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Cross talk between SOD1 and the mitochondrial UPR in cancer and neurodegeneration

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Abstract

The mitochondrial unfolded protein response (UPR^{mt}) is rapidly gaining attention. While the CHOP (ATF4/5) axis of the UPR^{mt} was the first to be described, other axes have subsequently been reported. Validation of this complex pathway in *C. elegans* has been extensively studied. However, validation of the UPR^{mt} in mouse models of disease known to implicate mitochondrial reprogramming or dysfunction, such as cancer and neurodegeneration, respectively, is only beginning to emerge. This review summarizes recent findings and highlights the major role of the superoxide dismutase SOD1 in the communication between the mitochondria and the nucleus in these settings. While SOD1 has mostly been studied in the context of familial amyotrophic lateral sclerosis (fALS), recent studies suggest that SOD1 may be a potentially important mediator of the UPR^{mt} and converge to emphasize an increasingly vital role of SOD1 as a therapeutic target in cancer.

Keywords

ROS; mitochondria; UPR^{mt}; SOD1; SOD2; SIRT3; estrogen receptor; cancer; ALS; neurodegeneration

Introduction

A common denominator between cancer and neurodegeneration is the elevation in oxidative stress through the formation of reactive oxygen species (ROS). As the activity of the electron transport chain, embedded in the mitochondrial inner membrane, is responsible for the production of the majority of ROS, mitochondria are especially prone to the effects of ROS. On one hand, increased ROS levels act as signaling molecules to promote cancer formation [1,2]. Notably, this increase in ROS facilitates the switch from oxidative phosphorylation to glycolysis through the stabilization of HIF1α [3,4]. On the other hand, oxidative stress leads to damage to lipids, DNA, and proteins and contributes to protein misfolding and complex misassembly[5]. Therefore, adaptive mechanisms including increased expression of

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antioxidant machinery, mitochondrial proteases and chaperones, mitochondrial biogenesis and mitophagy must be activated in order to restore mitochondrial fitness and avoid cellular death.

In recent years, the mitochondrial unfolded protein response (UPR^{mt}) has gained much attention as a complex response that orchestrates several signaling cascades in parallel to coordinate the up-regulation of these adaptive mechanisms. Since multiple sources of mitochondrial stress have now been reported to activate the UPR^{mt} and several axes have been described, suggestion to rename this response, the integrated mitochondrial stress response has obtained popularity. However, for the purpose of this review, we will refer to this pathway as the UPR^{mt}.

The mitochondrial unfolded protein response (UPR^{mt})

The UPR^{mt} was originally discovered by the Hoogenraad group using overexpression of the matrix misfolded protein OTC delta[6,7]. Using this system, they described a retrograde signaling axis from the mitochondria to the nucleus mediated through the transcription factor CHOP, resulting in the induction of mitochondrial proteases and chaperones such as ClpP, HSP10, and HSP60 [7–12] (Figure 1). Following this original finding of the CHOP axis of the UPR^{mt} in mammalian cells, much of the subsequent studies of the UPR^{mt} were performed in *C. elegans* using HSP60 as a reporter of UPR^{mt} activation. These important studies identified ATFS-1 and the DVE-1/UBL5 complex as transcriptional activators of the UPR^{mt} [11–16]. More recently, ATF5 was identified as the mammalian homolog of ATFS-1[17]. Since ATF5 works downstream of CHOP[16], the finding of ATF5 in the setting of the UPR^{mt} nicely complements the seminal finding of the Hoogenraad group. This axis of the UPR^{mt} has been extensively reviewed[18–26].

In mammalian cells, our group reported a SIRT3-axis of the UPR^{mt} ($UPR^{mt\text{-}SIRT3}$) using the same model system as the Hoogenraad group. We also reported that this axis is independent of the CHOP-axis, as inhibition of CHOP did not affect the SIRT3-axis and conversely inhibition of SIRT3 did not affect activation of markers of the CHOP-axis[27]. We found that the SIRT3-axis orchestrates the induction of antioxidant genes, notably the dismutase SOD2, mitochondrial biogenesis, and mitophagy[18,19,27–29] (Figure 1). A strikingly similar sirtuin axis of the UPR^{mt}, leading to activation of SOD2, has also been discovered in *C. elegans*, suggesting the evolutionary conservation of this signaling pathway[30].

