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Metabolism and the UPR^{mt}

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SUMMARY

During mitochondrial dysfunction or the accumulation of unfolded proteins within mitochondria, cells employ a transcriptional response known as the mitochondrial unfolded protein response (UPR^{mt}) to promote cell survival along with the repair and recovery of defective mitochondria. Considerable progress has been made in understanding how cells monitor mitochondrial function and activate the response, as well as in identifying scenarios where the UPR^{mt} plays a protective role such as during bacterial infection, hematopoietic stem cell maintenance or general aging. To date, much of the focus has been on the role of the UPR^{mt} in maintaining or re-establishing protein homeostasis within mitochondria by transcriptionally inducing mitochondrial molecular chaperone and protease genes. In this review, we focus on the metabolic adaptations or rewiring mediated by the UPR^{mt} and how this may contribute to the resolution of mitochondrial unfolded protein stress and cell type-specific physiology.

Mitochondrial recovery via the UPR^{mt}

Mitochondria are a dynamic network of double membrane bound organelles responsible for the vast majority of ATP generation in non-dividing differentiated cells. In addition to housing the tricarboxylic acid (TCA) cycle and oxidative phosphorylation (OxPhos) machinery, mitochondria are also important contributors to amino acid, lipid, and nucleotide metabolism. Because mitochondrial function impacts numerous essential cellular and organismal functions, it is perhaps not surprising that mechanisms or pathways have evolved to monitor mitochondrial function and rapidly respond to mitochondrial stress to recover organelle activity. Such pathways are typically referred to as retrograde responses as the upstream signal initiates at mitochondria and communicates the status to the cytosol and nucleus to impact gene transcription and protein synthesis in a protective manner (Liu and Butow, 2006). Here, we focus on the mitochondrial unfolded protein response (UPR^{mt}), which is a transcriptional response originally discovered to increase mitochondrial localized molecular chaperones and proteases to promote the recovery of organellar protein homeostasis (proteostasis) (Yoneda et al., 2004; Zhao et al., 2002). However, the UPR^{mt} also promotes a rewiring of cellular metabolism that includes an increase in glycolysis and

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amino acid catabolism genes with a simultaneous repression of TCA cycle and OxPhos-encoding genes potentially to relieve mitochondrial stress and/or alter cellular metabolism to promote survival (Nargund et al., 2015).

Many potential mechanisms exist to evaluate mitochondrial activity or function including monitoring mitochondrial metabolites or products such as ATP or iron-sulfur clusters (Hardie et al., 2015). However, a number of recent studies demonstrate that an effective strategy is to monitor mitochondrial protein import efficiency (Harbauer et al., 2014). Mitochondria are composed of over 1000 proteins of which ~99 percent are encoded by nuclear genes and translated on cytosolic ribosomes. Thus, in order for mitochondria to function properly, these proteins must be imported into mitochondria where they are appropriately folded and assembled. Transit across the mitochondrial inner membrane not only requires the Tim23 complex, but also an intact TCA cycle and OxPhos system that maintains the membrane potential, as well as mitochondrial chaperones located within the matrix (Chacinska et al., 2009; Shariff et al., 2004; van der Laan et al., 2006). Thus, the efficiency of the protein import process reflects diverse aspects of mitochondrial function.

