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# Evaluating endoplasmic reticulum stress and unfolded protein response through the lens of ecology and evolution

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## ABSTRACT

Considerable progress has been made in understanding the physiological basis for variation in the life-history patterns of animals, particularly with regard to the roles of oxidative stress and hormonal regulation. However, an underappreciated and understudied area that could play a role in mediating inter- and intraspecific variation of life history is endoplasmic reticulum (ER) stress, and the resulting unfolded protein response ($UPR^{ER}$). ER stress response and the $UPR^{ER}$ maintain proteostasis in cells by reducing the intracellular load of secretory proteins and enhancing protein folding capacity or initiating apoptosis in cells that cannot recover. Proper modulation of the ER stress response and execution of the $UPR^{ER}$ allow animals to respond to intracellular and extracellular stressors and adapt to constantly changing environments. ER stress responses are heritable and there is considerable individual variation in $UPR^{ER}$ phenotype in animals, suggesting that ER stress and $UPR^{ER}$ phenotype can be subjected to natural selection. The variation in $UPR^{ER}$ phenotype presumably reflects the way animals respond to ER stress and environmental challenges. Most of what we know about ER stress and the $UPR^{ER}$ in animals has either come from biomedical studies using cell culture or from experiments involving conventional laboratory or agriculturally important models that exhibit limited genetic diversity. Furthermore, these studies involve the assessment of experimentally induced qualitative changes in gene expression as opposed to the quantitative variations that occur in naturally existing populations. Almost all of these studies were conducted in controlled settings that are often quite different from the conditions animals experience in nature. Herein, we review studies that investigated ER stress and the $UPR^{ER}$ in relation to key life-history traits including growth and development, reproduction, bioenergetics and physical performance, and ageing and senescence. We then ask if these studies can inform us about the role of ER stress and the $UPR^{ER}$ in mediating the aforementioned life-history traits in free-living animals. We propose that there is a need to conduct experiments pertaining to ER stress and the $UPR^{ER}$ in ecologically relevant settings, to characterize variation in ER stress and the $UPR^{ER}$ in free-living animals, and to relate the observed variation to key life-history traits. We urge others to integrate multiple physiological systems and investigate how interactions between ER stress and oxidative stress shape life-history trade-offs in free-living animals.

*Key words*: endoplasmic reticulum stress, unfolded protein response, life history, reproduction, performance, development, ageing, oxidative stress, protein folding

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## I. INTRODUCTION

Ecologists and evolutionary biologists have long been intrigued by inter- and intraspecific variation in life-history strategies and the trade-offs that arise from the interactions among life-history traits (Stearns, 1992; Zera & Harshman, 2001). Considerable effort has been spent attempting to elucidate the physiological mechanisms that underlie individual variation in life-history traits such as physical performance (Irschick & Higham, 2016; Killen, Calsbeek, & Williams, 2017; Scott, Guo, & Dawson, 2018), longevity (Miller *et al.*, 2011; Munro & Pamenter, 2019), reproduction (Harshman & Zera, 2007; Williams, 2012*a*; Zhang & Hood, 2016), and growth and development (Mueller *et al.*, 2015). Recently, researchers have focused on bioenergetics and oxidative stress (Monaghan, Metcalfe, & Torres, 2009; Zhang & Hood, 2016; Munro & Pamenter, 2019), as well as hormonal regulation (e.g. sex steroids, glucocorticoids) (Crespi *et al.*, 2013; Vera, Zenuto, & Antenucci, 2017; Eyck *et al.*, 2019), as potential physiological mechanisms mediating life-history trade-offs. Although significant progress has been made, our ability to explain the mechanisms responsible for life-history trade-offs is still limited, in part due to research and analysis methodology (Williams, 2008; Wilson & Nussey, 2010; Careau & Wilson, 2017), but also due to our inadvertent neglect of important aspects of animal physiology.

The survival and performance of individuals is determined by their ability to adapt to ever-changing endogenous and exogenous conditions (Nevo, 2011; Lane, 2016). Intracellular proteins carry out a multitude of biological functions that allow cells to respond to these challenges. Proteins catalyse cellular reactions, provide structure, transport, and allow cells to respond to stressors (Nelson & Cox, 2008). In order to carry out their functions, proteins must be folded in their native conformation. The endoplasmic reticulum (ER), or sarcoplasmic reticulum in skeletal muscle, plays a central role in synthesis, folding, modification, and transport of proteins (Tu & Weissman, 2004; Wu & Kaufman, 2006; Nelson & Cox, 2008; Cao & Kaufman, 2012; Sherwood, 2016). Specifically, secreted proteins in the ER may undergo a series of post-translational modifications before folding (Feldman, Chauhan, & Koong, 2005). The process of ER protein folding or post-translational modification is achieved with the help of molecular chaperones and molecular oxygen, which initiates oxidative folding as the major electron acceptor in the electron relay system (Tu & Weissman, 2004; Feldman *et al.*, 2005).

Proper processing of proteins requires tight regulation of ER homeostasis. In an unstressed cell, the vast majority of proteins are folded in their native conformation and are functionally active. However, the difference in free energy between the folded and unfolded states of proteins under normal physiological conditions is small and thus the native conformation of proteins is only marginally stable. Many proteins readily unfold, or do not fold properly, when exposed to small changes in the cellular environment such as increased heat, change in pH, altered redox status, viral/bacterial infection, and rapid increase in rate of protein synthesis (Gething & Sambrook, 1992; Hartl, Martin, & Neupert, 1992; Nelson & Cox, 2008). For example, heat stress causes misfolding and other structural changes to proteins that negatively affect enzyme functions (Tomanek, 2014; Lee *et al.*, 2019); some bacterial and viral infections disrupt homeostasis such that the rate of protein synthesis outpaces the capacity of cells to fold proteins (Celli & Tsolis, 2015; Liu *et al.*, 2020). In specialized secretory cells, the task of maintaining protein homeostasis is especially challenging because of their high demand for protein synthesis and processing (Nelson & Cox, 2008). High levels of misfolded and/or unfolded proteins can impair functionality of enzymes and transport proteins by preventing substrate binding, as well as causing protein aggregations that disrupt other cellular components (Nelson & Cox, 2008). This prevents cells from functioning properly and can result in either cellular necrosis and reduced organ capacity or the malignant transformation of cells which causes them to become cancerous (Ni & Lee, 2007; Sigurdsson & Miharada, 2018).

ER stress occurs when cells are overloaded with unfolded or misfolded proteins and when protein production rates exceed the cells' protein folding capacities (Wu & Kaufman, 2006; Cao & Kaufman, 2012; Bravo *et al.*, 2013; Hong *et al.*, 2017). In response to ER stress, organisms evolved a suite of machineries, including the unfolded protein response ($UPR^{ER}$) that maintains proper folding and processing of intracellular proteins (Tu & Weissman, 2004; Bravo *et al.*, 2013; Díaz-Hung, Martínez, & Hetz, 2020). Herein, we propose that the $UPR^{ER}$ could play a role in mediating inter- and intraspecific variation of life-history strategies (Fig. 1). Throughout this review, we will refer to stressors as any environmental or physiological challenges that disrupt cellular homeostasis, and stress as the physiological responses to these challenges (see Table 1 for a glossary of

