A transition to degeneration triggered by oxidative stress in degenerative disorders

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Abstract

Although the activities of many signaling pathways are dysregulated during the progression of neurodegenerative and muscle degeneration disorders, the precise sequence of cellular events leading to degeneration have not been fully elucidated. Two kinases of particular interest, the growth-promoting Tor kinase and the energy sensor AMPK, appear to show reciprocal changes in activity during degeneration, with increased Tor activity and decreased AMPK activity reported. These changes in activity have been predicted to cause degeneration by attenuating autophagy, leading to accumulation of unfolded protein aggregates and dysfunctional mitochondria, the consequent increased production of reactive oxygen species (ROS), and ultimately oxidative damage. Here we propose that this increased ROS production not only causes oxidative damage but also ultimately induces an oxidative stress response that reactivates the redox-sensitive AMPK and activates the redox-sensitive stress kinase JNK. Activation of these kinases re-activates autophagy. Because at this late stage, cells have become filled with dysfunctional mitochondria and protein aggregates, which are autophagy targets, this autophagy reactivation induces degeneration. The mechanism proposed here emphasizes that the process of degeneration is dynamic, that dysregulated signaling pathways change over time and can transition from deleterious to beneficial and vice versa as degeneration progresses.

Similar signaling pathway disruptions are observed in neurodegenerative and muscle degenerative disorders

Although the neurodegenerative and muscle degenerative disorders such as Alzheimer's disease (AD), Parkinson's disease (PD) and muscle disuse/denervation atrophy (MDA) are distinct entities with unique properties, these various disorders display similarities in the types of signaling pathways and cellular processes that are disrupted. Here we describe how activities of two kinases, the growth-promoting kinase Tor (reviewed in Schmelzle and Hall[1]) and the AMP-activated kinase AMPK (reviewed in Hardie, 2011[2]), as well as the transcription factor Foxo change during degeneration (Figure 1A). We also describe

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evidence that these changes in activity have causal roles in promoting degeneration (Figure 1B).

a) Increasing Tor kinase activity, decreasing AMPK and Foxo activities, in degeneration

The Tor kinase is activated under conditions of rapid growth, and when active, increases growth rate and decreases stress resistance. Several investigators have reported the progressive activation of Tor during the progression of AD[3–5], PD[6–8], and MDA[9]. In contrast, activity of AMPK, which is activated in cells under energy stress and tends to inhibit growth, has been reported to decrease during degeneration in both AD and MDA[10, 11]. AMPK activity also decreases during aging[12, 13], which is a strong risk factor in all degenerative disorders. The transcription factor Foxo is also implicated in development and progression of degenerative disorders. Foxo is encoded by single genes in *C. elegans* and Drosophila, but in mammals comprises a family of related factors encoded by distinct genes. Foxo family members tend to be co-expressed within cells and exhibit functional redundancy[14], although discrete roles of specific family members are sometimes observed[15]. The effects of Foxo activity, which are growth inhibition, tumor suppression, and stress resistance[16], tend to be similar to those of AMPK but opposite to those of Tor. Although dynamics of Foxo activity during progression of most degenerative disorders have not been intensely studied, expression of the pro-apoptotic gene *beclin*, which is induced transcriptionally by Foxo[17], declines during AD development in the mouse model[18], which is consistent with a loss of Foxo activity in AD.

b) Effects of altered Tor, AMPK, and Foxo activities on degeneration

Several reports indicate that these changes in Tor, AMPK and Foxo activities have functional consequences, specifically that activating Tor or inhibiting either AMPK or Foxo promotes degeneration. Thus, therapeutic effects have been reported in rodent or Drosophila models of applying the Tor inhibitor rapamycin or of inhibiting Tor targets such as S6 Kinase. These observations suggest that Tor activation contributes to the pathology in these disorders[6, 9, 19–29]. In contrast, chemical or genetic activation of AMPK can be therapeutic in rodent or Drosophila degeneration models, whereas chemical inhibition of AMPK, or expression of a dominant negative AMPK transgene ($AMPK^{DN}$) can exacerbate degeneration in a PD cell culture model[30–33]. Similarly, many reports indicate that Foxo, like AMPK, has a protective role in degenerative disorders and that blocking Foxo can be deleterious. In particular, blocking Foxo activity by expressing a $Foxo^{DN}$ transgene induces ROS production and loss of dopaminergic neurons in the rat. Similarly, in Drosophila, the *Foxo* null mutation confers degeneration in a manner similar to loss of the PD gene *PINK1*[34, 35], whereas *Foxo*+ overexpression protects dopaminergic neurons from degeneration caused by *PINK1* mutations. Taken together, these results support the notion that the increasing Tor and the decreasing AMPK and Foxo activities observed in degeneration actively promote the degeneration process.