Indeed, signaling molecules have been identified that are activated by mitochondrial dysfunction or stresses that reduce mitochondrial import efficiency. For example, the transcription factor ATFS-1, which regulates the UPR^{mt} in *C. elegans* has both a mitochondrial targeting sequence (MTS) and a nuclear localization sequence (NLS). Normally, ATFS-1 is efficiently imported into mitochondria where it is rapidly degraded. However during mitochondrial stress, reduced import efficiency causes many mitochondrial-targeted proteins to accumulate in the cytosol. Most are recognized and targeted for degradation by the proteasome (Wrobel et al., 2015) so as to prevent toxicity of mislocalized protein accumulation (Wang and Chen, 2015). But, because ATFS-1 has a NLS it traffics to the nucleus to activate the UPR^{mt} (Nargund et al., 2012) (Figure 1A). Included in the stresses that perturb import and activate the UPR^{mt} are depletion of mtDNA (Martinus et al., 1996; Yoneda et al., 2004), accumulation of misfolded proteins within mitochondria (Papa and Germain, 2011; Zhao et al., 2002), mitochondrial ribosome impairment (Houtkooper et al., 2013; Moullan et al., 2015), mitochondrial chaperone and protease inhibition (Yoneda et al., 2004), OxPhos perturbation (Liu et al., 2014; Nargund et al., 2012), high glucose consumption (Tauffenberger et al., 2016) and high levels of reactive oxygen species (Runkel et al., 2013; Yoneda et al., 2004). Thus, the mitochondrial import capacity of the entire organellar network controls expression of a mitochondrial recovery program. Of note, while many of the conditions outlined above have been reported to deplete membrane potential, none of them cause complete membrane depolarization. To our knowledge the relationship between the inner membrane potential and UPR^{mt} activation has not been explicitly evaluated. Regardless, it is clear that depletion of the mitochondrial inner membrane potential is not necessary to activate the UPR^{mt} (Jin and Youle, 2013).

A second pathway regulated by mitochondrial protein import efficiency is a form of organelle quality control known as mitophagy (Narendra et al., 2008). Similar to ATFS-1, the kinase PINK1 has a MTS, which allows it to be efficiently imported into healthy organelles and processed leading to its degradation in the cytosol (Tanaka et al., 2010). However, when import efficiency is severely impaired, PINK1 integrates into the outer

membrane of the defective compartment where it serves several functions. The most well-characterized function involves the subsequent phosphorylation of ubiquitin (Kane et al., 2014; Kazlauskaite et al., 2014; Koyano et al., 2014) and the recruitment of the ubiquitin ligase Parkin (Matsuda et al., 2010; Narendra et al., 2010; Okatsu et al., 2015; Vives-Bauza et al., 2010) that ultimately results in isolation of the defective organelle, or subcompartment, and targeting to the lysosome for degradation (Heo et al., 2015; Lazarou et al., 2015; McLelland et al., 2014; Yang and Yang, 2013). Thus, the mitochondrial network is self-monitoring as import deficiency directly initiates the downstream activation of at least two protective responses. By activating a protective transcriptional response and eliminating the most defective mitochondria, the UPR^{mt} and mitophagy pathways function to improve or recover the health of the mitochondrial network.

Regulated expression of TCA cycle and OxPhos components

In flies, worms and mammals, the UPR^{mt} includes the induction of mitochondrial proteostasis machinery such as mitochondrial molecular chaperones and proteases as well as anti-oxidant genes to limit damage due to increased generation of reactive oxygen species (Nargund et al., 2012; Owusu-Ansah et al., 2013; Wu et al., 2014; Zhao et al., 2002). Additionally, the UPR^{mt} includes the induction of multiple metabolic pathways including genes required for glycolysis and amino acid catabolism. Interestingly, the UPR^{mt} also limits the accumulation of transcripts that encode the highly expressed TCA cycle and OxPhos components (Nargund et al., 2015) (Figure 1B).

The OxPhos complexes are large multi-subunit structures located within the mitochondrial inner membrane. With the exception of the succinate dehydrogenase complex (Complex II), the other three respiratory chain complexes and the ATP synthase are composed of proteins encoded by both the nuclear and mitochondrial genomes (mtDNA). 100s of mtDNA copies exist per cell, with multiple copies per mitochondrion. They encode 13 OxPhos subunits as well as tRNAs and rRNAs required for their synthesis. Therefore, to insure efficient complex assembly and biogenesis, transcription from both genomes must be coordinated to promote stoichiometric expression and prevent the accumulation of OxPhos subunits that fail to integrate or assemble into specific complexes (Jovaisaite and Auwerx, 2015).

