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Mitochondrial behaviour, morphology, and animal performance

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ABSTRACT

We have a limited understanding of the proximate mechanisms that are responsible for the development of variation in animal performance and life-history strategies. Provided that components of an organism's successful life history – for example, mate competition, gestation, lactation, etc. – are energetically demanding, increased energy production within mitochondria is likely the foundation from which organisms are able to perform these tasks. Mitochondrial behaviour (positioning within the cell and communication between mitochondria) and morphology affect variation in energy production at the molecular, cellular, and organismal levels. Therefore, adaptations in mitochondrial behaviour and morphology that favour efficient energy production likely influence variation in animal performance. Previous work has linked greater proportions of inter-mitochondrial junctions and density of the inner mitochondrial membrane, among other traits, with increased energetic demand. Future research should focus on how inter-mitochondrial junctions and morphology of the inner mitochondrial membrane, in particular, influence animal performance in accordance with mitochondrial density, fission, and fusion.

Key words: density, inner mitochondrial membrane, inter-mitochondrial junctions, life history, reproductive success

CONTENTS

I. INTRODUCTION

The efficiency with which dietary and endogenous nutrient stores can be converted to adenosine triphosphate (ATP) plays an important role in determining individual and species-specific patterns of whole-animal performance (Drent & Daan, 1980; Gittleman & Thompson, 1988; Kenagy *et al.*, 1990; Scantlebury, Butterwick, & Speakman, 2001; McBride *et al.*, 2015; Salin *et al.*, 2015). Herein, animal performance is defined as an animal's ability to produce enough ATP to support growth, self-maintenance, reproduction, and other energetically demanding activities that promote survival and future reproductive efforts. Investigators have taken a number of approaches to understanding energy expenditure among individuals and species including, but not limited to, measuring whole-animal and basal metabolic rates, relating energy intake to performance, measuring oxidative stress in relation to mitochondrial performance, and most recently, measuring oxygen use and ATP production of mitochondria (e.g. Gittleman & Thompson, 1988; Reinhold, 1999; Biro & Stamps, 2010; Burton *et al.*, 2011; Speakman *et al.*, 2015; Mowry *et al.*, 2017; Hill *et al.*, 2019). For example, Salin *et al.* (2019) recently showed that individual differences in the growth rate of brown trout (*Salmo trutta*)

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are correlated with the efficiency of ATP production by the liver. While recent studies have made great strides in understanding the relationship between energy production and whole-animal performance, there is still considerable, unexplained variation in performance among individuals and species. The capacity to support the production of offspring is, arguably, the most important measure of an animal's performance. The behaviours and physiological processes that support each reproductive event, such as territory acquisition and maintenance, intraspecific competition for mates, gestation, and offspring nourishment, typically require a large increase in nutrient intake or mobilization of endogenous fuel stores to support energy production. Thus, the efficient production of ATP within mitochondria is an important determinant of animal performance.

The mechanisms underlying variation in energy production, and how that variation influences whole-organism performance, are poorly understood. Investigators are beginning to understand better what drives variation in mitochondrial physiology, but the link between cellular and whole-organism performance is an area of inquiry in need of further research. This lack of a clear relationship between energy production and whole-organism performance has led researchers to evaluate mitochondrial respiratory performance and, in particular, how oxidative stress modifies mitochondrial performance. Variation in mitochondrial behaviour and morphology have been largely ignored in studies of functional ecology. An increasing number of studies have shown that the behaviour and morphology of mitochondria are highly dynamic, influencing energy production and the capacity of mitochondria to respond to both endogenous and exogenous stressors (Youle & Van Der Bliek, 2012; Rafelski, 2013). By studying these aspects of mitochondria, we may gain insight into how organization and performance at the cellular level influence whole-organism performance.