We also reported an additional axis of the UPR^{mt}, which is regulated by the estrogen receptor alpha (ERα)[31]. Rather than promoting the activation of mitochondrial matrix chaperones and proteases, we found that this axis results in the activation of Akt by ROS, leading the phosphorylation of the ERα and the transcription of the IMS protease HTRA2/OMI, the mitochondria biogenesis transcription factor NRF1, as well as the up-regulation of the activity of the proteasome[31] (Figure 1). Further, in contrast to the discovery of the other axes of the UPR^{mt}, the ERα-axis was discovered using overexpression of misfolded proteins in the intermembrane space (IMS) of the mitochondria.

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The IMS of the mitochondria

As the mitochondria are composed of the inner membrane and outer membrane, the presence of such double membranes results in two sub-compartments; the space in between these membranes, therefore referred to as the intermembrane space (IMS) and the matrix. Most studies on the mitochondria focus on the matrix or components of the outer and inner membranes. Notably, the inner membrane is central to the study of the electron transport chain, and the outer membrane is important for regulation of mitochondrial fusion and fission[32]. The matrix has also been intensively studied due to its role in the Krebs cycle, amino acid metabolism, and mitochondrial DNA transcription and translation[32]. The IMS, on the other hand, is largely considered as a passive storage compartment for pro-apoptotic proteins. In contrast, the IMS comprises over one hundred proteins, accounting for approximately ten percent of the mitochondrial proteome[33]. These proteins are important in various functions such as ROS detoxification, ROS-mediated signaling, oxidative protein folding, protein import, electron transport chain assembly, transport of metabolites, and metabolism processes[32,34]. Collectively, these observations indicate that the IMS plays an active role in many mitochondrial processes and suggest that defects in the IMS have the potential to impact the entire organelle.

Given that the inner membrane of the mitochondria is the site of oxidative phosphorylation and that ROS is produced on both sides the electron transport chain[35], ROS accumulation also occurs in the IMS. In addition, oxidative protein folding in the IMS also contributes to ROS levels[34]. Collectively, the combined effects of the electron transport chain and oxidative folding make the IMS the most oxidative environment of any cellular compartment. Further, the IMS does not contain heat shock proteins and has a limited number of proteases involved in protein quality controls[32,33]. Since ROS can lead to oxidation of cysteine residues, misfolding, and aggregation[36], the IMS appears uniquely susceptible to the accumulation of misfolded proteins (Figure 2). The detrimental effect of the accumulation of misfolded proteins in the IMS is best illustrated by the role of misfolded copper/zinc superoxide dismutase (SOD1) in the IMS in familial ALS.

The role of SOD1

SOD1 is an abundant antioxidant enzyme responsible for the conversion of superoxide to hydrogen peroxide[36]. SOD1 is ubiquitously expressed in many cellular compartments, including the IMS of the mitochondria[37–41]. In contrast, the manganese superoxide SOD2 localizes exclusively to the matrix of the mitochondria[42]. The function of superoxide dismutases was first discovered by McCord and Fridovich[43], who established the landmark study in support of the oxidative toxicity theory. Subsequent studies revealed that SOD1 is a dimeric enzyme, containing a copper ion and zinc ion in its catalytic core and that its main function is to convert superoxide ($O_2^{\bullet -}$) into hydrogen peroxide (H_2O_2)[44]. The $O_2^{\bullet -}$ radical is directed to the catalytic site through a positively charged channel, where the dismutation reaction is catalyzed by the copper ion[45]. The copper chaperone CCS facilitates copper insertion and disulfide bridge formation in SOD1[46]. Copper/zinc insertion and proper formation of the SOD1 homodimer are important for its enzymatic activity[47]. SOD1 is

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predominantly a cytosolic protein, but is also localized in the nucleus, and the IMS of the mitochondria[37–41].