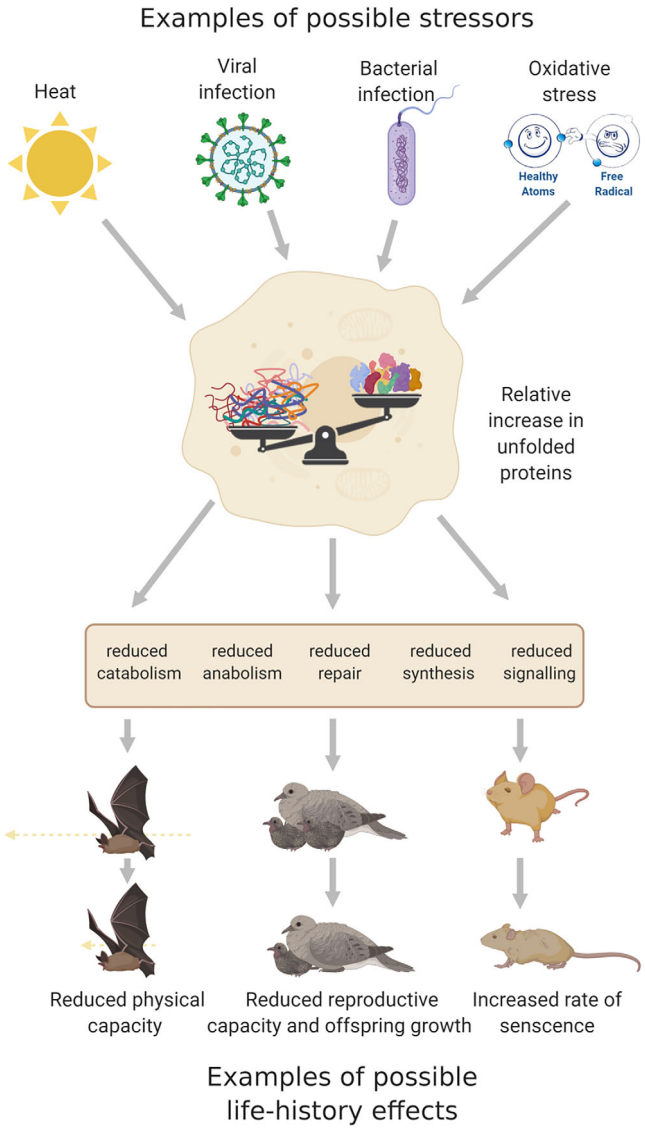


**Fig 1.** The balance between folded and unfolded proteins can shift when exogenous or endogenous stressors disturb homeostasis within cells. Labile proteins can unfold and many proteins can misfold or remain unfolded when folding mechanisms cannot keep pace with increased protein syntheses. This increase in intracellular unfolded proteins is referred to as endoplasmic reticulum (ER) stress. ER stress has the capacity to impact animal performance negatively*via*changes in capacity for growth, reproduction, activity, and self maintanence.

terms). We acknowledge that these definitions are very general, especially in the context of ER stress where protein homeostasis can be easily perturbed. However, we will follow these broad definitions throughout to ensure that our use of terminologies is consistent with how ER stress is defined in the biomedical literature.

The molecular pathway of ER stress and the resulting UPR$^{ER}$ has been extensively reviewed by other authors (Wu *et al.*, 2011; Cao & Kaufman, 2012; Bravo *et al.*, 2013; Bohnert, McMillan, & Kumar, 2018; Fiorenza *et al.*, 2018; Sigurdsson & Miharada, 2018). We provide a brief description of the UPR$^{ER}$ herein and refer our readers to those reviews for more extensive descriptions of the UPR$^{ER}$ pathways. When protein load and/or misfolded proteins surpass a critical threshold, the UPR$^{ER}$ is activated to alleviate ER stress. The UPR$^{ER}$ is governed by three ER transmembrane sensors, namely protein kinase R-like endoplasmic reticulum kinase (PERK), inositol-requiring protein 1α (IRE1α), and activating transcription factor 6 (ATF6) (Wu & Kaufman, 2006; Cao & Kaufman, 2012). IRE1α and ATF6 are associated mostly with the adaptive phase of the UPR$^{ER}$ while PERK is primarily associated with the apoptotic phase. During resting/unstressed conditions, the ER chaperone protein binding immunoglobulin protein (BiP; also called GRP78) binds to the transmembrane sensors to inhibit their oligomerization and phosphorylation (Fig. 2A) (Wu & Kaufman, 2006; Cao & Kaufman, 2012; Afroze & Kumar, 2019). According to a widely accepted model, during mild and/or transient ER stress due to accumulation of misfolded or unfolded proteins, BiP dissociates from IRE1α and ATF6, but not PERK. IRE1α is dimerized and phosphorylated to induce splicing of X-box binding protein-1 (XBP-1). At the same time, BiP dissociation causes translocation and cleavage of ATF6 (Fig. 2B). Both processes reduce the secretory protein load, enhance ER protein folding, and increase clearance capacity through degradation pathways such as the ER-associated degradation pathway (ERAD) (Fig. 2C) (Wu & Kaufman, 2006; Wu *et al.*, 2011; Cao & Kaufman, 2012; Sigurdsson & Miharada, 2018). During prolonged and severe ER stress, BiP also dissociates from PERK, induces phosphorylation of a downstream protein, eukaryotic translation initiation factor 2α (eIF2α), which in turn causes induction of the transcription factor C/EBP homologous protein (CHOP) that initiates the apoptotic pathway (Fig. 2D) (Wu & Kaufman, 2006; Wu *et al.*, 2011; Cao & Kaufman, 2012; Sigurdsson & Miharada, 2018). At the same time, activation of PERK results in inhibition of protein translation, relieving the load on the ER of newly synthesized proteins (Wu & Kaufman, 2006; Cao & Kaufman, 2012; Afroze & Kumar, 2019).

This response has similarities with the better-known stress response involving the hypothalamic–pituitary–adrenal (HPA) axis, where transient increases in glucocorticoid levels due to acute stress are generally adaptive and promote survival, while prolonged elevated levels of glucocorticoids due to chronic stress are generally maladaptive and can lead to immunosuppression, disease, or even death (Levine, 1993; Sapolsky, 2004; Crespi *et al.*, 2013). Other physiological systems that maintain cellular proteostasis and that are arguably more commonly evaluated in an ecological context include the heat-shock response (HSR) that manages cytosolic denatured proteins *via* the action of heat-shock factors such as HSF1 and HSF2, and the mitochondrial unfolded protein response (UPR$^{mt}$) that facilitates protein folding and maintains proteostasis within the mitochondria through the

Table 1. Glossary of terms

| Term | Definition |
|---|---|
| Apoptosis | A form of programmed cell death. |
| Clearance capacity | The capacity to remove misfolded and/or unfolded proteins from cells. |
| Endoplasmic-reticulum-associated protein degradation (ERAD) | A cellular process responsible for degradation of misfolded/unfolded proteins. |
| Endoplasmic reticulum unfolded protein response ($UPR^{ER}$) | A conserved cellular response that increases the ER protein folding capacity, downregulates translation of protein, and enhances clearance of misfolded/unfolded proteins. |
| Erythropoiesis | The process of red blood cell synthesis. |
| Heat shock response (HSR) | A cellular stress response that is activated upon cellular stress and induces transcription of molecular chaperones to manage misfolded/unfolded proteins in the cytosol. |
| Hypothalamic–pituitary–adrenal (HPA) axis | An endocrine system that regulates a suite of metabolic processes and production of glucocorticoids. |
| Mitochondria-associated membrane (MAM) | Close contact sites between the ER and mitochondria that allow communication and exchange of molecules between the two organelles. |
| Mitochondrial unfolded protein response ($UPR^{mt}$) | A conserved cellular response that maintains proteostasis of mitochondria by activating mitochondrial chaperones upon sensing accumulation of misfolded/unfolded proteins within mitochondrial compartments. |
| Molecular chaperone | Proteins that assist in folding and assembly of other cellular proteins. |
| Myogenesis | The process of muscular tissue formation. |
| Proteostasis | Maintenance of protein homeostasis. |
| Stress | Physiological responses to environmental challenges. |
| Stressors | Environmental or physiological challenges that disrupt cellular homeostasis. |
| Thapsigargin | A common ER stress inducer that inhibits sarco/endoplasmic reticulum calcium ATPase (SERCA) in cells. |
| Tunicamycin | A common ER stress inducer that inhibits N-linked glycosylation in cells. |

actions of mitochondrial heat-shock proteins, including mtHSP70 and mtHSP60 (Gidalevitz, Prahlad, & Morimoto, 2011; Hill *et al.*, 2013; Jovaisaite, Mouchiroud, & Auwerx, 2014; Wada, 2019). The $UPR^{ER}$, $UPR^{mt}$ and HSR work together to allow organisms to adapt to constantly changing environments by conferring on them the ability to respond to a multitude of intracellular and extracellular stressors.