c) Cross-talk among Tor, AMPK and Foxo signaling molecules.

The opposing nature of AMPK and Foxo activities versus Tor is also revealed through cross-talk among these signaling molecules. AMPK inhibits Tor, both through direct Tor phosphorylation[36] and by phosphorylation and activation of the Tor inhibitor Tsc2[37].

Furthermore, AMPK directly phosphorylates each Foxo isoform[38] and activates Foxo1 and Foxo3[39, 40]. Thus, decreasing AMPK activity during degeneration might be responsible, at least in part, for the loss of Foxo activity and increased Tor activity observed during degeneration.

Disrupted autophagy is critical for driving degeneration forward

How might Tor activation, or AMPK or Foxo inhibition, contribute to progression of degenerative disorders? One pathway regulated in common by Tor, AMPK and Foxo is autophagy. Tor inhibits autophagy, whereas AMPK and Foxo each promote autophagy. In particular, Tor phosphorylates and inhibits the autophagy inducer ATG1 as well as ATG13[41, 42], whereas AMPK phosphorylates and activates ATG1[36, 43]. Foxo, in turn, activates autophagy by inducing transcription of critical autophagy genes such as LC3 (also known as ATG8) and ATG12[44]. These effects of Tor, AMPK and Foxo likely contribute to the defective autophagy observed in AD[45, 46] and PD[7, 26, 47]. This autophagy inhibition, in turn, likely contributes to the observed accumulation of protein aggregates containing poly-ubiquitin in AD[48] and α-synuclein in PD, as such aggregates are normally degraded by autophagy[49–55]. Given the toxic nature of these protein aggregates[56, 57] it is possible that the loss of autophagy and consequent accumulation of these aggregates contributes to degeneration.

A critical role for mitochondrial autophagy (mitophagy) in degeneration

However, some evidence indicates that deficits in one specific form of autophagy, mitochondrial autophagy (mitophagy) is particularly important for progression of degeneration. Mitophagy is a critical mitochondrial quality control process and disruptions of mitophagy increase the persistence of dysfunctional mitochondria[58]. In fact, both disrupted mitophagy and accumulation of dysfunctional mitochondria are widely observed in tissues from degenerating samples such as postmortem samples from AD patients, and in mouse AD models[59, 60]. These observations have led several investigators to suggest that disrupted mitophagy might be causal for AD pathology[61, 62]. Accumulation of dysfunctional mitochondria also plays a key role in the initiation of MDA as well[63, 64]. For example, Trevino et al., (2019)[65] reported that mitochondrial dysfunction was observed within three days of initiating muscle disuse in mice, and prior to onset of degeneration.

The importance of mitophagy in degeneration is most directly demonstrated for PD. At least two PD disease genes, *PINK1* and *Parkin*, encode proteins specifically required for mitophagy[66–68], and deficits in these genes are likely responsible for the attenuated mitophagy and mitochondrial dysfunction observed both in PD patients and animal models[30, 69–71]. Given that Foxo directly induces transcription of *PINK1*[72, 73], the loss of Foxo activity that occurs during degeneration is predicted to attenuate *PINK1* transcription and hence attenuate mitophagy.

Oxidative damage in degeneration

How might an accumulation of dysfunctional mitochondria cause degeneration? In addition to decreasing ATP production, dysfunctional mitochondria also increase production of reactive oxygen species (ROS)[74–77], which can lead to oxidative damage to proteins, lipids and nucleic acids. Such oxidative damage is widely observed in several different degenerative disorders, and the accumulation of damaged macromolecules has been implicated as causal for degeneration[63, 69, 70, 74–85].