Many studies suggest that SOD1 plays a key role in protecting cells against oxidative damage[36,48–50]. For instance, overexpression of SOD1 in yeast confers resistance to oxidative stress[51]. Conversely, ablation of SOD1 in yeast leads to oxidative damage in the mitochondria[52–54]. In mammals, SOD1 knockout mice demonstrate widespread oxidative damage[49,55–57] and studies in normal human fibroblasts showed that knockdown of SOD1 induces senescence[58]. Emerging studies have also demonstrated that SOD1 is at the center of nutrient and oxygen sensing[59,60]. The Culotta group showed that SOD1 is important for transmitting signals from glucose and oxygen to repress respiration[59]. Another study showed that nutrient deprivation increases SOD1 activity to reduce oxidative damage and promote cell survival[60]. They report that mTORC1 regulates SOD1 activity through phosphorylation in response to nutrients[60]. In addition, they show that SOD1 activation promotes cell survival and tumor growth in the ischemic tumor microenvironment and protects against cell death by the chemotherapeutic agent cisplatin[60]. Taken together, SOD1 and its localization may play important roles in maintaining ROS levels below a critical threshold compatible with cell viability.

SOD1-G93A in familial ALS (fALS)

Amyotrophic lateral sclerosis (ALS), also known as Lou Gehrig's disease, is a fatal, neurodegenerative disease characterized by damage of motor neurons of the spinal cord, which leads to paralysis. While sporadic cases of no known etiology account for the majority of ALS cases, mutations in SOD1 are responsible for approximately 20% of familial ALS (fALS)[61,62]. More than 180 different causative mutations in the SOD1 gene have been identified in fALS patients[63]. It is widely accepted that SOD1-linked fALS is partly caused by a toxic gain-of-function of the SOD1 mutant rather than loss of function[62]. This interpretation is supported by the fact SOD1 mutants without enzymatic activity also cause ALS[64].

The exact mechanism by which SOD1-linked fALS mediates its effect remains incompletely understood but mitochondrial dysfunction has been shown to play a role[65–67]. In addition, mutant SOD1 has been shown to cause abnormalities in multiple organelles, such as the endoplasmic reticulum[68] and peroxisomes[65] in addition to the mitochondria[65–67,69–73]. Mutant SOD1 also affects neuronal cytoskeleton integrity, which potentially impairs normal trafficking along axons and dendrites[74]. Further, mutant SOD1 suppresses protein quality control[75], increases production of free radicals[76], activates pro-apoptotic signaling[77,78], deregulates multiple signaling pathways[79], and affects levels of critical transporters and receptors, such as astrocytic glutamate transporter and Glur2[80]. SOD1-linked fALS has also been demonstrated to be a cell non-autonomous disease, in which the mutant protein has been shown to be toxic in multiple cell types, such as glia and astrocytes, and mutant SOD1 is also secreted, which may stimulate neuroinflammatory responses, and the resulting effects are likely additive[81,82].

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The most commonly studied mutation in SOD1 is the G93A amino acid substitution[83]. The SOD1-G93A transgenic mouse model ubiquitously overexpresses the mutant SOD1 under the control of endogenous SOD1 promoter. SOD1-G93A mice recapitulate phenotypes associated with fALS in humans. They experience rapid motor neuron degeneration, resulting in onset of paralysis and depending on genetic background, die within four to five months of age[83]. Work from several groups in this mouse model has provided key insights into the role of mitochondrial dysfunction in SOD1-linked fALS. In the mitochondria, mutant SOD1 accumulates on the outer membrane where it interacts with important mitochondrial proteins such as Bcl2 and VDAC[69,70]. *In vitro* studies have also demonstrated that mitochondrial localization of mutant SOD1 impairs mitochondrial morphology and leads to cell death[66,67].

Mutant SOD1 has also been shown to accumulate in the IMS, where it has the potential to alter import, assembly, and maturation of mitochondrial proteins[47,84]. In agreement, mutant SOD1 specifically targeted to the IMS was shown to cause mitochondrial fragmentation and impaired mitochondrial dynamics and these lead to impairment in neuritic processes[47,84]. In addition, a new mouse model that expresses IMS-targeted mutant SOD1-G93A has been shown to develop similar ALS phenotypes, such as motor neuron defects and mitochondrial abnormalities, however symptoms develop much later[85]. These findings support a pathogenic role for accumulation of mutant SOD1 in the IMS.