It has been shown that ER stress responses are heritable (Dombroski *et al.*, 2010) and that there is considerable individual variation in $UPR^{ER}$ phenotype in humans and non-human animals, both in terms of baseline levels of $UPR^{ER}$-associated genes such as *BiP*, *GRP94*, *calnexin*, and *CHOP*, as well as stress-induced levels of the same genes (Dombroski *et al.*, 2010; Havighorst *et al.*, 2019; Zhang *et al.*, 2019), suggesting that ER stress and $UPR^{ER}$ phenotype can be subjected to natural selection. Variation in $UPR^{ER}$ phenotype and plasticity presumably reflects the ability to modulate the $UPR^{ER}$ in the face of ER stress. For instance, animals with higher baseline levels of chaperones such as BiP and calnexin, or animals that exhibit a more intense $UPR^{ER}$ upon exposure to environmental or physiological stressors, could be more capable of dealing with ER stress. At the same time, an elevation in $UPR^{ER}$ thresholds or inducibility may render individuals more prone to ER stress-associated apoptosis, which could impact ER stress-associated phenotypes linked to ageing. Animals in nature exhibit behaviours that increase activity and energy expenditure (i.e. exercise) (Sinclair *et al.*, 2014; Halsey, 2016; Yap, Serota, & Williams, 2017), and are regularly exposed to fluctuating environmental conditions (Swanson & Garland, 2009; Storz, Scott, & Cheviron, 2010; Nilsson & Nilsson, 2016; Scott & Dawson, 2017), both of which have been shown to induce ER stress (Deldicque *et al.*, 2010; Bohnert *et al.*, 2018). Therefore, it is plausible that animals with different $UPR^{ER}$ phenotypes should adopt different life-history strategies to cope with these energy demands and environmental stressors. Indeed, there is some evidence suggesting that $UPR^{ER}$ phenotype is linked to behavioural phenotype in rodents, especially behaviours pertaining to energy consumption and expenditure, learning and memory, as well as circadian rhythm (reviewed in Díaz-Hung *et al.*, 2020). We speculate that animals found in harsh environments with unpredictable food availability have a $UPR^{ER}$ phenotype that confers on them the ability to cope with high levels of ER stress. However, the same $UPR^{ER}$ phenotype could be maladaptive in a different environment, where high $UPR^{ER}$ responsivity could lead to development of cancer or metabolic diseases (Ni & Lee, 2007; Bravo *et al.*, 2013; Havighorst *et al.*, 2019). Hence, selection should not always favour high $UPR^{ER}$ responsivity as it does not necessarily lead to high fitness. We suspect that variable environments will act to maintain diversity in $UPR^{ER}$ over time as a mechanism of environmental adaptation.

To date, most of what we know about ER stress and the $UPR^{ER}$ in animals has either been from biomedical studies using cell culture (Salmon *et al.*, 2009; Harper *et al.*, 2011), from experiments involving conventional laboratory model systems such as *Caenorhabditis elegans* (Prahlad & Morimoto, 2009; Sadighi Akha

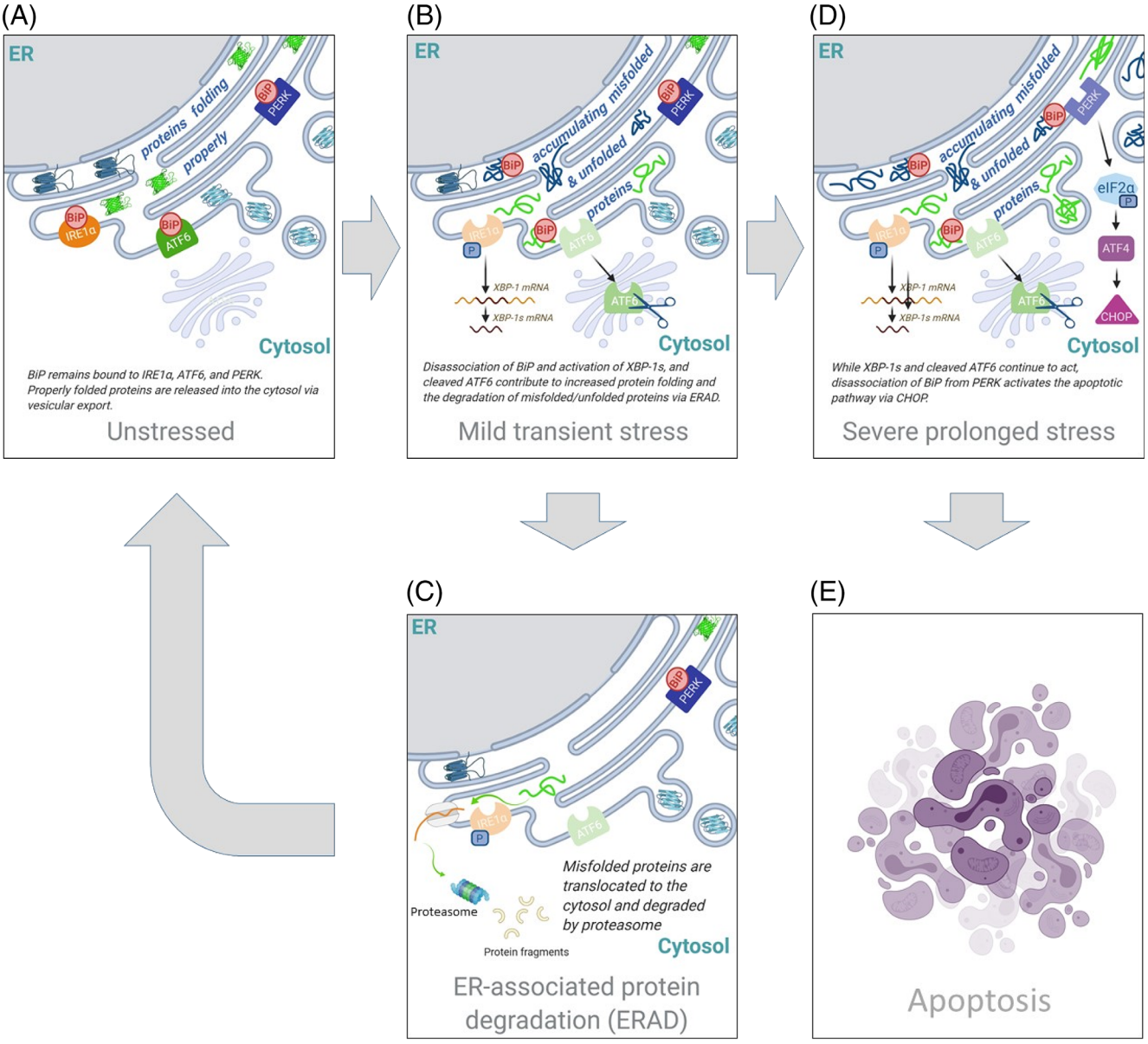


**Fig 2.** (A) Under unstressed conditions, properly folded proteins are released into the cytosol from the ER lumen*via*vesicular export. The chaperone BiPs are bound to IRE1α, ATF6, and PERK. (B) Under mild and transient stress, where moderate load of misfolded/unfolded proteins are found in the ER, BiP dissociates from IRE1α and ATF6 to bind to misfolded and unfolded proteins, and induces activation of XBP-1 and cleavage of ATF6. (C) Activation of XBP-1 and cleavage of ATF6 lead to degradation of misfolded and unfolded proteins*via*ERAD, where misfolded proteins are translocated into the cytosol and degraded by proteasomes. (D) Under severe/prolonged stress, where there is an overload of misfolded/unfolded proteins in the ER, BiP dissociates from PERK to activate the downstream apoptotic pathway*via*CHOP, (E) eventually leading to apoptosis. ATF6, activating transcription factor 6; BiP, binding immunoglobulin protein; CHOP, C/EBP homologous protein; ER, endoplasmic reticulum; ERAD, ER-associated degradation; eIF2α, eukaryotic translation initiation factor 2α; IRE1α, inositol-requiring protein 1α; mRNA, messenger RNA; PERK, protein kinase R-like endoplasmic reticulum kinase; XBP-1, X-box binding protein-1.