Here, we propose that the development of energetically demanding behaviours and life-history strategies are enhanced by changes in the behaviour (positioning and communication) and morphology of mitochondria within tissues that directly influence animal performance. These changes include structural modifications such as the small-scale coordination of cristae within individual mitochondria (Zick, Rabl, & Reichert, 2009) that can alter ATP production and influence the large-scale function of tissues within and between organ systems (Fig. 1; see Strohm & Daniels, 2003). This idea builds on our understanding of protein functions that control mitochondrial behaviour and morphology (e.g. Schrepfer & Scorrano, 2016) by aiming to understand how small-scale changes in organelle structure can influence large-scale changes in tissue and organ function. Although studies of mitochondrial behaviour and morphology are becoming more common, most studies examine how these two facets of mitochondria change in response to extreme conditions (e.g. disease, parasitism, starvation; Mannella, 2006*a*). By investigating mitochondrial behaviour and morphology, we can understand the proximate mechanisms that are causally responsible for variation in animal performance, as opposed simply to characterizing further the variation itself.

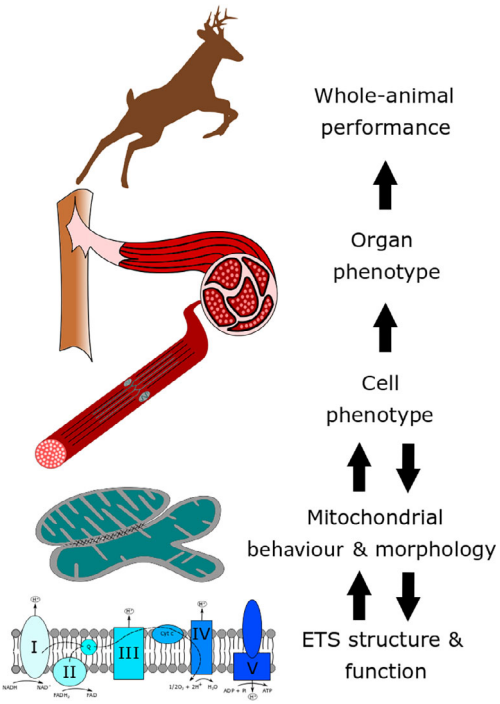

Fig. 1. Illustration of how variation in morphology and organization within and between mitochondria translates to variation in whole-animal performance. From the bottom of the figure, the structure and function of the electron transport system (ETS) influences the behaviour and morphology of mitochondria, which influence cell phenotype. In turn, cell phenotype influences organ phenotype, leading to variation in whole-animal performance. Cell phenotype may also influence mitochondrial behaviour and morphology, leading to changes in structure and function of the ETS. Cyt c, cytochrome c; FAD, oxidized flavin adenine dinucleotide; $FADH_2$, reduced flavin adenine dinucleotide; NAD^+, oxidized nicotinamide adenine dinucleotide; NADH, reduced nicotinamide adenine dinucleotide; Q, ubiquinone; I, NADH dehydrogenase; II, succinate dehydrogenase; III, cytochrome c reductase; IV, cytochrome c oxidase; V, ATP synthase.

This review outlines how mitochondrial behaviour and morphology are inherently linked to animal performance by first discussing how mitochondrial behaviour and morphology directly influence mitochondrial performance. In addition, we outline how mitochondrial morphology and performance are both influenced by, and directly alter, oxidative stress. We briefly summarize how measures of mitochondrial behaviour and morphology are predicted to offer insight into our understanding of individual and species-specific variation in reproductive performance and reproductive strategies, respectively. Lastly, we provide an overview of how future research may better clarify the link between mitochondrial morphology and variation in animal performance, both among individuals within populations

and among closely related taxa that have developed variants of certain life-history strategies.

II. MITOCHONDRIAL BEHAVIOUR, MORPHOLOGY, AND PERFORMANCE

To understand how mitochondria are linked to organism performance, we must first understand how mitochondrial behaviour and morphology influence mitochondrial performance. Mitochondria are highly dynamic organelles that continuously change their function, position, and structure to meet the energetic demands of any given cell (Zick *et al.*, 2009; Rafelski, 2013). To do so, individual mitochondria not only undergo fission and fusion, but readily change their size and relative proportions of inner membrane, intermembrane space, matrix, and outer membrane, density (Mannella, 2006*b*), and structural connections with one another (Fig. 2). These changes form the foundation from which mitochondria can respond to changes in energetic demand (Paumard *et al.*, 2002).

