demands of diverse environmental challenges, such as those that occur in the intertidal zone, at high altitude, or in habitats experiencing thermal extremes. Understanding how this variation contributes to variation in performance and fitness across individuals and species requires that bioenergetics and redox variables are measured in a manner that reflects the conditions that the mitochondria experience *in vivo*. This is particularly relevant in studies where the thermal conditions that the mitochondria are exposed to can vary within the animal or across species. By highlighting the mitochondrial basis of animal life history variation throughout this special issue, we hope to foster collaborations whereby physiologists and geneticists can work with ecologists to fully exploit the potential of cross-disciplinary perspectives and technologies in understanding complex biological questions.

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