*et al.*, 2011) and inbred laboratory mice (*Mus musculus*) (Deldicque *et al.*, 2010; Banerjee *et al.*, 2011), and from agriculturally important species such as cattle (*Bos taurus*) (Gessner *et al.*, 2014; Yonekura *et al.*, 2018) that exhibit limited genetic diversity, and almost all studies were conducted in controlled settings that are often quite different from the conditions animals experience in nature (Fonseca *et al.*, 2014; Yap *et al.*, 2017). Furthermore, these studies conventionally involve the study of qualitative changes in gene expression, exemplified by loss of function or overexpression of specific UPR-associated genes under investigation, ignoring the impact of subtle quantitative changes that are frequently seen in naturally existing populations. However, given that ER stress

and the UPR$^{ER}$ involve evolutionarily conserved pathways, findings from the aforementioned studies should allow us to make predictions pertaining to free-living organisms in natural settings. Here, we review studies that investigated ER stress and the UPR$^{ER}$ in relation to key life-history traits including growth and development, reproduction, bioenergetics and physical performance, and ageing and senescence. We then ask if these studies can inform us about the role of ER stress and the UPR$^{ER}$ in mediating these life-history traits in free-living animals. Finally, we discuss challenges of studying ER stress and the UPR$^{ER}$ in free-living animals and non-conventional model systems and propose ways not only to study ER stress and the UPR$^{ER}$ in natural populations, but also to integrate other physiological pathways to understand better the mechanisms underlying life-history trade-offs in animals.

## II. GROWTH AND DEVELOPMENT

Development and growth, especially during early life, are periods of rapid cellular proliferation and transformation. To support these processes, rates of protein synthesis and secretion by the ER are high in many cell types, particularly secretory cells (Shaffer *et al.*, 2004; Hetz, 2012). The UPR$^{ER}$ and ERAD pathway play vital roles both in supporting these developmental processes and in protecting young from environmental stressors. Knockout experiments have highlighted the importance of the ability to respond to ER stress during development. Embryos with homozygous knockouts of many ER stress chaperones are largely inviable (Ni & Lee, 2007). For example, the transcription of BiP is upregulated in both the mammalian trophoblast and the inner cell. Embryos lacking BiP do not hatch from the zona pellucida and display massive apoptosis as the inner cell mass starts to form (Luo *et al.*, 2006). The ERAD pathway is responsible for moving misfolded and unassembled proteins into the cytosol where they are degraded by the ubiquitin–proteasome system (Ni & Lee, 2007). Sasagawa, Yamanaka, & Ogura (2007) found that inhibition of key ligases (p97 and E3 ubiquintin ligases) in the ERAD pathway inhibits the removal of misfolded proteins, hinders intestinal function, and ultimately reduces growth in *C. elegans*. These studies confirm that natural processes that occur during development contribute to ER stress and that ERAD and the UPR$^{ER}$ play necessary roles in mitigating ER stress. The extent to which natural variation in the expression of the UPR$^{ER}$ and ERAD proteins impacts development, as well as how this variation relates to animals with different growth rates (e.g. mouse *versus* elephant), is unknown and warrants further investigation.

The stressors that animals experience during development and postnatal growth can have lasting impacts on the phenotypes that they display throughout life (Barker, 1990; Monaghan, 2008; Gardner, Ozanne, & Sinclair, 2009; Kasumovic, 2013). While little studied, the UPR$^{ER}$ and ERAD likely play vital roles in buffering young animals from these stressors. In viviparous species, uterine development buffers offspring from the external environment prior to birth and thus many of the stressors that alter offspring phenotype are maternally derived. It is likely that some maternal stressors contribute to ER stress in their developing embryos and activate the UPR$^{ER}$ and ERAD. It has been shown that the maternal consumption of a high-fat diet contributes to ER stress and transgenerational increases in the ratio of phosphorylated eIF2α to unphosphorylated eIF2α and CHOP in the liver of male offspring later in life (Li *et al.*, 2012). This suggests that there is progressive accumulation of unresolved ER stress across generations (Li *et al.*, 2012). Whether maternal high-fat intake contributed to ER stress in young *in utero* was not evaluated but it is possible that early-life activation of ER stress could be responsible for the increase in ER stress markers seen from one generation to the next.

Because the barrier between the embryo and its environment is more limited, oviparous species have a greater probability of environmental perturbation during development than viviparous species. Thus, oviparous species may be more likely to experience increased ER stress associated with exogenous variables. Skeletal muscle myofibrils proliferate during early development (van der Ven *et al.*, 1991). As a result, disturbances that alter skeletal muscle development *in ovo*, can have lifelong effects on muscle performance. Indeed, a 1°C increase in incubation temperature during the second half of incubation has been shown to reduce skeletal muscle mass and upregulate genes associated with the ER stress response in Peking ducks *Anas platyrhynchos domestica* (Liu *et al.*, 2015). Li *et al.* (2017) repeated this experiment and compared birds that experienced an increase of 1°C in incubation temperature to birds that received no thermal manipulation but instead received a dose of tunicamycin. Administration of tunicamycin inhibits N-glycosylation and is commonly used experimentally to induce ER stress in animals. They found that the mass of the breast muscle of embryos in both the thermal and tunicamycin groups were lower than the normothermic and untreated controls. Further, messenger RNA (mRNA) markers of ER stress, including ATF6, BiP, eIF2α, and XBP-1, were upregulated in both thermal and tunicamycin groups, suggesting that ER stress is likely responsible for the decline in the breast muscle mass of duck embryos subjected to thermal stress (Li *et al.*, 2017). It remains to be seen if lower muscle mass in ducks exposed to thermal stress and ER stress during development lead to lower muscle performance later in life.

Taken together, we hypothesize that ER stress and the UPR$^{ER}$ are more tightly regulated at earlier stages of development compared to later stages of development or during ageing. We also hypothesize that during development, oviparous species have more tolerance for ER stress and have higher UPR$^{ER}$ responsivity than viviparous species.

## III. REPRODUCTION

Reproduction, along with survival, are the key determinants of lifetime fitness (Roff, 2008; Wilson & Nussey, 2010).

Reproduction can be a highly physiologically demanding event and the potential costs of reproduction have been relatively well studied (Calow, 1979; Speakman, 2008; but see Williams, 2012*b*, 2018). Many reproductive events and stages, including gametogenesis, lactation, and morphological changes in reproductive organs, require drastic changes in rates of protein synthesis and folding (Guzel *et al.*, 2017) and thus likely impact the ER and regulation of the $UPR^{ER}$. However, research effort to date aiming to elucidate potential mechanisms for individual variation in reproductive performance has largely ignored ER stress and the $UPR^{ER}$, and has mainly focused on the endocrine system and oxidative stress (Jones *et al.*, 1987; Clutton-Brock, 1988; Hamel *et al.*, 2009; Williams & Fowler, 2015). Only recently have ER stress and ER dysfunction been investigated as a possible cause for infertility in limited biomedical studies (Guzel *et al.*, 2011; Yang *et al.*, 2016; Karna *et al.*, 2019). To our knowledge, the role of ER stress and the $UPR^{ER}$ in animal reproduction has not been evaluated in the context of ecology and evolution.