Variation in organism performance has been attributed to variation in mitochondrial physiology (e.g. Salin *et al.*, 2012, 2015; Zhang & Hood, 2016; Mowry *et al.*, 2017; Hill *et al.*, 2019). Genetic and environmental factors can have direct impacts on animal performance such as lifespan and reproductive output (Navarro *et al.*, 2005; Liau *et al.*, 2007), but they also affect mitochondrial morphology (Sogo & Yaffe, 1994; Visser *et al.*, 1995; Zick *et al.*, 2009; Putti *et al.*, 2016). In particular, energy production can increase significantly from changes in the morphology of the inner mitochondrial membrane (IMM; Mannella, Lederer, & Jafri, 2013; Nielsen *et al.*, 2017; Afzal *et al.*, 2019). Previous work using cryo-electron tomography in rat liver and cattle heart has shown that cristae structure modulates bioenergetic capacity through the positioning of ATP synthase dimers and the folding of cristae (Strauss *et al.*, 2008; Cogliati, Enriquez, & Scorrano, 2016). Additionally, inter-mitochondrial junctions (IMJs) are present in greater proportions in more active types of tissue (e.g. heart and diaphragm; Picard *et al.*, 2015) and also increase in density following a rise in metabolic demand from events such as running (Picard *et al.*, 2013*a*). IMJs are electron-dense regions connecting two or more adjacent mitochondria (Fig. 3; Duvert, Mazat, & Barets, 1985), where the cristae of adjacent mitochondria align in a parallel fashion. This form of 'kissing communication' between mitochondria has been linked to cardiac function in rats (Cao & Zheng, 2019) and exercise in mice (Picard *et al.*, 2013*a*; see also Daghistani, Rajab, & Kitmitto, 2018). Thus, the density of IMM and proportion of IMJs may be crucial morphological components of mitochondrial performance.

The relative area covered by the IMM has a direct impact on ATP production. Protein complexes I, III, and IV of the electron transport system (ETS) are embedded within the inner membrane and are responsible for pumping protons