In addition to trafficking to the nucleus during mitochondrial dysfunction and limiting the expression of nuclear-encoded OxPhos components, a percentage of ATFS-1 also accumulates within mitochondria where it limits the accumulation of the OxPhos transcripts encoded by mtDNA (Figure 1A). ATFS-1-dependent repression of mtDNA-encoded transcripts appears to be direct as ATFS-1 binds the mtDNA promoter region, which contains the same sequence motif that ATFS-1 binds in the nuclear genome to activate mitochondrial proteostasis gene transcription. Combined, these observations suggest that ATFS-1 and the UPR^{mt} simultaneously limit expression of OxPhos components from both genomes to promote efficient stoichiometric expression and assembly of the OxPhos complexes (Nargund et al., 2015). Thus, in addition to increasing the expression of the machinery required to assemble the OxPhos complexes, the UPR^{mt} limits the influx of nascent OxPhos components so as to not overwhelm the protein folding and complex assembly capacity of the defective organelle. Concomitantly, the deficit in ATP production

is maintained by increased glycolysis gene expression (Fig. 1C). Supporting the role of matching substrate load and mitochondrial proteostasis capacity, additional pathways are also in place to reduce the burden on the potentially deficient mitochondrial protein-folding environment during stress by reducing cytosolic protein synthesis (Baker et al., 2012; Wang and Chen, 2015).

Metabolic adaptation in physiology and diseases

The cellular benefits of what appears to be a metabolic shift similar to that observed in rapidly growing cells (Vander Heiden et al., 2009) are potentially numerous during mitochondrial dysfunction. An increase in glycolysis is potentially a means to maintain ATP production in the presence of compromised OxPhos, which would promote cell survival as well as the regeneration of defective mitochondria and the OxPhos complexes. However, the induction of glycolysis and repression of TCA cycle and OxPhos transcripts could also serve to rewire cellular metabolism to effect cellular proliferation, growth or differentiation. Here, we explore the role of UPR^{mt}-mediated metabolic adaptations in several physiologic scenarios where the UPR^{mt} is known to play a role.

Innate immunity during bacterial infection

In addition to inducing genes that promote mitochondrial recovery, the UPR^{mt} also includes xenobiotic detoxification genes as well as innate immunity genes (Liu et al., 2014; Pellegrino et al., 2014) (Figure 1B). And perhaps not surprisingly, a number of bacterial-produced OxPhos inhibitors such as antimycin and oligomycin, as well as mitochondrial ribosome inhibitors (Moullan et al., 2015) activate the UPR^{mt} in *C. elegans* and mammals (Liu et al., 2014; Pellegrino et al., 2014; Runkel et al., 2013). These observations suggest a means to detect pathogenic, or toxic, bacteria by monitoring mitochondrial function and initiating an innate immune response accordingly. In support of this idea, pathogenic strains of *Pseudomonas aeruginosa* cause mitochondrial dysfunction and activate the UPR^{mt}. Activation of the UPR^{mt} requires the *P. aeruginosa* virulence response, which includes the production of cyanide (a respiratory chain inhibitor) and iron chelators (Kirienko et al., 2013). Worms lacking ATFS-1 are sensitive to *P. aeruginosa* infection while worms with a constitutively active UPR^{mt} are resistant to the pathogen and limit the intestinal accumulation of the bacteria. Thus, it appears that cells perceive mitochondrial stress or damage as a potential bacterial infection, which may be an important strategy to detect toxic bacteria in non-sterile environments such as the intestine or skin. Increased intestinal clearance of *P. aeruginosa* suggests the UPR^{mt} provides anti-bacterial activity, but the role of the UPR^{mt}-mediated metabolic adaptations is less clear. Perhaps the simplest explanation is that in response to the cytochrome c oxidase (Complex IV) inhibitor cyanide, the UPR^{mt} increases glycolysis genes to maintain energy levels and limits OxPhos biogenesis so as not to exacerbate the accumulating mitochondrial damage until the animal clears the infection (Melo and Ruvkun, 2012; Pellegrino et al., 2014).

Aging

A decline in mitochondria function is a hallmark of aging (Lopez-Otin et al., 2013), and multiple studies suggest that increased UPR^{mt} activation can recover or prolong

mitochondrial function in a variety of tissues and promote longevity. Modest OxPhos dysfunction in worms, flies and mice results in lifespan extension and causes UPR^{mt} activation (Durieux et al., 2011; Houtkooper et al., 2013; Lapointe et al., 2009; Owusu-Ansah et al., 2013). In worms it has been demonstrated that ATFS-1 (Schieber and Chandel, 2014), and other UPR^{mt} signaling components are required for this form of lifespan extension (Durieux et al., 2011; Houtkooper et al., 2013). However, it should be noted that UPR^{mt} activation alone is not sufficient to prolong lifespan (Bennett et al., 2014; Rauthan et al., 2013), suggesting multiple pathways are in place to respond to mitochondrial stress in addition to the UPR^{mt}. It is unclear which UPR^{mt}-mediated activities specifically contribute to longevity, however recent work points towards a role in the recovery of mitochondrial function via mitochondrial biogenesis (Houtkooper et al., 2013; Mouchiroud et al., 2013; Nargund et al., 2015).