One of the main components of reproductive success is fecundity, a measure of an animal's maximum reproductive potential (Bradshaw & McMahon, 2008). In females, fecundity is determined, in part, by the process of oogenesis. Protein synthesis is vital to proper oocyte development and maturation and the ER plays a key role in meeting oocyte protein demand (Guzel *et al.*, 2017). The effects of ER stress and the $UPR^{ER}$ on oocyte maturation and preimplantation embryonic development have recently been reviewed by Lin *et al.* (2019). Studies in mice (Zhang *et al.*, 2012*a*), pigs (Zhang *et al.*, 2012*b*; Lin *et al.*, 2016), and cattle (Song *et al.*, 2014; Sharma *et al.*, 2015) show that ER stress induction *via* tunicamycin negatively impacts oocyte maturation by causing protein misfolding and inducing apoptosis (Lin *et al.*, 2019). Similarly, another study found that ER stress caused abnormal mouse oocyte development during *in vitro* maturation when treated with high levels of palmitic acid (Wu *et al.*, 2012). Taken together, these studies showed that experimentally induced ER stress negatively impacts oocyte development and that the $UPR^{ER}$ could influence overall female reproductive success.

Along the same lines, spermatogenesis and sperm function rely on the ER for protein synthesis and development with the implication that ER function affects male fertility (Karna *et al.*, 2019). Most studies have shown that ER stress induction increases apoptosis in the testes and decreases sperm quality. For example, a study conducted by Ji *et al.* (2012) exposed male mice to cadmium, a testicular toxin that induces ER stress and the $UPR^{ER}$ by increasing oxidative stress, and found significantly higher numbers of apoptotic cells in the testes, as well as increased expression of CHOP, IRE1α, XBP-1, and BiP. Exposure to fine particulate matter is known to decrease sperm quality. Sprague–Dawley rats exposed to fine particulates displayed increased expression of BiP, XBP-1, and CHOP, as well as more apoptotic cells in the testis and epididymis (Liu *et al.*, 2017). This finding indicates that relatively high expression of the $UPR^{ER}$ in the reproductive tract will likely correlate with reproductive success in male animals. One study produced *Drosophila melanogaster* lines that had excessive ER stress, either by increasing the expression of a misfolded protein or by knocking down BiP expression in the male accessory gland, which excretes seminal proteins essential for reproduction. Interestingly, this study found that in both lines of *Drosophila melanogaster* with excessive ER stress, males were almost completely infertile and produced no progeny, despite having similar sperm production to controls (Chow *et al.*, 2015). This finding suggests that even though ER stress may not affect spermatogenesis in flies directly, the $UPR^{ER}$ and ER stress still play a major role in reproductive success of males.

Outside of oocyte and sperm development and function, ER stress and the $UPR^{ER}$ have been linked to other aspects of reproduction. Most other studies have focused on how the ER and $UPR^{ER}$ interact with female reproduction in mammals, and these studies have been extensively reviewed elsewhere (Yang *et al.*, 2016; Burton, Yung, & Murray, 2017; Guzel *et al.*, 2017). A few of the areas that ER stress and/or the $UPR^{ER}$ have been linked to are follicle atresia (Lin *et al.*, 2012), preimplantation embryonic development (Kim, Kim, & Lee, 1990; Zhang *et al.*, 2012*a*; Basar *et al.*, 2014), embryonic implantation and decidualization (Gao *et al.*, 2012; Lin *et al.*, 2014), corpus luteum development and regression (Kogure *et al.*, 2013; Park *et al.*, 2013), and in the endometrium throughout the menstrual cycle (Guzel *et al.*, 2011). Upregulation of the $UPR^{ER}$ has also been explored as a possible mechanism and treatment for human infertility and reproductive problems such as endometriosis, and endometrial, cervical, and ovarian cancers (Guzel *et al.*, 2017). There is also a link between the expression of BiP and oestradiol production (Guzel *et al.*, 2011, 2017), which is a major steroid hormone that regulates female reproduction and has been linked to variation in reproductive success in various taxa (Williams, 2012*b*; Verderame & Scudiero, 2018). All of the evidence above points to the potentially important role of ER stress and the $UPR^{ER}$ in determining fertility of females, especially in placental mammals.

One key determinant of reproductive success that is unique to mammals is capacity for milk synthesis. Lactation is a physiologically stressful event due to a sharp increase in demand for the synthesis of milk fats and proteins, which can lead to ER stress and activation of the $UPR^{ER}$ (Invernizzi, Naeem, & Loor, 2012). Most studies investigating the links between ER stress, the $UPR^{ER}$, and lactation and milk yield have been conducted in dairy cows. Many dairy cows are susceptible to liver diseases like fatty liver and ketosis because of a negative energy balance during early lactation, and the $UPR^{ER}$ has been implicated as a possible mechanism for these diseases (Ringseis, Gessner, & Eder, 2015). Multiple studies have also shown that dietary supplements or changes that reduce the overall amount of ER stress usually increase overall milk yield (Winkler *et al.*, 2015; Nichols *et al.*, 2017). A study conducted by

Yonekura *et al.* (2018) showed a positive correlation between XBP-1 expression and milk yield, as well as a negative correlation between CHOP expression and milk yield, suggesting that both the IRE1α arm and the PERK arm of the $UPR^{ER}$ system work in tandem to regulate lactation in dairy cows. Specifically, the IRE1α arm of the $UPR^{ER}$ system is responsible for maintaining the milk production machinery, while the PERK arm of the $UPR^{ER}$ system is responsible for supressing apoptosis during lactation (Yonekura *et al.*, 2018). Thus, it seems plausible that females that are able to modulate the IRE1α arm and the PERK arm of the $UPR^{ER}$ system efficiently are more likely to wean more young post-parturition.

Many studies support the link between the $UPR^{ER}$, ER stress, and reproduction. However, current research is biased towards mammals, and more research needs to be conducted in a diverse range of taxa to understand this link better. There is also a lack of studies that connect the $UPR^{ER}$, ER stress, and whole-organism or population-level reproductive success. Although oocyte and sperm development, the health of the female reproductive environment, and capacity for lactation no doubt affect reproductive success, to our knowledge, there is no study looking directly at how intra- and interspecific variation of the $UPR^{ER}$ affect reproductive success. We hypothesize that females that are better able to cope with ER stress during reproduction, either by having higher levels of chaperones such as BiP and calnexin, or by exhibiting a more intense $UPR^{ER}$ in the face of ER stress, will have higher reproductive performance. Further, according to life-history theory, it seems plausible the same $UPR^{ER}$ phenotype that leads to higher reproductive performance could also lead to negative ramifications on the lifespan or survival of animals. However, more empirical tests need to be conducted to address this hypothesis.

## IV. BIOENERGETICS AND PHYSICAL PERFORMANCE

An important determinant of Darwinian fitness is physical performance of animals. Traits that lead to superior physical and exercise performance can allow individuals to forage more, escape from predators, and attract high-quality mates (Le Galliard, Clobert, & Ferrière, 2004; Lailvaux & Husak, 2014; Killen *et al.*, 2017), although presumably at a cost (Lailvaux & Husak, 2014; Husak, Ferguson, & Lovern, 2016; Husak, Roy, & Lovern, 2017). Considerable progress has been made regarding physiological and biomechanical mechanisms that underpin inter- and intraspecific variation in exercise performance (Lailvaux & Husak, 2014; de Albuquerque, Bonine, & Garland, 2015; Sathe & Husak, 2015; Irschick & Higham, 2016; Yap *et al.*, 2017). However, one area that has largely been overlooked by ecological and evolutionary physiologists so far is the role of ER stress and the $UPR^{ER}$ in mediating animals' capacity to engage in moderate- to high-intensity physical activity (i.e. exercise), as well as the effects of sustained activity (for example, exercise training in humans) on ER physiology.