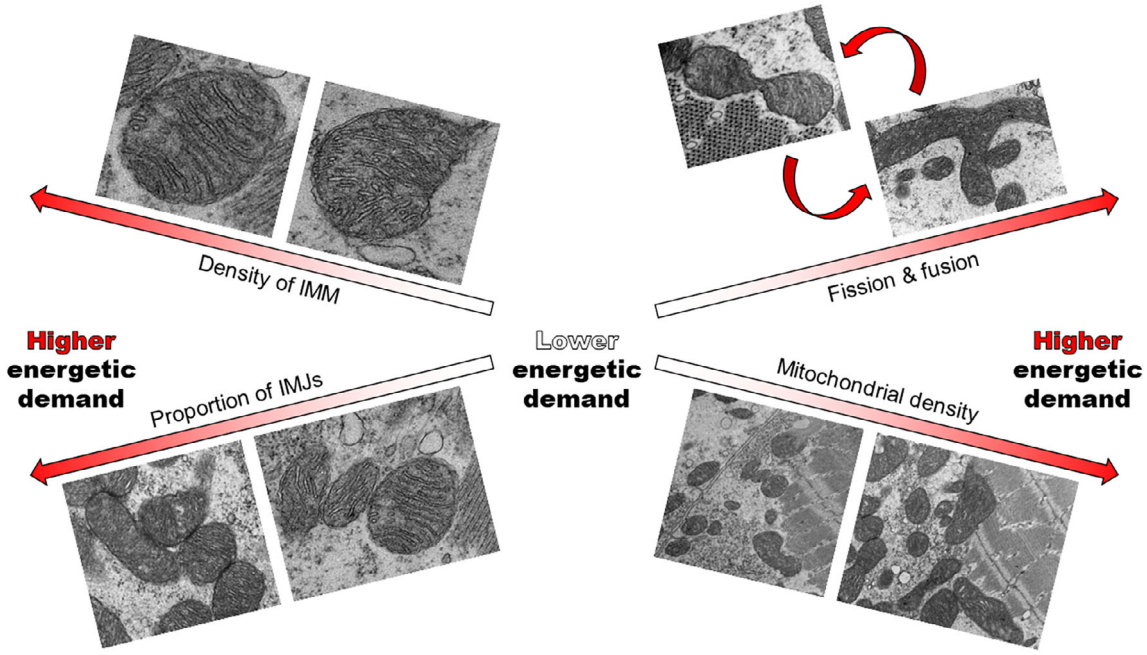

Fig. 2. Proposed changes in mitochondrial behaviour and morphology under increased energetic demand, including: density of inner mitochondrial membrane (IMM), proportion of inter-mitochondrial junctions (IMJs), mitochondrial density, and mitochondrial fission and fusion. The first three traits are predicted to increase (to an extent) under increased energetic demand, whereas the rates of fission and fusion will depend on the need to discard damaged regions of mitochondria and rescue organelle dysfunction. The proportions of these traits relative to one another influences the function of each individual mitochondrion and cellular function as a whole. All micrographs are of myocytes of the copepod *Tigriopus californicus*.

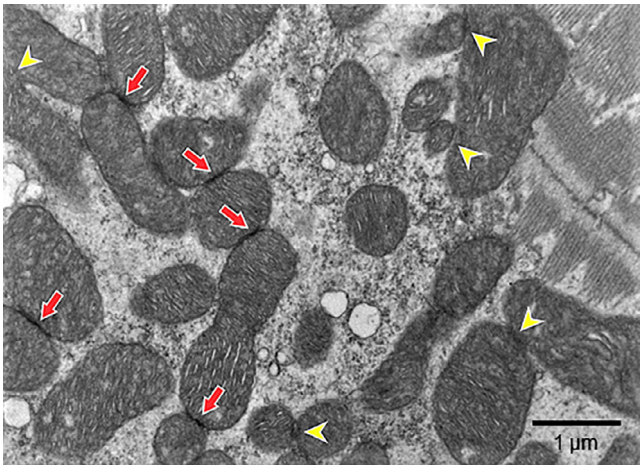

Fig. 3. Transmission electron micrograph of a myocyte from the copepod *Tigriopus californicus* containing electron-dense (darker regions) inter-mitochondrial junctions shown by red arrows. Contact sites showing no increase in electron density (lighter regions) between mitochondria are shown by yellow arrowheads.

across the IMM into the inter-membrane space, as Complex II delivers electrons to the quinone pool where they also enter the ETS through Complex I (Fig. 1). This proton gradient ultimately leads to the production of ATP as protons flow down an electrochemical gradient and through Complex V, as Complex IV reduces oxygen to water (Hatefi, 1985). The presence of complexes I–V, and their proportion relative to the amount of inter-membrane space, mitochondrial matrix, and mitochondrial size, directly influences the amount of ATP any given mitochondrion can produce (Figs 1 and 2; Afzal *et al.*, 2019). A greater amount of IMM can be populated with more ETS complexes, but this change may come with costs of increased oxidative stress (see Section III). For example, Strohm & Daniels (2003) correlated an increase in density of IMM within the flight muscle mitochondria of beewolf wasps (*Philanthus triangulum*) with the wasps' ability to provision honeybees to their offspring. In this example, wasps with a greater energetic capacity of their flight muscles were able to collect and carry more bees back to their broods within a given amount of time. Such work has demonstrated that a greater density of the IMM may be linked to greater reproductive success. However, area of the IMM is not the only morphological feature that impacts functional capacity.

Not only do protein complexes embedded in the IMM contribute to its morphology (Paumard *et al.*, 2002), but fission and fusion of the IMM directly influence the formation of cristae (Mannella, 2006*b*) and efficiency of the ETS [see Zick *et al.*, 2009 for a review of how protein function is related to cristae morphology; Chen, Liu, & Dorn, 2011; Cogliati *et al.*, 2016]. Such changes resulting from fission and fusion processes can regulate different mitochondrial conformations (condensed, orthodox, etc.) that result from changes in energetic demand and/or nutrient availability (Hackenbrock, 1966). As is the case in bacteria (Lane, 2006), the size of mitochondria is directly linked to efficiency of the ETS within any given cell, limiting the amount of IMM that can exist within a single mitochondrion. However, density of IMM cannot increase indefinitely with mitochondrial size, as respiratory efficiency may decrease when mitochondrial volume and density of IMM greatly exceed the surface area of the mitochondrion (Navratil, Terman, & Arriaga, 2008); this may be one of many reasons why there are thousands rather than a few mitochondria within a given cell. Additionally, mitochondrial function can be upregulated by increasing mitochondrial density irrespective of the density of IMM. Therefore, mitochondrial function can be altered beyond changes in morphology through changes in mitochondrial behaviour.