A preliminary model for degeneration: loss of autophagy causes accumulation of protein aggregates and increases ROS production and oxidative damage.

These data support, as a first approximation, a model in which degeneration develops as a consequence of long-term Tor activation, and Foxo and AMPK inhibition. The consequent mitophagy inhibition causes accumulation of dysfunctional mitochondria that overproduce ROS and increase oxidative damage of essential cellular structures. Combining this increase in oxidative damage with inhibited general autophagy, which prevents the clearance of damaged molecules, leads to accumulation of aggregates containing damaged proteins. These various pathologies and stressors ultimately lead to cell death.

This model predicts that administering autophagy inducers such as the Tor inhibitor rapamycin would be beneficial for degenerative disorders[4, 86–88]. Such therapies have been administered in both animal models and human patients, albeit with variable results.

Not so fast……..

Despite its appeal, the simple model described above fails to explain several features of degenerative disorders and therefore requires modification. First, decreased mitophagy is not always observed in degenerating tissues, as increased mitophagy has been reported in some human AD postmortem samples[89, 90]. Second, deleterious effects of Tor on degeneration have not always been observed. For example, it was reported that Tor activation, via Cre-mediated deletion of the Tor repressor *PTEN*, protects dopaminergic neurons from degeneration in a mouse PD model[91]. Similarly, Tor inhibition was reported to exacerbate degeneration, rather than protect from degeneration, in certain animal PD models[92]. In addition, some reports have indicated that amyloid-β oligomers decrease, rather than increase Tor activity[93]. Third, several reports investigating a variety of cell types indicate that autophagy is not always protective in degenerative disorders, but rather can contribute to cell death[47, 94–99]. Finally, Foxo activity is not always beneficial in degenerative conditions, but rather shows a complex relationship with cell survival in degeneration models. For example, Foxo is activated late in the MDA process and directly triggers degeneration by inducing transcription of the genes encoding the ubiquitin ligases atrogin and MuRF1[9], while expressing a *Foxo^DN* transgene attenuates degeneration in MDA[100]. Foxo expression has also been reported to be up-regulated in both PD and AD brains[101, 102] and some

evidence indicates that this Foxo activation promotes apoptosis[102], thereby conferring deleterious effects on afflicted cells.

To resolve these apparent contradictions, several investigators have noted that changes in activity of Tor, AMPK and Foxo are not static, but rather can change as degeneration progresses. For example, Tor is activated early in MDA, but Foxo is activated late in this process[9]. In contrast, AMPK activity decreases early in MDA, but increases late in this process[11, 103].

These activity changes during disease progression were also reported to have important consequences on degeneration. As described above, the late stage Foxo activation during MDA is the proximate trigger for degeneration[9, 104]. In addition, it was proposed that both AMPK and Foxo transition from protective to deleterious during AD progression[33, 105]. Finally, it was suggested that administration of rapamycin might be beneficial early in degeneration, but might become ineffective late, when protein aggregates have stabilized and become too large for autophagy[4]. Taken together, these data indicate that the activities of Tor, AMPK and Foxo might confer distinct phenotypic consequences on degeneration dependent on timing, with AMPK and Foxo activities beneficial early in degeneration but deleterious late, and Tor demonstrating reciprocal effects. However, neither the timing nor the cellular changes underlying such an early to late transition have been identified.

Central hypothesis: induction of an oxidative stress response triggers an early to late transition during progression of degenerative disorders.