It has been well documented that free-living animals experience radical changes in their morphology and physiology during life-history stages that are particularly energetically demanding and involve elevated physical performance, particularly physical performance that involves aerobic traits. For instance, prior to and during migration, migratory birds, mammals, and fishes upregulate the rate of erythropoiesis (Fudickar *et al.*, 2016; Krause *et al.*, 2016; Yap, Tsai, & Williams, 2019), myogenesis (Swanson, 2010; Palstra *et al.*, 2014; Fudickar *et al.*, 2016), mitochondrial biogenesis (Bremer & Moyes, 2011; McClelland, 2012; Fudickar *et al.*, 2016), and metabolic enzyme activities (Weber, 2009; Guglielmo, 2010, 2018; Price *et al.*, 2011; McGuire, Fenton, & Guglielmo, 2013; Morash *et al.*, 2014; Fudickar *et al.*, 2016), all of which require proper regulation of ER stress and $UPR^{ER}$ pathways (Bohnert *et al.*, 2018; Sigurdsson & Miharada, 2018). More specifically, these physiological processes involve increased proliferation and differentiation of adult stem cells, changes in the rate of protein synthesis and folding in mature differentiated cells, vascular remodelling and angiogenesis (Phillips *et al.*, 2013), all of which are controlled or mediated by various arms of the $UPR^{ER}$ system (Trumpp, Essers, & Wilson, 2010; Bohnert *et al.*, 2018; Sigurdsson & Miharada, 2018; Liu *et al.*, 2019; Merle *et al.*, 2019; Mohammad *et al.*, 2019).

Dormant adult stem cells such as muscle satellite cells and haematopoietic stem cells typically have low levels of oxidative phosphorylation as well as low rates of protein synthesis (Mohammad *et al.*, 2019). Under proliferative conditions, which can be induced by injury or the need to increase physical performance (e.g. exercise), adult stem cells need to deal with increased protein production rate. This increase in protein synthesis rate could potentially cause dysregulation of proteostasis in cells, leading to ER stress and the $UPR^{ER}$ (Sigurdsson & Miharada, 2018). Hence, tight regulation of ER stress and $UPR^{ER}$ signals is essential for the health of proliferating and differentiating adult stem cells, and for safeguarding downstream physiological processes such as erythropoiesis and myogenesis.

Most studies to date have used injury and regeneration models to study the role of ER stress and the $UPR^{ER}$ on erythropoiesis, an important determinant of aerobic capacity (Sigurdsson & Miharada, 2018). The precise ER stress and $UPR^{ER}$ pathway responsible for regulating erythropoiesis is still under investigation, mainly due to difficulties in establishment of haematopoietic stem cells *in vitro*. However, an *in vivo* study found that XBP-1 knockout mice developed hypoplastic liver and severe anaemia, although development of anaemia and lethality was mostly attributed to impaired hepatocyte growth rather than erythropoiesis *per se* (Reimold *et al.*, 2000; Sigurdsson & Miharada, 2018). Another study found that oestrogen administration augments regeneration capacity of haematopoietic stem cells in mice by binding to a promoter region of IRE1α and directly modulating the IRE1α arm of the $UPR^{ER}$ system (Chapple

*et al.*, 2018; Sigurdsson & Miharada, 2018). Adaptive modulation of haematological parameters is important for optimal physical performance of animals, especially in environments with fluctuating oxygen levels (Fedde, 1990; Prats *et al.*, 1996; Yap *et al.*, 2018). Given the central role of the IRE1α arm of the $UPR^{ER}$ system in regulating erythropoiesis, it seems plausible that individuals with the ability to adaptively modulate IRE1α expression or the $UPR^{ER}$ in general will be able to optimize their aerobic performance better in different environments. Indeed, there is some evidence showing that deer mice *Peromyscus maniculatus* adapted to a high-altitude environment have a distinct polymorphism in the *BiP* promoter and exhibit a more intense $UPR^{ER}$ to ER stress (Havighorst *et al.*, 2019). However, it is not entirely clear whether this distinct $UPR^{ER}$ phenotype is directly linked to adaptation to a high-altitude environment. It remains to be seen whether IRE1α expression differs between migratory *versus* non-migratory animals.

Performance traits that are largely anaerobic such as sprint speed and bite force are determined in part by muscle phenotype and physiology (Husak & Lailvaux, 2017). Regulation of muscle physiology and myogenesis by ER stress and $UPR^{ER}$ pathways has been well studied and reviewed extensively (Bohnert *et al.*, 2018; Afroze & Kumar, 2019; Mohammad *et al.*, 2019). A study conducted by Xiong *et al.* (2017) found that upon muscle injury, satellite cells showed increases in levels of PERK and IRE1α. However, inhibition of PERK, but not IRE1α in satellite cells negatively affected muscle regeneration in adult mice, suggesting that the PERK arm of the $UPR^{ER}$ system is the main regulator of regeneration myogenesis. Another important cellular process that occurs during myogenesis is apoptosis, where differentiation-incompetent myoblasts are eliminated from the system (Nakanishi, Sudo, & Morishima, 2005; Nakanishi, Dohmae, & Morishima, 2007; Afroze & Kumar, 2019). This process is mainly mediated by the ATF6 arm of the $UPR^{ER}$ system (Nakanishi *et al.*, 2005, 2007; Afroze & Kumar, 2019). Furthermore, a study conducted in muscle cells isolated from ducks showed that myoblast proliferation and myotube hypertrophy are mediated through ER-stress-dependent pathways (Sun *et al.*, 2013). Together, the PERK arm and ATF6 arm of the $UPR^{ER}$ system regulate the physiological process of myogenesis, ultimately determining muscle phenotype and consequently the physical performance of animals.

Aside from haematological parameters and muscle physiology, both anaerobic and aerobic performance of animals are also determined by the capacity of their metabolic enzymes and to some extent, mitochondrial density (Coyle, 1999; Joyner & Coyle, 2008; Conley, 2016; Irschick & Higham, 2016; Yap *et al.*, 2017). Many studies have found exercise-induced upregulation of the transcriptional coactivator peroxisome proliferator-activated receptor gamma coactivator-1 alpha (PGC-1α) as a result of the activation of the ATF6 arm of the $UPR^{ER}$ system (Wu *et al.*, 2011; Bohnert *et al.*, 2018; Afroze & Kumar, 2019). Likewise, it has also been shown that the bile acid receptor, Takeda G-protein receptor 5 (Tgr5), that regulates energy metabolism in various tissues and promotes muscle cell differentiation and hypertrophy, is upregulated upon activation of the $UPR^{ER}$ (Sasaki *et al.*, 2018). Animals with higher muscle-specific Tgr5 expression also showed higher muscle strength (Sasaki *et al.*, 2018), further supporting the role of the $UPR^{ER}$ in determining variation in physical performance of animals. There is also ample experimental evidence showing increased ER–mitochondria coupling, activation of mitochondrial oxidative phosphorylation, and enhanced ATP synthesis during early stages of ER stress, indicating a strong link between $UPR^{ER}$ activation and mitochondrial function, oxidative metabolism, and energy homeostasis (Lin, Handschin, & Spiegelman, 2005; Bravo *et al.*, 2011, 2013; Wu *et al.*, 2011). A large-scale study conducted by Bowden-Davies *et al.* (2015) compared the proteome of two divergently selected high- and low-endurance running-capacity rats and found that low-capacity runners, which had lower endurance performance, had higher levels of BiP in their adipose tissue, despite not showing any major differences in mitochondrial enzyme content. However, due to the correlational nature of the data, we need to be cautious about inferring causal relationships between BiP level, mitochondrial enzyme content, and running performance. It remains to be seen whether experimental manipulation of either BiP level or the ATF6 arm of the $UPR^{ER}$ system (e.g. through overexpression or knockdown of genes) affects the energy metabolism and exercise performance of animals.

We predict that animals with a more energetically demanding life history (e.g. involving migration), or animals that live in harsher environments that require high aerobic and anaerobic performance will have a $UPR^{ER}$ phenotype that confers on them the ability to withstand high levels of ER stress. The plasticity of the $UPR^{ER}$ in relation to different life-history stages (e.g. moult *versus* migration) also warrants further investigation. Furthermore, we need to consider the different kinds of physical performance (i.e. aerobic *versus* anaerobic) that are sustained by different morphologies and physiological pathways, as these types of performance show specific pattens of life-history trade-offs (Lailvaux & Husak, 2014; Husak & Lailvaux, 2017). Animals with different life-history strategies that require optimisation of different kinds of physical performance likely modulate ER stress and the $UPR^{ER}$ differently.