In aged cells where mitochondria are potentially damaged, recovery of dysfunctional organelles may require a different, perhaps more tightly regulated, program than mitochondrial biogenesis in an otherwise healthy network. Studies in mice and worms have shown that NAD is reduced in aged tissues such as muscle (Canto et al., 2015; Pirinen et al., 2014), as well as in livers of mice fed a high fat and high sugar diet (Gariani et al., 2015). NAD is converted to NADH by the TCA cycle within mitochondria, which acts as an electron donor for the respiratory chain, which maintains the membrane potential across the mitochondrial inner membrane and can be used to generate ATP. Impressively, increasing NAD levels by genetic or pharmacologic means promotes mitochondrial function and prolongs lifespan (Andreux et al., 2013; Gariani et al., 2015; Mouchiroud et al., 2013). Increased NAD leads to mitochondrial recovery via sirtuin-mediated activation of the transcriptional co-activator PGC-1α, FOXO as well as UPR^{mt} activation, which combined yields efficient recovery of mitochondrial activity (Mouchiroud et al., 2013). In this context, we anticipate that UPR^{mt} activation orchestrates a very coordinated mitochondrial recovery program by fine-tuning OxPhos and TCA cycle expression to match the protein folding and complex assembly of the defective organelles while simultaneously increasing the mitochondrial proteostasis capacity. Interestingly, the UPR^{mt} may also play a role in maintaining a high NAD/NADH ratio by limiting TCA activity until mitochondrial activity has been recovered when normal TCA cycle gene transcription resumes.

Stem cell maintenance

Aging can also be attributed to deterioration of tissue-specific stem cells (Lopez-Otin et al., 2013). However, unlike somatic cells, quiescent stem cells maintain few mitochondria with relatively low metabolic activity (Kohli and Passegue, 2014). Interestingly, a recent study found that hematopoietic stem cells (HSC) utilize a signaling pathway involving a UPR^{mt} to repress mitochondrial biogenesis and OxPhos to coordinate the metabolism required for stem cell maintenance (Mohrin et al., 2015). Hematopoietic stem cell maintenance requires an interaction between the histone deacetylase SIRT7 and the transcription factor NRF1, which regulates the expression of genes that encode mitochondrial ribosome components (Scarpulla et al., 2012). In this context, SIRT7 expression is increased by mitochondrial protein folding stress associated with the burst of mitochondria biogenesis that occurs during stem cell proliferation. By inhibiting NRF1 activity, SIRT7 limits mitochondrial biogenesis

and OxPhos preserving stem cell metabolism (Figure 2). Therefore, SIRT7 promotes the maintenance of a pristine mitochondrial protein-folding environment keeping the organelles and the stem cells in a “youthful” state. Consistent with this idea, HSCs lacking SIRT7 have increased mitochondrial stress and an increased propensity to proliferate. Thus, HSCs require SIRT7 to limit mitochondrial stress and proliferation (Mohrin et al., 2015), which maintains their regenerative function (Miyamoto et al., 2007). Indeed, SIRT7 expression decreases in aged mice where HSC maintenance fails leading to a reduction in white blood cell number (Mohrin et al., 2015) suggesting that by simply limiting OxPhos complex biogenesis and unfolded protein accumulation, stem cell function can be preserved during aging.