Herein, mitochondrial behaviour refers to the movement and position of mitochondria within cells, including their position relative to other mitochondria that may possibly mediate communication between mitochondrial tubules. These mitochondrial movements stem, in part, from changes in mitochondrial morphology. One of the most recent strides in understanding mitochondrial morphology, and therefore behaviour, is the study of IMJs (Bakeeva, Chentsov, & Skulachev, 1983; Picard *et al.*, 2015). Two aspects of these structures infer why they likely influence mitochondrial function: (*i*) the alignment of cristae at a right angle to the IMJ and (*ii*) the increased proportion of IMJs in tissues with greater energetic demands (Picard *et al.*, 2015).

The alignment of cristae at IMJs has been suggested to regulate the communication of information between mitochondria, including gene expression (Ng & Bassler, 2009) and/or the transfer of electrochemical gradients (Ichas, Jouaville, & Mazat, 1997; Pacher & Hajnoczky, 2001; Santo-Domingo *et al.*, 2013); this would ultimately mediate differential function of mitochondrial populations, however, this relationship must be confirmed through empirical research. For example, in myocytes of *Mus musculus*, populations of inter-myofibrillar and subsarcolemmal mitochondria differ significantly in their morphology (Picard, White, & Turnbull, 2012) and, therefore, likely their function. Similar examples have been found in bar-headed geese (*Anser indicus*), where subsarcolemmal mitochondria are redistributed near the cell membrane to facilitate greater diffusion of oxygen in flight muscles at high altitudes (Storz, Scott, & Cheviron, 2010). A greater proportion of IMJs was also found in both inter-myofibrillar and subsarcolemmal mitochondria immediately following a single bout of exercise in mice, indicative of increased metabolic function (Picard *et al.*, 2013*a*). If IMJs are tightly coupled to mitochondrial function, then the presence of these structures may influence adaptations of life-history strategies that rely heavily on increased mitochondrial performance. For example, in outbred laboratory mice, food intake gradually increases to match energy demands until peak lactation when nutrient intake is five times greater than that of non-reproductive animals (Speakman & Król, 2005). Just as exercise increases the density of IMJs in skeletal muscle, the same may be true for mitochondria in the liver which provide energy needed for the mammary glands and milk synthesis.

Aside from changes in mitochondrial ultrastructure, metabolic function can also be influenced by non-morphological changes, for example, through increases in the amount of free intra-mitochondrial Ca^{2+} (McCormack, Halestrap, & Denton, 1990) or permeability of the IMM (Brand *et al.*, 1991). However, changes in metabolic function without changes in mitochondrial structure can only occur within certain limits. For instance, to increase the rate of conversion of ADP to ATP, a mitochondrion may increase the amount of substrate available within the mitochondrial matrix through several intra- and extracellular pathways such as those involving the supply of fatty acids (Brown, 1992). Such events may then lead to a greater proton gradient within the inter-membrane space as more electrons are passed across the IMM. However, without any significant change in mitochondrial size or the number of complexes embedded in a more densely packed IMM, there is likely a hard limit on the quantity of protons that can be pumped at a given rate into an inter-membrane space of a given size without a change in morphology (Willis *et al.*, 2016).

Significant increases in density of the IMM within mitochondria (Mannella, 2006*b*; Nielsen *et al.*, 2017) and the proportion of IMJs within a cell (Picard *et al.*, 2015) could influence tissue function and, therefore, whole-organism performance (e.g. Strohm & Daniels, 2003). However, the proximate function of IMJs warrants further research, and it remains to be established whether these relationships are causal or correlative. If changes in these two traits favour increased ATP production, then organisms that develop favourable changes in these traits may be able to develop more energetically demanding and successful means of reproduction (e.g. greater mate guarding durations, increased clutch size, greater provisioning of resources to young). Provided that certain aspects of mitochondrial behaviour and morphology vary among individuals and are heritable, such changes may be inherited by offspring of reproductively successful individuals and account for individual, if not species-specific, variation in animal performance. Not only is mitochondrial ultrastructure, along with fission and fusion dynamics, heritable in yeast (Sogo & Yaffe, 1994), but differences in the distribution of subsarcolemmal mitochondria have evolved in bar-headed geese in comparison to other species, irrespective of phylogenetic relatedness (Scott *et al.*, 2009).