SOD1-G93A in familial ALS and the UPR^{mt}

We have recently reported that IMS fraction of mutant SOD1 plays an important role in activation of the UPR^{mt} [86]. We reported that the UPR$^{mt\text{-}CHOP}$ axis is transiently activated in the spinal cord G93A-SOD1 mice in the late symptomatic phase. Most striking, we observed a significant sex difference in the activation of the UPR$^{mt\text{-}CHOP}$, where it was only significantly activated in female G93A-SOD1 mice but not in males[86]. In addition, we found that the female specific activation of the UPR^{mt} extended to the early activation of the UPR$^{mt\text{-}ER\alpha}$ axis. This was demonstrated by elevation in Akt phosphorylation, upregulation of NRF1, OMI, and proteasome activity in the spinal cord of female G93A-SOD1 mice[86]. The up-regulation of the proteasome correlated with a decrease in total ubiquitinated proteins in the spinal cords of female mice. Further, to ascertain whether the IMS fraction of mutant SOD1 was responsible for the activation of the UPR^{mt}, analysis of the UPR^{mt} was performed in the IMS-targeted G93A-SOD1 model. We found that in these mice, NRF1 was activated during the presymptomatic phase of the disease in both males and females, but only females showed an upregulation of OMI in the symptomatic phase[86]. These observations suggest that IMS-localized mutant SOD1 is sufficient to activate the UPR$^{mt\text{-}ER\alpha}$ *in vivo*. We further confirmed that ERα is required for protective effects of the UPR^{mt} by crossing the ERα knockout mice to the G93A-SOD1 mice. We found that the absence of ERα prevents the activation of the UPR$^{mt\text{-}ER\alpha}$ [86]. However, under these conditions, upregulation of the UPR$^{mt\text{-}CHOP}$ axis was observed, suggesting a compensatory mechanism of the activation of one axis in absence of another. The findings of our study provide the first demonstration of the activation of the UPR$^{mt\text{-}ER}$ axis in an *in vivo* model of fALS.

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Activation of the UPR^{mt} has also recently been identified in a novel mouse model of neurodegeneration. Work from the Manfredi lab has demonstrated that mutant CHCHD10 mice develop accumulation of misfolded proteins in affected tissue, and that this accumulation selectively aggregated in the mitochondria[87]. Similar to other models of neurodegeneration, this proteotoxic stress led to disruption of mitochondrial morphology and function[87]. Using RNA sequencing, they found that diseased tissue of CHCHD10 mutant mice show increased expression of CHOP and ATF5[87]. In addition, they also found that expression of various subunits of the ETC were downregulated, which further supports the notion that upregulation of the UPR^{mt} leads to a decrease in oxidative phosphorylation to limit oxidative stress[87]. These findings support the hypothesis that the UPR^{mt} plays an important role in maintaining mitochondrial proteostasis and integrity. Interestingly, female mice in this model showed delayed onset of disease, similar to the sex difference observed in the G93A fALS model. Whether the ERα axis of the UPR^{mt} plays a role in this sex difference in this new model has yet to be determined.

While the interest in SOD1 has largely been in the context of fALS, an emerging body of work is shedding light on the role of SOD1 in cancer biology.

The mitochondria and oxidative stress in cancer

Cancer cells are characterized by increased levels of ROS. While elevated levels of ROS can promote cancer cell proliferation by activating signaling pathways such as PI3K/AKT, excessive ROS can lead to cell death[1]. This increase in ROS, in addition to the switch to glycolysis, known as the Warburg effect, have led to the common misconception that in cancer cells mitochondria are non-essential. However, the importance of mitochondrial reprogramming to provide the metabolites required for the production of amino acids and lipids as the building blocks of rapidly dividing cells, is now appreciated. In the matrix, ROS levels are limited by antioxidant machinery regulated by the deacetylase SIRT3[19]. Notably, SIRT3 deacetylates and activates the manganese superoxide SOD2[88]. SOD2, similar to SOD1, catalyzes the conversion of superoxide to hydrogen peroxide. Additional mitochondrial matrix enzymes such as glutathione peroxidases, peroxiredoxins, and catalase reduce hydrogen peroxide to water. Numerous studies have focused on the role of the mitochondrial matrix antioxidant machinery in many diseases, including cancer[5,52,89–91].

The potential importance of SOD1 on mitochondrial function has been highlighted by recent work from the Haigis lab that showed that SIRT3 levels are decreased in 87% of breast cancers[92]. Considering that SIRT3 is important for the activation of SOD2, the observation that SIRT3 levels are low in breast cancer cells is in agreement with the reduced SOD2 activity in cancer. As a result, levels of ROS in the mitochondria of cancer cells are elevated. In addition, mutations in subunits of the electron transport chain in cancers also contribute to the accumulation of ROS in these cells [19,28,29]. One logical extension of these findings is that increasing levels of ROS in the IMS, which has limited antioxidant capacity, would likely lead to excessive oxidative stress in the mitochondria[93]. Several reports have now supported a critical role of SOD1 in cancer.