CONCLUSIONS AND PERSPECTIVES

We have highlighted scenarios identified in multiple organisms where the UPR^{mt} has been documented to play a protective role, focusing on the potential protective outputs of UPR^{mt}-mediated metabolic regulation rather than the maintenance of mitochondrial proteostasis. However, it should be noted that while the regulation of the UPR^{mt} in *C. elegans* relies on the transcription factor ATFS-1, less is known regarding the regulation of the UPR^{mt} in mammals or flies. A pressing question in the field is whether the UPR^{mt}-related observations in flies or mammals are regulated via mitochondrial protein import efficiency or through an alternative means. Unfortunately homology searches do not yield candidates with especially significant homology beyond the DNA binding domain. Interestingly, the yeast transcription factor Hap1 was recently found to harbor both a MTS and a NLS (Williams et al., 2014), suggesting it is regulated similarly to ATFS-1. Consistent with Hap1 responding to mitochondrial protein import impairment, it is activated when oxygen and heme are limiting and activates genes that promote heme biogenesis (Kwast et al., 1998). Because, multiple mammalian transcription factors have putative MTSs (Claros and Vincens, 1996) and have been found to localize to mitochondria (Marinov et al., 2014), we are optimistic a similar mode of regulation will be uncovered. However, other means of sensing and responding to mitochondrial stress should not be excluded.

While roles for the UPR^{mt} in adapting metabolism to promote recovery of the mitochondrial network are only beginning to emerge, considerable data suggests multiple pathologic scenarios where improved mitochondrial health may be beneficial. Interestingly, a dichotomy may be emerging where the UPR^{mt} affects proliferating cells differently than post-mitotic cells such as muscles or neurons, which likely reflects each cell types preferred means of glucose utilization. In response to mitochondrial dysfunction, mitotic and post-mitotic cells employ aerobic glycolysis (or Warburg metabolism) by increasing glycolytic while impairing TCA cycle and OxPhos gene expression. In proliferating cells, perpetual or prolonged UPR^{mt} activation may promote glycolysis while maintaining or stabilizing mitochondrial function (Mohrin et al., 2015). Promoting aerobic glycolysis in stem or cancer cells is potentially a concern, but recent work demonstrates that these cells require mitochondrial function and maintenance of the membrane potential in order to proliferate (Martinez-Reyes et al., 2015). Presumably muscle cells or neurons employ the UPR^{mt} over shorter periods of time to promote repair or recovery of mitochondrial function without permanently rewiring cellular metabolism (Lamech and Haynes, 2015). As additional

physiologic roles of the UPR^{mt} are identified, coupled with a better understanding of the underlying regulatory mechanisms in mammals (Arnould et al., 2015), we are optimistic that strategies to engage this pathway therapeutically will develop. In addition to neurodegenerative diseases such as Parkinson's where loss of mitochondrial function contributes to dopaminergic neuronal loss, diverse metabolic diseases may also be considered. For example, increased muscle mitochondrial biogenesis is a proposed strategy to limit or prevent insulin resistance, a precursor to type 2 diabetes (Egan and Zierath, 2013).