Changes in mitochondrial morphology between individuals within populations is predicted to be exacerbated across populations of organisms and closely related taxa as selective pressures change over evolutionary time. Future research should aim to understand how the behaviour and morphology of mitochondria change in response to adverse and detrimental conditions that affect whole-animal performance, such as aging and the collapse of biological systems (Gottschling & Nyström, 2017). As we have outlined above, the function of mitochondria is often linked to mitochondrial behaviour and morphology. However, such molecular studies should be interpreted with care, and the limitations of using experimental as opposed to natural systems should be made explicit and discussed at length (Picard *et al.*, 2013*b*). Additionally, mitochondrial behaviour and morphology likely play formative roles in the regulation of, and damage due to, oxidative stress, which ultimately influences mitochondrial function.

III. OXIDATIVE STRESS AND MITOCHONDRIAL MORPHOLOGY

Mitochondrial behaviour and morphology directly impact mitochondrial performance, however, the production of ATP is only a single variable among a suite of traits that impact both cellular and organismal performance (Eisner, Picard, & Hajnóczky, 2018). Therefore, we must take into account other traits that change in relation to mitochondrial function. One such trait that has a major impact on ETS function is the production of reactive oxygen species (ROS). ROS are produced by a number of endogenous (e.g. oxidative phosphorylation) and exogenous (e.g. radiation) factors and inevitably impact the stability and performance of mitochondria (Zhang *et al.*, 2017) and, therefore, whole-animal performance (Zhang *et al.*, 2018; Heine *et al.*, 2019).

ROS are highly reactive molecules that contain oxygen (e.g. hydrogen peroxide, hydroxyl radicals, superoxide) and are formed, in part, as byproducts of the ETS. Due to the reactive nature of ROS, these molecules can readily damage DNA, lipids, and proteins within the cell (Finkel & Holbrook, 2000) and have the potential to decrease mitochondrial function and/or act as signalling molecules (Zhang *et al.*, 2017; Hood *et al.*, 2018, 2019). To mediate ROS-induced damage and improve performance, mitochondria can alter their behaviour and morphology to reduce and/or repair oxidative damage. This can be accomplished through fission and fusion dynamics that either eliminate damaged regions of mitochondria or rescue organelle dysfunction, respectively (Westermann, 2010). These dynamics likely result from significant changes in membrane morphology (Cogliati *et al.*, 2016; Cao & Zheng, 2019) and may stem from (or produce) IMJs, although IMJs are present following the knockout of proteins responsible for inter-mitochondrial tethering (mitofusins 1 and 2). Further evidence suggests that IMJs are closely related to increased mitochondrial function (Picard *et al.*, 2015). Additionally, the density of IMM may directly influence the regulation of ROS.

Oxidative damage is known to induce mitochondrial fragmentation *via* lipid peroxidation (Fan, Hussien, & Brooks, 2010) and, therefore, significantly remodel mitochondrial structure. This can occur either directly *via* oxidative damage to IMM or indirectly through mitochondrial fission and repair mechanisms, changing the density of IMM within a mitochondrion of a given size. In both cases, the amount of ATP produced is likely to change under elevated ROS production. Although ATP production can be upregulated from a more densely packed IMM (Nielsen *et al.*, 2017), we should consider

whether or not this benefit is balanced against the cost of increased ROS production and oxidative damage (see Strohm & Daniels, 2003). Aside from antioxidants that are capable of quenching ROS (Ristow, 2014), ROS can be regulated through changes in morphology as mentioned above. Since IMJs and density of IMM have been linked to increased energetic demand (Mannella, 2006*a*; Picard *et al.*, 2013*a*; Afzal *et al.*, 2019), it is plausible that these traits regulate mitochondrial function concurrently in response to oxidative stress.