Taken together, the results described above suggest that degeneration comprises an early stage and a late stage. During the early stage, Tor activity increases while AMPK and Foxo activities decrease. As a result of impaired autophagy and mitophagy, protein aggregates and dysfunctional mitochondria accumulate. The increase in mitochondrial ROS generation caused by dysfunctional mitochondria progressively oxidizes the cytoplasm. We propose that this cytoplasmic oxidation ultimately becomes sufficient to induce an oxidative stress response. We hypothesize that the induction of this oxidative stress response marks the switch from the early to the late, degenerative, stage of degeneration. We suggest that oxidative stress induces the late, degenerative, stage by reactivating the redox-sensitive AMPK as well as by activating a second kinase, the stress- and redox-activated kinase JNK, which is described in more detail below. AMPK and JNK, in turn, together reactivate Foxo and inhibit Tor. We suggest that the consequent reactivation of autophagy and the proteasome during this late stage is the direct cause of degeneration (Figure 1). Below we describe the experimental data supporting this hypothesis.

Evidence supporting a role for oxidative stress in the transition to degeneration

a) Role of JNK in degeneration

Several reports indicate that JNK is activated in degenerative disorders, and that this activation participates in degeneration. In particular, JNK activation is observed both in

postmortem brain samples from AD patients[106–108] and in a transgenic mouse AD model[109]. Furthermore, the extent of JNK activity is correlated with the extent of cognitive decline as well as the levels of Aβ4 protein. Finally, inhibiting JNK in a mouse AD model restores normal synaptic function. These observations suggest a causal role for activated JNK in AD.

Similarly, studies in PD show that JNK inhibitors are protective in mouse MPTP models[110–112] and that JNK activation is required for degeneration in a PC12 PD model[113, 114].

Finally, a role for JNK activation is reported for MDA. JNK is activated in a rat disuse atrophy model[115]. In addition, it was reported that disuse atrophy activates JNK, which then activates Foxo indirectly, via phosphorylation of IRS-1, which detaches the insulin receptor from PI3K, thus preventing activation of the Foxo inhibitor Akt[116].

b) Activation of AMPK and JNK by oxidative stress.

Oxidative stress activates AMPK either via the upstream activating kinase ATM[36, 117, 118] or via direct oxidation[119]. Similarly, oxidative stress activates JNK[120] by relieving the JNK-activating kinase ASK1 from inhibition by reduced thioredoxin[121] or via the Ral GTPase[122].

c) Foxo activation and Tor inhibition by AMPK and JNK

As described above, AMPK inhibits Tor via direct phosphorylation or by activating the Tor inhibitor Tsc1/Tsc2 complex, whereas AMPK activates Foxo by direct phosphorylation. Furthermore, JNK activates Foxo4 by direct phosphorylation[122] and also activates Foxo1 and Foxo3[123, 124], possibly by phosphorylating the 14-3-3 scaffold to prevent Foxo binding[125]. Either phosphorylation event activates Foxo by causing its nuclear translocation, enabling transcription of target genes. This Foxo activation, combined with AMPK activation and Tor inhibition, is anticipated to re-activate autophagy, mitophagy, and the proteasome[122, 125–12844–46, 104].

The two faces of Foxo and AMPK: benevolent protectors and merciless executioners.

AMPK and Foxo are generally considered protective for organismal viability, longevity and stress resistance, whereas Tor is thought to promote growth at the expense of longevity and stress resistance. In particular, increasing either AMPK or Foxo activity, or inhibiting Tor, increases lifespan in model organisms[129–135]. Furthermore, administering the AMPK activator metformin or the Tor inhibitor rapamycin has likewise been reported to increase lifespan in both invertebrate and mammalian species[136–139]. Thus, it is well established that AMPK and Foxo, or inhibited Tor, are beneficial to organismal survival. How can the activation of these beneficial pathways be the proximate cause for the degeneration observed in degenerative conditions?

We propose that cellular context determines whether these AMPK, Tor, Foxo and autophagy activities are beneficial or deleterious (Figure 2). In particular, we propose that in young cells, few dysfunctional mitochondria and few oxidized, unfolded or aggregated proteins are

present. In this context, activating the AMPK/Foxo pathway increases lifespan and stress resistance by increasing the timely, autophagy-dependent removal of the few dysfunctional structures present (Figure 2, left panel). However, as cells age, progressively attenuating autophagy enables accumulation of aggregates of unfolded proteins and dysfunctional mitochondria (Figure 2, center panel); these mitochondria, albeit damaged, are generating ATP necessary for survival. Ultimately, the ROS generated by these dysfunctional mitochondria oxidize the cytoplasm sufficiently to induce an oxidative stress response. The consequent reactivation of autophagy and the proteasome now triggers removal of aggregates of unfolded proteins, other damaged cellular structures, and most importantly, the removal of damaged, but essential mitochondria (Figure 2, right panel). The result of this overzealous removal of these damaged structures is a precipitous decline in ATP production, degeneration and loss of cell viability.