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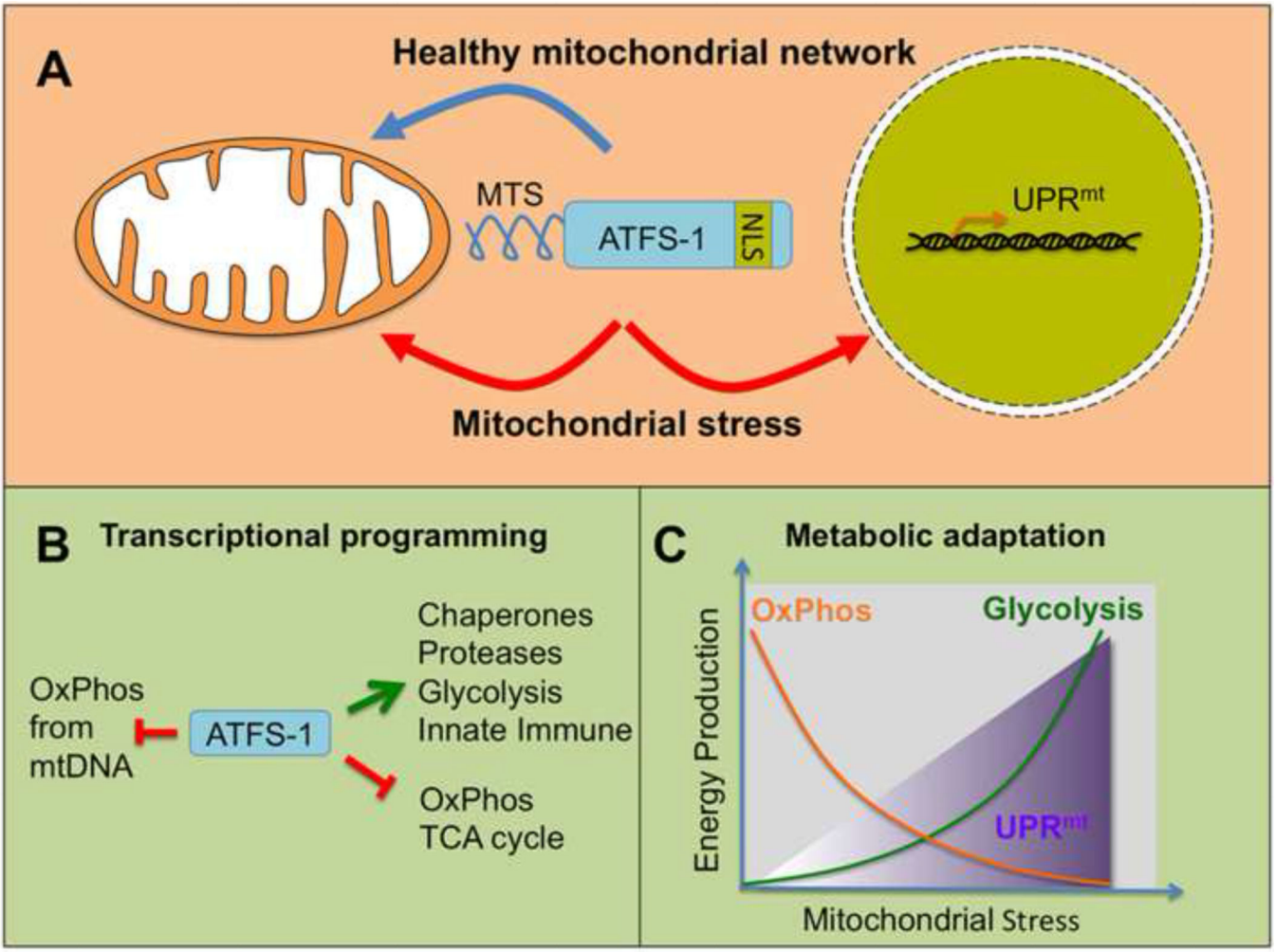

Figure 1. ATFS-1 represses OxPhos and TCA cycle gene expression while inducing mitochondrial proteostasis and glycolysis genes during mitochondrial dysfunction

(A) Beause ATFS-1 contains a mitochondrial targeting sequence (MTS), it is efficiently imported into mitochondria and degraded. However during mitochondrial stress, import efficiency of ATFS-1 is reduced causing a percentage of it to traffic to the nucleus via its nuclear localization sequence (NLS) where it regulates the UPR^{mt}.

(B) In the nucleus, ATFS-1 regulates expression of over 400 genes including the induction of mitochondrial proteostasis genes (chaperones, proteases) as well as glyolysis and innate immune genes. Simultaneously, ATFS-1 limits the accumulation of the highly expressed TCA cycle and oxidative phosphorylation (OxPhos) transcripts. During stress, a percentage of ATFS-1 is also stabilized within mitochondria where it limits the accumulation of mtDNA-encoded OxPhos transcripts.

(C) UPR^{mt} activation results in a reduction of nuclear and mtDNA-encoded OxPhos transcripts to promote stoichiometric complex assembly and reduce the substrate burden on the overwhelmed proteostasis environment in stressed mitochondria. Together, ATFS-1 promotes the regeneration of OxPhos complexes while increasing glycolytic capacity to maintain ATP levels.