IV. ANIMAL PERFORMANCE AND REPRODUCTIVE SUCCESS

The ability to maximize ATP production to support reproductive performance could begin with changes in mitochondrial behaviour and morphology that improve bioenergetic efficiency. Within a given population, we predict that individuals that are most efficient at converting available nutrients into ATP will typically have higher reproductive success than those that do so less efficiently. Greater efficiency of ATP production will be achieved, in part, by changes in mitochondrial behaviour and morphology.

Reproductive success can be defined as the ability of an organism to produce viable offspring (Clutton-Brock, 1988); this can be quantified as the number of offspring produced either per reproductive bout or over an organism's lifetime and varies greatly among eukaryotic organisms. Different species and taxonomic groups vary in the strategy used to maximize reproductive performance (e.g. gestation, iteroparity, lactation, mate guarding), and individuals vary in their capacity to allocate resources to, and modify, each of these variables. For instance, variation in reproductive success is often linked to body size (Clutton-Brock, 1985; Bosch & Vicens, 2006; Milenkaya *et al.*, 2015), however, body size alone explains a small portion of variation in reproductive success. To carry out the aforementioned strategies, organisms must have access to sufficient food or stored nutrients to elevate ATP production well above maintenance. When access to ATP is sufficient, an organism should be able to fuel any changes in morphology and organ structure that support gamete production, mating, and offspring nourishment. Further, any individual that is able to allocate relatively more resources to reproduction is likely to achieve enhanced reproductive success *via* the production of more and/or higher quality offspring. This energy is produced almost entirely by mitochondria and regulated, in part, by mitochondrial behaviour and morphology. For energy to be allocated efficiently to reproduction, mitochondria must up- or downregulate energy production, as required, across different types of tissue and organs. Although increased energy intake can be important in accomplishing this, how nutrients are utilized within the mitochondrion is influenced by mitochondrial structure. Therefore, energy allocation to reproductive strategies, through changes in mitochondrial behaviour and morphology, largely influences variation in reproductive success.

Numerous reproductive strategies exist among eukaryotic organisms. Although vast differences exist between taxa, individuals of the same species in the same environment may differ in the number and quality of the young they produce. Both genetic and environmental factors influence strategies of reproduction. As a consequence, reproductive strategies have evolved over large time scales to maximize reproductive success under typical conditions, but short-term plasticity allows animals to modify their effort to match current conditions and their physiological state (Bernardes, 1996; Gross, 1996). Therefore, intra- or interspecific differences in energy allocation to reproduction likely stem from differences in physiology. Mate guarding is a prime example of a reproductive strategy that can be highly energetically demanding and varies greatly among extant taxa (Grafen & Ridley, 1983; Boxshall, 1990) but also varies at an individual level (Tsuboko-Ishii & Burton, 2017), leading to differential reproductive success. For such energetically demanding behaviours to be sustained, large amounts of energy would need to be produced over short periods of time. In addition to reproductive success, changes in mitochondrial behaviour and morphology are also likely to occur following high energetic demands of other performance correlates, such as rapid development, response to an immune challenge, and migration.

V. CONCLUSIONS

(1) The behaviour and morphology of mitochondria play a vital role in efficient ATP production. Although research to date has successfully characterized variation in animal performance and energy expenditure, we do not fully understand the physiology behind how that variation in energy production develops. We propose that individual differences in the behaviour and morphology of mitochondria contribute to variation in energetic capacity among individuals.

(2) Further, we propose that the development of energetically demanding behaviours and life-history strategies are enhanced by the behaviour and morphology of mitochondria that increase ATP production in relevant organs. In particular, we argue that an increase in the proportion of IMJs and density of the IMM facilitate an upregulation of ATP production.

(3) The hypothesis presented here provides a mechanism for how energy production can vary among individuals within populations and between closely related taxa, partly leading to some of the variation we see in animal performance. Yet, there are currently few data that support these ideas in an ecological context. We believe that evaluating the relationships between mitochondrial behaviour, morphology, and animal performance will be a fruitful avenue of research. We encourage others to consider the importance of variation in mitochondrial behaviour and morphology in

both intra- and interspecific variation in animal performance and reproductive success.

VI. ACKNOWLEDGEMENTS

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VII. AUTHOR CONTRIBUTIONS

The study was conceived by K. B. H. Both authors contributed to developing and writing the manuscript and are accountable for all views published herein.

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