## V. AGEING AND SENESCENCE

For decades, evolutionary biologists have been trying to uncover the physiological basis of ageing and senescence – a process characterized by decline in tissue and cellular function (Speakman, 2005; Miller *et al.*, 2011; Selman *et al.*, 2012; Gorbunova *et al.*, 2014; Childs *et al.*, 2015). How physiological processes break down with ageing and senescence has been well established in conventional laboratory model systems (Morley & Morimoto, 2004; Higuchi-Sanabria

*et al.*, 2018). Perhaps the best-studied theory for the physiological basis of ageing and senescence is Harman's 'free radical theory of ageing', which posits that reactive oxygen species (ROS)-induced oxidative damage accumulates as animals age and ultimately determines the lifespan of animals (Harman, 1992; Beckman & Ames, 1998; Metcalfe & Alonso-Alvarez, 2010; Selman *et al.*, 2012). Since the publication of Harman's seminal paper in Harman, 1992, countless ecological studies have been conducted to evaluate the role of oxidative stress in ageing and senescence, but support for the theory has been equivocal (Selman *et al.*, 2012; Gladyshev, 2014; Hood, Williams, & Hill, 2019). One key area that has so far been overlooked by the ecology and evolution community is the role of ER stress and $UPR^{ER}$ on ageing and senescence (Pluquet, Pourtier, & Abbadie, 2015).

As organisms age, there is a marked change from protective processes of the $UPR^{ER}$ (i.e. IRE1α and ATF6; Fig. 2B) to more pro-apoptotic processes of the $UPR^{ER}$ (i.e. PERK; Fig. 2D) (Paz Gavilán *et al.*, 2006; Szegezdi *et al.*, 2006; Hussain & Ramaiah, 2007; Naidoo *et al.*, 2008). CHOP is considered a key pro-apoptotic marker of sustained ER stress, and as the ageing process continues organisms show increased CHOP expression in both the cerebral cortex (Naidoo *et al.*, 2008) and the hippocampus (Paz Gavilán *et al.*, 2006), as well as other body tissues including the lung, liver, kidney and spleen (Hussain & Ramaiah, 2007). This suggests that as ageing occurs, organisms experience increased rates of apoptosis and cell death.

One of the hallmarks of ageing is cellular senescence (Childs *et al.*, 2015; Pluquet *et al.*, 2015). The various interconnections between $UPR^{ER}$ signalling and the different aspects of the cellular senescence programs, as well as their functional implications have been elegantly reviewed by Pluquet *et al.* (2015). With cellular senescence, elevated CHOP levels have been shown to sensitise cells to oxidative stress (McCullough *et al.*, 2001; Shizuo *et al.*, 2018). In addition to CHOP, an apoptotic protein, c-Jun N-terminal kinase (JNK) activated by IRE1α is upregulated as cells and tissues senesce (Davis, 2000; Hussain & Ramaiah, 2007). Senescent cells exhibit enhanced ER–mitochondrial tethering, leading to an increase in calcium flux between the mitochondria and the ER (Madreiter-Sokolowski *et al.*, 2019). Although the increased linkage results in increased mitochondrial respiration, it also increases production of ROS, which in turn makes senescent cells more vulnerable to oxidative damage and calcium-overload-induced cell death (Madreiter-Sokolowski *et al.*, 2019). These factors together could account for an increased sensitivity to ER stress as cellular senescence occurs (Chadwick & Lajoie, 2019).

Ageing and senescence are often accompanied by cellular decline and in some cases, ER stress and the associated $UPR^{ER}$ have been linked to cellular decline (Taylor & Dillin, 2013). Current data suggest that age-related decline is associated with an inability to activate ER stress pathways and other protective processes, and thus may be a key reason why the physiological effects of ageing are so easily seen (Taylor & Dillin, 2013). An organism's ability to respond to and cope with environmental stimuli and stress declines with age and this decline in ability is linked in part to ER stress and the associated $UPR^{ER}$ (Taylor & Dillin, 2013). In many species, the ability to undergo the $UPR^{ER}$ has been noted to decline sharply during ageing, possibly as processes shift from the protective arms (i.e. IRE1α and ATF6; Fig. 2B) to the pro-apoptotic arm (i.e. PERK; Fig. 2D) of the $UPR^{ER}$ (Hussain & Ramaiah, 2007; Higuchi-Sanabria *et al.*, 2018). Ageing cells have been shown to have both an altered capacity to transcribe, translate and degrade proteins, as well as a lowered number of important ER chaperones (Erickson, Dunning, & Holtzman, 2006; Nuss *et al.*, 2008), indicating that certain ER stress pathways and $UPR^{ER}$ activation are negatively impacted with ageing. In *C. elegans*, activation of the IRE1α arm of the $UPR^{ER}$ along with its downstream targets and other transcription factors result in promotion of longevity (Henis-Korenblit *et al.*, 2010). Interestingly, it has been shown that primary fibroblasts from long-lived rodents such as the naked mole rat *Heterocephalus glaber* and Snell dwarf mice are more sensitive to ER stress inducers like tunicamycin and thapsigargin, which inhibit N-linked glycosylation and sarco/endoplasmic reticulum calcium ATPase (SERCA), respectively (Salmon *et al.*, 2009), suggesting that there may be species-specific differences in how longevity is influenced by ER stress and the associated $UPR^{ER}$. It would be interesting to find out whether repeated ER stress exposure and activation of the $UPR^{ER}$ throughout an animal's life has an effect on its longevity.

In addition to cellular decline, ER stress and the $UPR^{ER}$ have also been linked to a number of neurodegenerative diseases (Yoshida *et al.*, 2001; Harding & Ron, 2002; Lindholm, Wootz, & Korhonen, 2006; Fonseca *et al.*, 2014). In the brain, breakdown of the $UPR^{ER}$ and ER stress pathways are often linked to a decreased responsivity to the ER stress chaperone BiP, and downstream regulators PERK, CHOP and IRE1α (Lindholm *et al.*, 2006). Rabek, Boylston & Papaconstantinou (Rabek, Boylston III, & Papaconstantinou, 2003) showed a 50% reduction in BiP protein expression in aged mouse liver and a 30% decrease in the cerebral cortex. Decreased hippocampal concentration of BiP has also been shown in aged rats (Paz Gavilán *et al.*, 2006). As a result of decreased BiP levels, hippocampal PERK mRNA downregulates significantly as an organism ages, and the expression of PERK was limited in aged individuals compared to 3-month-old mice (Paz Gavilán *et al.*, 2006). Additionally, it has been found that brain eIF2α kinase activity is less efficient in aged animals than in younger individuals (Hussain & Ramaiah, 2007). Specifically, phosphorylation of PERK and eIF2α is lowered in an aged individual, which impacts the ability of the $UPR^{ER}$ to mitigate ER stress (Hussain & Ramaiah, 2007). Calnexin, another molecular chaperone associated with glycan binding in the ER lumen, has also been implicated in a number of ageing-related diseases (Hebert & Molinari, 2007). Specifically, calnexin loss increases a cell's sensitivity to apoptotic factors through the activation of ganglioside GD3 (Tomassini *et al.*, 2004).

Most studies regarding ageing and senescence in relation to the $UPR^{ER}$ and ER stress have been completed in a laboratory setting, under tightly controlled conditions or using cell culture lines. Very little research has investigated the effects of ER stress and the $UPR^{ER}$ on free-living, ageing animals under natural conditions. We speculate that the shift from protective to pro-apoptotic processes of the $UPR^{ER}$ likely happens earlier in animals with shorter lifespans. Developing a clear and generic hypothesis regarding $UPR^{ER}$ phenotype and longevity is challenging due to species and taxon differences. Harper *et al.* (2011) found that although fibroblasts isolated from long-lived bird species are resistant to multiple forms of stress, their resistance to ER stress is similar to birds with shorter lifespans. Surprisingly, Salmon *et al.* (2009) found that fibroblasts isolated from naked mole rats, which typically show minimal signs of senescence, are less resistant to ER stress than other short-lived rodent species. However, we need to be cautious about generalizing findings from fibroblasts to other tissues and whole organisms. Nevertheless, this gap in knowledge leaves many questions unanswered about how ER stress and the $UPR^{ER}$ are related to ageing and senescence in organisms in the wild. Additionally, it should be noted that ER stress and the $UPR^{ER}$ can affect ageing both directly, as discussed in this section, as well as indirectly through their effects on other life-history variables that also mediate ageing (e.g. reproduction) (Maklakov *et al.*, 2017; Maklakov & Chapman, 2019).