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SOD1 in cancer

Several groups have identified SOD1 as a potential therapeutic target in cancer. SOD1 was the top hit in an extensive high throughput small molecule screen in lung cancer cells, by the Varmus group. They identified LCS-1 (lung cancer screen-1) among 189,000 small molecules as a selective inhibitor of lung cancer cell growth[94,95]. Using affinity proteomics and gene expression analysis, they identified SOD1 as the target of LCS-1[95]. Their findings revealed that inhibition of SOD1 by siRNA inhibited growth of LCS-1 sensitive cell lines, and conversely, SOD1 overexpression increased lung cancer cell proliferation and decreased apoptosis[95]. More importantly, the Varmus group also found that LCS-1 is a potent growth inhibitor in most cell lines in the NCI-60 human tumor cell line panel, including breast cancer cell lines[95]. The findings support the previous finding that SOD1 is a potent anti-cancer target in leukemia[96]. Huang et al. reported that inhibition of SOD1 leads to accumulation of superoxide and oxidative damage and subsequent selective death of myeloid leukemia cell lines[96]. A recent study similarly demonstrated that inhibition of SOD1 decreases cell proliferation and enhanced the effects of the common leukemia chemotherapy agent cytarabine[97]. These data suggest an essential role for SOD1 in adaptation to oxidative stress in cancer cells.

In agreement with these findings, the Chandel group also showed that SOD1 is a potent therapeutic target in cancer. They confirmed that SOD1 inhibition by with shRNA or the SOD1 inhibitor ATN-224 induces cell death in various non-small-cell lung cancer cells lines, and had minimal effects on normal lung epithelial cells[98]. They found that inhibition of SOD1 by ATN-224 increases superoxide levels, which decreases the enzymatic activity of glutathione peroxidase, resulting in elevated hydrogen peroxide levels. They further showed that increased hydrogen peroxide levels leads to p38 MAPK activation and subsequently results in a decrease in the anti-apoptotic factor MCL1[98]. It was also recently reported that SOD1 inhibition in nasopharyngeal carcinoma inhibits cell growth and promotes apoptosis[99]. These observations suggest that one mechanism by which SOD1 inhibition reduces cancer cell growth is through apoptosis.

Our group has shown that treatment of breast cancer cells with LCS-1 leads to increased mitochondrial superoxide and altered mitochondrial morphology as indicated by increased fragmentation and matrix swelling[100]. These observations suggested that the mitochondrial IMS fraction of SOD1 may be of particular importance in cancer cells. Collectively, these results suggest that SOD1 may be a potent target in cancer, however, since all experimental evidence arose from work performed *in vitro*, a definitive demonstration of the role of SOD1 in cancer awaited evidence *in vivo*.

SOD1 is essential for oncogene-driven proliferation but not normal proliferation

The observation that SIRT3 and consequently SOD2 activity are decreased in 87% of breast cancers[92] led us to hypothesize that the resulting elevation in mitochondrial oxidative stress may be counterbalanced by SOD1 upregulation. Consistent with this idea, we found that SOD1 is overexpressed in a panel of breast cancer cell lines while SIRT3 is decreased

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compared to the non-malignant cell line MCF10A, which show high SIRT3 and low SOD1 expression levels[100]. We confirmed this inverse relationship of SIRT3 and SOD1 in panel of human breast tumor specimens by immunohistochemistry[100]. Further, we found that SOD1 is overexpressed in tumors of three independent mouse models of breast cancer (MMTV-Wnt, MMTV-erbB2, and MMTV-Myc), compared to normal mammary ducts that showed no detectable SOD1 levels[100]. Therefore, these results suggest that the upregulation SOD1 occurs frequently in breast cancer regardless of the subtype or the oncogene driving tumor progression.