This proposed mechanism supports the notion that decreased ATP production might underlie degeneration[140]. Despite intense investigation, the role of diminished energy production in degeneration has been difficult to demonstrate unambiguously, due in large part to lack of reporters with sufficient spatial and temporal precision. However, several indirect observations support the possibility that decreased energy utilization correlates with degeneration[140, 141]. These observations include reduced glucose uptake in degenerating neurons[142, 143], increased lactate accumulation in Huntington's Disease (HD) brains[144], low ATP levels in PD brains[145], and decreased ATP levels in *PINK1* knockout mice[146]. In addition, using a novel ATP reporter, Pathak et al.[147] showed decreased ATP production in the Leigh's neurodegenerative disorder. Taken together, these data are consistent with the possibility shown in Figure 2 that declining energy production at least partially underlies degeneration.

Differential sensitivity of various cell types to degeneration

It is not known with certainty why specific neuronal or muscle subtypes show differential sensitivity to degeneration. However, one possible explanation could be cell type specific expression of pro-degeneration genes. For example low expression of *PGC-1α*, which inhibits Foxo, could explain the increased sensitivity of 2B muscle fibers to degeneration[148]. In addition, neurons particularly sensitive to degeneration could have increased energy requirements, leading to increased sensitivity to mitochondrial stressors[141, 149]. In this regard, neurons exhibiting functional plasticity might be more sensitive to degeneration than others[150] because continuous retraction and regrowth of synapses could increase demand for ATP.

Oxidative stress-triggered degeneration induced by various causes

Although the mechanism shown in Figure 2 most directly relates to neurodegeneration caused by aging, other factors have been reported to advance the onset of neurodegenerative disorders. These include genetic factors, metabolic factors such as insulin resistance, or physiological factors such as neuroinflammation or accumulation of senescent cells[151–157]. In some cases, a direct link to altered Tor and Foxo signaling is apparent. For example, insulin resistance arises as a consequence of long-term increases in insulin signaling, which

activates Tor and inhibits Foxo. Such long-term increases in Tor activity and decreases in Foxo activity are predicted to accelerate progression through the early stage of degeneration (see Figure 1) and advance the onset of the late, degenerative stage. Likewise, results from a transgenic mouse model, in which mutant *Amyloid Precursor Protein* and *Presenilin-1* genes are co-overexpressed, support the notion that AD comprises an early stage of Tor activation and Foxo inhibition, followed by a late, degenerative stage of Tor inhibition and Foxo activation[158]. Thus, accelerating the changes in Tor and Foxo activities during the early stage might be a general property of factors that advance the onset of neurodegeneration. For other factors, although no obvious mechanisms directly link to Tor/Foxo/JNK signaling, many are predicted to induce oxidative stress, which would likewise advance the onset of the late, degenerative stage[159].

Oxidative stress-triggered degeneration in other neurodegenerative or muscle degeneration disorders

A similar involvement of oxidative stress, mitochondrial dysfunction and autophagy impairment contributes to the development and progression of other neurodegenerative disorders, such as HD and Amyotrophic Lateral Sclerosis (ALS)[160–169]. Furthermore, alterations in activities of Tor, AMPK and JNK have been observed in these disorders, with therapeutic effects of Tor, AMPK or JNK inhibition reported[170–173]. Consistent with the model presented in Figure 2 and with what was described above for MDA, AMPK activity suppresses HD phenotypes, in a Foxo-dependent manner, early in disease progression[174], while enhancing HD phenotypes late in disease progression[175]. These results suggest that transitions of signaling pathways from beneficial to deleterious or vice versa during disease progression might be a common property of neurodegenerative disorders.