## VI. DISCUSSION: CHALLENGES MOVING FORWARD AND INTEGRATION WITH OTHER PHYSIOLOGICAL SYSTEMS

A multitude of biomedical studies have shown support for the essential role of ER stress, the $UPR^{ER}$, and associated downstream pathways in modulating aspects of animal reproduction, growth and development, bioenergetic capacity and physical performance, and ageing and senescence. However, these studies are largely conducted in conventional laboratory-based model systems and in environments that are not ecologically relevant. Perhaps rather unsurprisingly, there tends to be a bias towards mammalian models in the current literature regarding ER stress and the $UPR^{ER}$. We argue that there is a need to develop more ecologically relevant studies to understand how ER stress and the $UPR^{ER}$ are related to various life-history traits in free-living animals. An obvious place to start is characterizing ER stress and $UPR^{ER}$ phenotypes in free-living animals and investigating how inter- and intraspecific variation in phenotypes relate to life-history traits such as growth and development, reproduction, whole-organism performance, and ageing and senescence. To achieve this, identifying key biomarkers to characterise the $UPR^{ER}$ phenotype representative of the whole organism is essential. As discussed in Section V, $UPR^{ER}$ phenotype shown by primary fibroblasts have provided valuable insights in studies of ER stress but it is unclear whether the ER stress response of primary fibroblasts can serve as a reliable indicator for tissues throughout the body. Additionally, commonly employed ER stress inducers (e.g. tunicamycin, thapsigargin, brefeldin A, bortezomib, etc.) often elicit drug-specific physiological effects that are not related to the $UPR^{ER}$ (Chidawanyika *et al.*, 2018). Hence, it remains to be seen whether there is a universal marker or metric that encompasses all forms of ER stress. Nevertheless, studies should capitalize on existing populations of free-living animals with large and distinct variation in ER stress responsivity, such as the high- and low-altitude populations of *P. maniculatus* reported by Havighorst *et al.* (2019), and ask how life-history traits differ between these two populations, as well as along the ER stress-responsivity continuum. Another approach is to manipulate ER stress experimentally in animals housed in natural or semi-natural enclosures using ecologically relevant stressors such as infection and measure fitness-related traits including reproductive output, growth rate, and survival.

Another area of potential value is to focus not on the levels of expression of individual chaperones as markers of $UPR^{ER}$ efficiency, but rather on the degree of $UPR^{ER}$ coordination. As it is a well-orchestrated response involving several molecular components, it is plausible that the degree to which the $UPR^{ER}$ is coordinated across tissues and at the whole-organism level during exposure to environmental stressors will be of particular value in deciphering the role of ER stress in environmental adaptation and evolution. It is still unclear how differential regulation of the $UPR^{ER}$ in different tissues is integrated with $UPR^{ER}$ intensity at the organismal level. To that end, tissue-specific modifiers of the $UPR^{ER}$ may exist and operate independently, influencing the organism's response to ER stress.

To accomplish these tasks, a number of barriers need to be overcome. First, despite being a rather conserved physiological pathway (Hollien, 2013), the ability to quantify physiological ER stress at the protein level has only been developed in recent years (Gupta *et al.*, 2010; Qi, Yang, & Chen, 2011) and there are specificity concerns regarding commercial antibodies for detection of ER stress markers (Haataja *et al.*, 2008). Secondly, there are also logistical barriers with animal tracking and non-lethal sampling of animals. However, recent advances in methods for wildlife tracking and bio-logging (Wilmers *et al.*, 2015) now allow biologists to track animals effectively. ER stress and $UPR^{ER}$ phenotypes can also be characterized in primary culture of fibroblasts (Havighorst *et al.*, 2019), which can be isolated from small skin biopsy samples (Khan & Gasser, 2016). However, how different cell and tissue types (e.g. secretory *versus* non-secretory cells) respond to ER stress is variable, making quantification of the impact of ER stress on performance at the organismal level challenging. Thus, it remains to be seen whether findings from primary fibroblasts can be extrapolated to other tissues or to the whole-organism level. Furthermore, animals could be housed and experimentally manipulated in natural or semi-natural enclosures

(Mokkonen *et al.*, 2011; Lonn *et al.*, 2017), which would allow for exposure to environmental conditions and stressors typical of their natural habitat, while at the same time allowing easy tracking and close monitoring by researchers.

Cellular organelles such as the ER are generally very dynamic; they often interact with other organelles to regulate physiological functions and homeostasis. These intricate interactions among organelles ultimately determine physiological phenotype at the cell and organ levels, which eventually contribute to expression of whole-organism phenotype (Tu & Weissman, 2004; Csordás *et al.*, 2006; Giorgi *et al.*, 2009; Lebiedzinska *et al.*, 2009; Janikiewicz *et al.*, 2018; Gordaliza-Alaguero, Cantó, & Zorzano, 2019). It has been shown recently that close contact sites between the ER and mitochondria, known as the mitochondria-associated membrane (MAM), play an important role in ageing processes and longevity (Janikiewicz *et al.*, 2018). Mitochondrial dysfunction and ER stress impair calcium and redox homeostasis, which may initiate a cycle of increasing oxidative stress, causing further calcium homeostasis dysregulation, which in turn disrupts ER protein folding and increases mitochondrial ROS production, eventually leading to further ER and mitochondrial dysfunction (Malhotra & Kaufman, 2007; Chaudhari *et al.*, 2014; Janikiewicz *et al.*, 2018). Therefore, given the extensive research on how oxidative stress influences life-history in the realm of ecology and evolution (Monaghan *et al.*, 2009; Metcalfe & Alonso-Alvarez, 2010; Selman *et al.*, 2012; Olson, 2020), and the tight link between the ER and mitochondria (Giorgi *et al.*, 2009; Lebiedzinska *et al.*, 2009; Chaudhari *et al.*, 2014; Janikiewicz *et al.*, 2018), it is important to integrate ER physiology and mitochondrial physiology when studying the physiological basis of life-history trade-offs.

## VII. CONCLUSIONS

(1) The ER is vital for protein folding and synthesis. ER stress and the $UPR^{ER}$ maintain proteostasis in cells to ensure proper cellular functions. Animals vary in their ability to respond to ER stress and undergo the $UPR^{ER}$. This variation in ER stress and $UPR^{ER}$ phenotype should lead to variation key life-history traits, including growth rate, reproductive performance, physical performance, and ageing.

(2) Various biomedical studies have documented the role of ER stress and the $UPR^{ER}$ in determining variation in life-history traits. However, the vast majority of these studies were conducted in captive animals and cell cultures in laboratory settings that are drastically different from those experienced in nature. We hypothesize that animals found in different environments and adopting different life-history strategies should exhibit different ER stress responsivity and $UPR^{ER}$ phenotypes that allow them to cope with the unique challenges and characteristics of these environments and life histories. Efforts should be made to characterize variation in ER stress and the $UPR^{ER}$ in free-living animals, and to relate the observed variation to key life-history traits.

(3) The ER interacts with other cellular organelles dynamically to regulate cellular functions. In particular, there is tight interaction between the ER and mitochondria, leading to significant crosstalk between ER stress pathways and oxidative stress pathways. We urge ecological and evolutionary biologists to investigate how interactions between ER stress and oxidative stress shape life-history trade-offs in free-living animals.

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## IX. AUTHOR CONTRIBUTIONS

This review was jointly conceived by K.N.Y. and W.R.H. All authors contributed to the writing and development of the manuscript.

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