Following these observations, we aimed at validating the role of SOD1 in breast cancer *in vivo*. We crossed the MMTV-Wnt and inducible MMTV-rtTa/TetO-NeuNT mice, which develop mammary tumors at high frequency, with SOD1 knockout mice. In both models, we found that absence of SOD1 abolishes mammary tumor formation[101]. Moreover, we show that genetic ablation of SOD1 is specific to oncogene-driven proliferation as hyperproliferation of the mammary gland ductal tree normally observed during pregnancy is not affected in absence of SOD1[101]. Further, the architecture and physiological functions of highly proliferative normal tissues such as the skin and the gut were also not affected. These results suggest that SOD1 is necessary for oncogene-driven proliferation but not normal proliferation.

We reasoned that increased mitochondrial ROS may be the factor that distinguishes oncogene–driven proliferation from normal proliferation. Indeed, we found that mitochondrial ROS is elevated upon oncogene activation but not during proliferation of the ductal epithelial cells during pregnancy. We then investigated the mode of cell death in absence of SOD1. Consistent with findings by other groups, we found that genetic ablation or pharmacological inhibition of SOD1 in cancer cells induces apoptosis. In addition, we found that SOD1 is critical to evade oncogene-induced senescence during transformation[101]. Finally, we validated our findings in human breast cancer patients. We found that high expression of SOD1 is associated with worse clinical outcomes, regardless of breast cancer subtype. These findings indicate that SOD1 may be essential for cancer cells to survive the elevation in oxidative stress observed during transformation and has the potential to be a selective target for cancer therapy.

Overexpression of SOD1 in the nucleus and the IMS may participate in the induction of the mitochondrial unfolded protein response

An incidental finding in our study of SOD1 in human primary breast cancers was the observation of a significant increase in SOD1 in both the mitochondria and the nucleus. Interestingly, SOD1 has been shown to bind the estrogen receptor alpha (ERα) when bound to DNA[102]. The interaction of SOD1 with ERα was also reported to increase the transcriptional activity of ERα[102]. It is therefore tempting to hypothesize that SOD1 may have multiple functions: first, its canonical function as a dismutase, in limiting oxidative damage; second, a signaling function through its accumulation in the IMS and the activation of the $UPR^{mt\text{-}ER\alpha}$ axis; and third, a role in the enhancement of the transcriptional activity of

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the ERα in the nucleus. Collectively, these functions will place SOD1 as a key regulator of the communication between the nucleus and the mitochondria.

Concluding Remarks

The interest in the study of the UPR^{mt} in cancer and neurodegenerative diseases is mounting. Our work in both fALS and cancer suggests that the IMS of the mitochondria may be an important sub-compartment to signal mitochondrial stress to the nucleus. The unique oxidative environment of the IMS combined with the absence of chaperones and the minimal number of proteases involved in protein quality control in this sub-compartment, synergize to prime the IMS for proteotoxic stress. We suggest that as a result, the IMS is ideal as a signaling sub-compartment. Our work indicates that SOD1 may play a key role in this mitochondria-nucleus communication signaling (Figure 3). Further, the involvement of the ERα in the UPR^{mt} and the finding of sex differences in its activation highlight the fact that much remains to be understood in this pathway and that its activation may be tissue and sex specific. Future investigations will be required to shed light on these possibilities.

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Highlights

The mitochondrial unfolded protein response (UPR^{mt}) is rapidly gaining attention. However, validation in mouse models of neurodegenerative diseases and cancer is only beginning to emerge. This review focuses on the recent studies describing the UPR^{mt} in mouse models of familial ALS and breast cancer, with a special focus on the role of the dismutase SOD1 in these settings.

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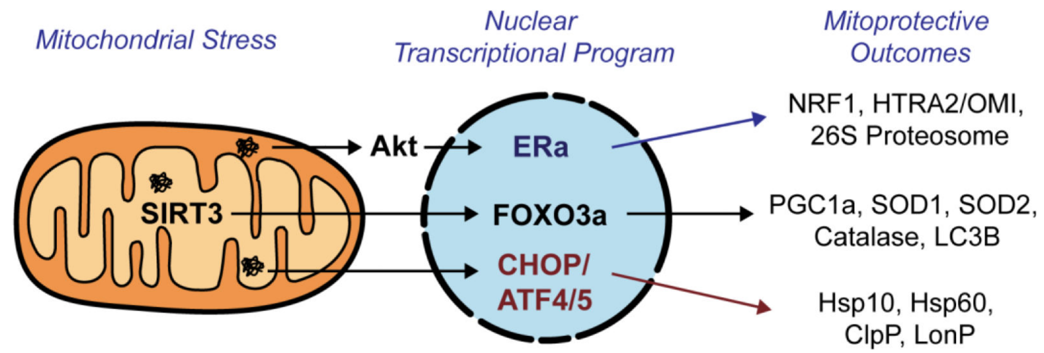

Figure 1. The mitochondrial unfolded protein response (UPR^{mt}).