ROS-induced oxidative stress and mitochondrial dysfunction have likewise been implicated in two additional muscle degeneration disorders, cachexia and sarcopenia[176–184]. In addition, previous reports indicate that both JNK and Foxo are activated during cancer cachexia, and this activation is required for the observed loss of muscle tissue[185–187]. These results are consistent with the role described above for JNK and Foxo in AD, PD and MDA. However, in cachexia, the transcription factor NF-κB is also activated, via ROS or TNF-α. This pathway appears to play a major role in degeneration via induced transcription of proteolysis genes[188–190]. This pathway might operate in parallel to a JNK-Foxo pathway in inducing degeneration.

Relevance to treatment of degenerative disorders

We emphasize that the progression of degeneration is a dynamic process; activities of specific signaling pathways change over time, and specific signaling pathways can transition from beneficial to deleterious, or vice versa, as degeneration progresses. Thus, for example, rapamycin or metformin administered early in disease progression might be beneficial, but deleterious when administered in the late stage. We anticipate that considering these timing issues will help clarify the roles of altered signaling molecule activity in progression of degenerative disorders.

Acknowledgements:

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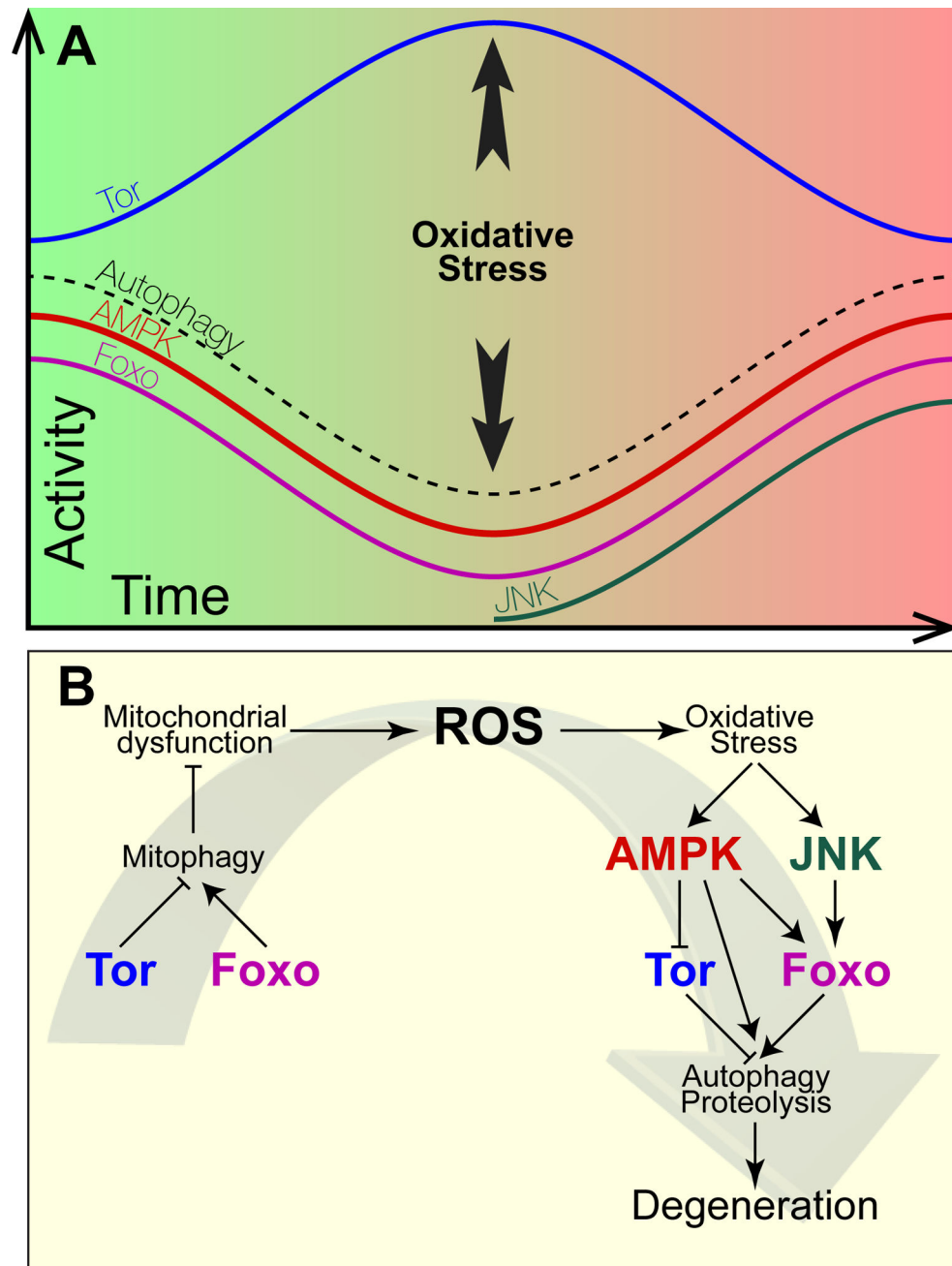
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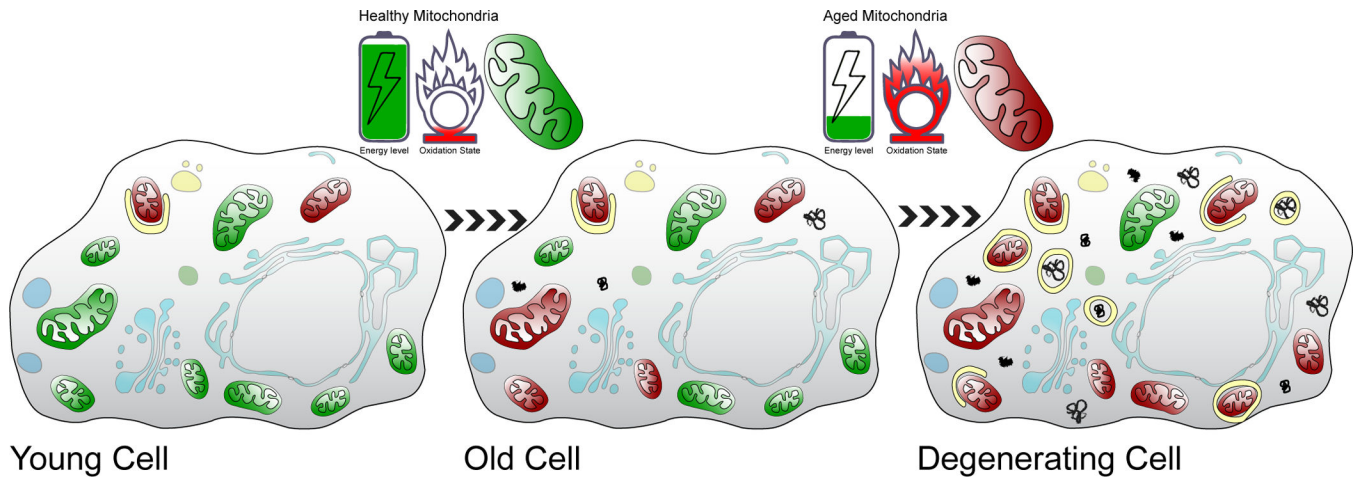
Figure 1:
Mechanisms regulating the changes in signaling pathway activities during progression of degeneration. Upper panel: Changes in activity of the indicated signaling molecules or processes as a function of time during the progression of degeneration. Green shading represents a reduced cytoplasm, red shading represents an oxidized cytoplasm. The time at which the appearance of the oxidative stress response, which activates AMPK and JNK, is indicated. Lower panel: Causal relationships among observed changes in signaling pathway activities. Bars indicate repression, arrows indicate activation.

Figure 2:

Accumulation of damaged structures during cell aging. Cells at three different stages (young, old and degenerating) are shown. Green mitochondria: healthy, polarized, non-oxidatively damaged. Red mitochondria: dysfunctional, depolarized, oxidatively damaged (see upper panels). Black shapes indicate protein aggregates. Yellow circles or semi-circles indicated autophagic vesicles. Shaded blue indicates other cellular structures.