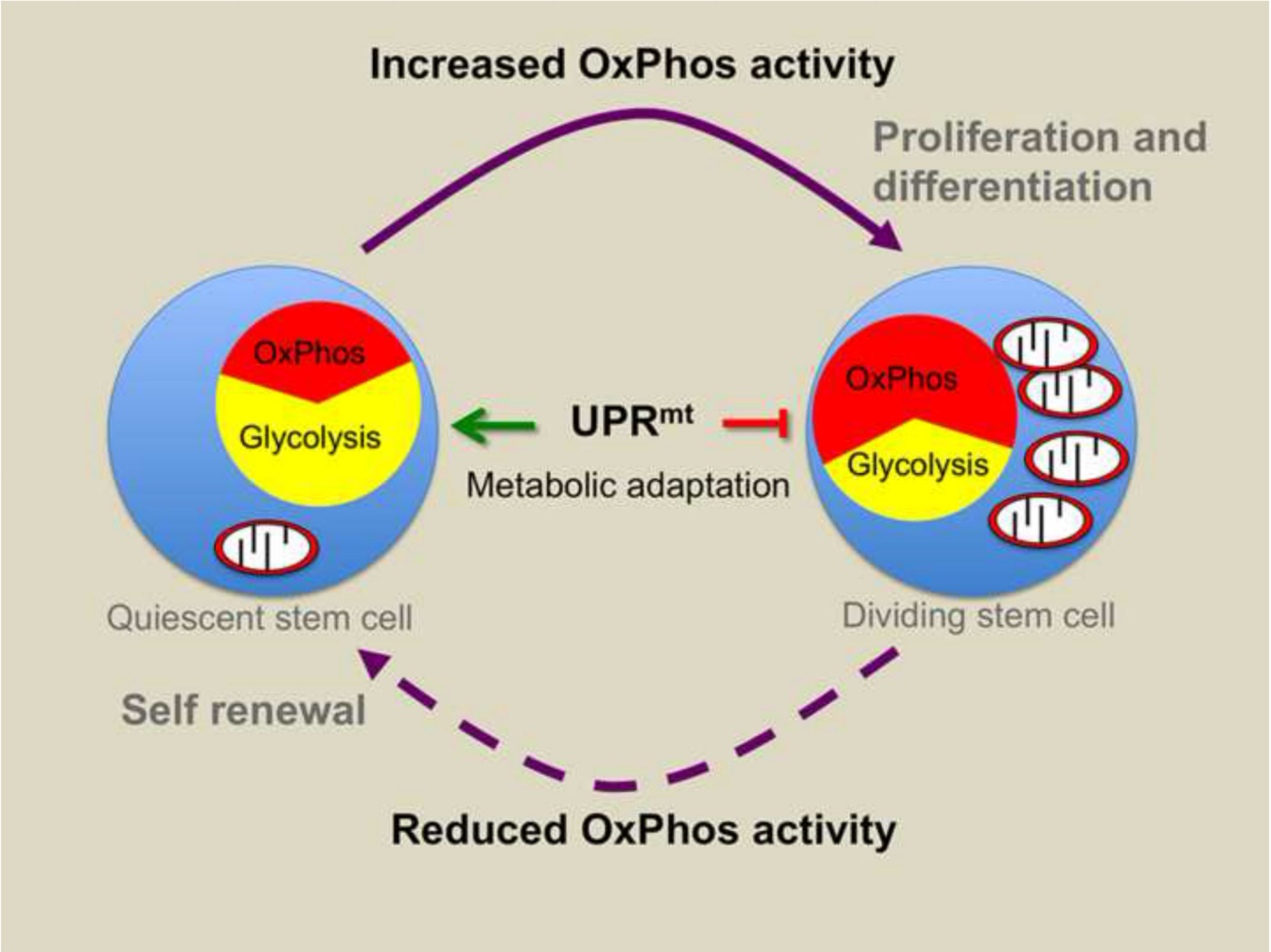

Figure 2. A metabolic checkpoint involving a UPR^{mt} via SIRT7 is required for stem cell maintainance

Quiescent stem cells rely heavily on glycolysis. However, stem cell proliferation and differentiation is accompanied by increased mitochondrial biogenesis and a shift to oxidative phosphorylation (OxPhos). SIRT7 is a histone deacetylase transcriptionally induced during the mitochondrial stress associated with mitochondrial biogenesis in proliferating hematopoietic stem cells (HSCs). SIRT7 expression is induced during mitochondrial unfolded protein stress potentially to reduce the number of OxPhos proteins expressed so as to not further perturb a dysfunctional protein folding environment. In the context of HSCs, SIRT7 promotes a pristine mitochondrial proteostasis environment, which also limits mitochondrial biogenesis, cell proliferation and differentiation.