Collectively, the three parallel axes of the UPR^{mt} coordinate a global mito-protective program against mitochondrial stress by activating antioxidant machinery, increasing protein quality control, inducing mitochondrial biogenesis, and promoting mitophagy.

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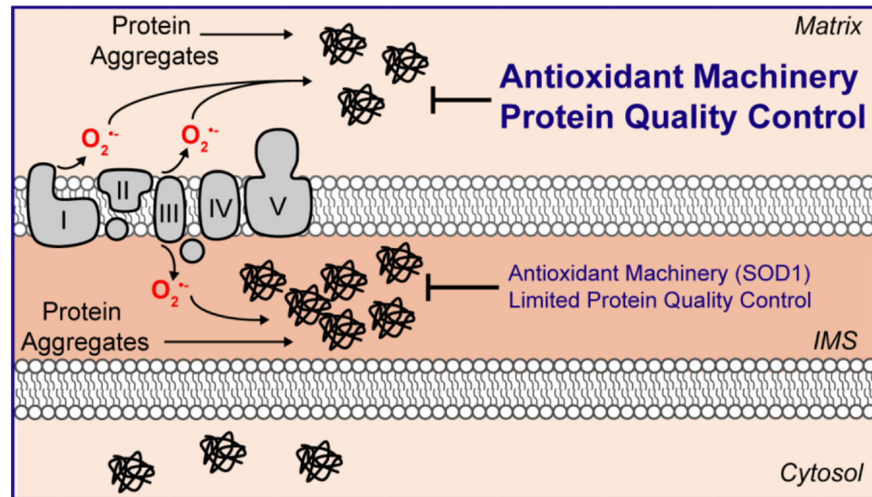

Figure 2. The IMS of the mitochondria is highly susceptible to proteotoxic stress.

The IMS of the mitochondria has limited protein quality control mechanism and poor antioxidant capacity, which makes this sub-compartment prone to the accumulation of misfolded proteins.

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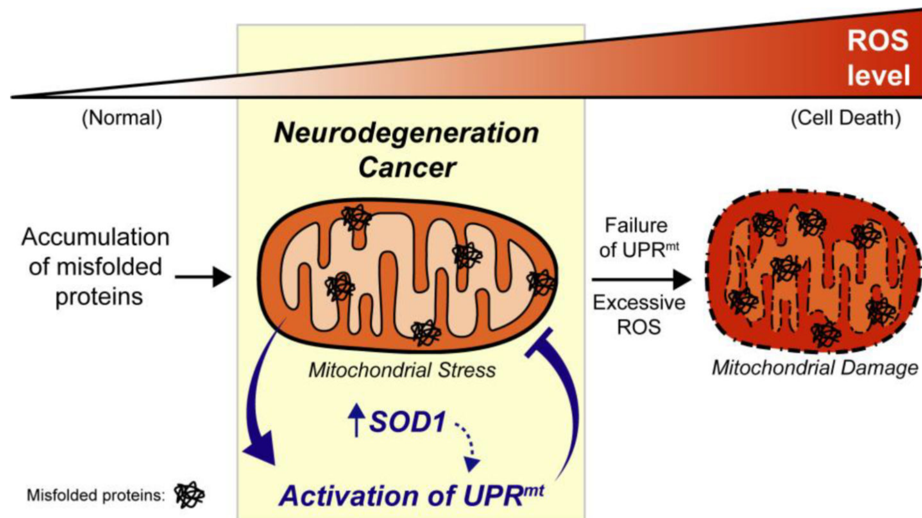

Figure 3. Crosstalk between SOD1 and the mitochondrial UPR in neurodegeneration and cancer.
Upregulation of SOD1 and activation of the UPR^{mt} protects cells from mitochondrial damage and cell death in models of neurodegeneration and cancer. It is possible that SOD1 plays a critical role in mito-nuclear communication as both a signaling function through its accumulation in the IMS and through enhancement of transcriptional activity of ERα, leading to activation of the UPR^{mt}.