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Protein Import Regulation of Mitochondrial Quality Control

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Mitochondrial protein import requires the electrical potential across the inner membrane to drive initial steps of insertion through the TIM import complex. If mitochondria are damaged to the extent they lose this membrane potential, PINK1 accumulates on the outer mitochondrial membrane from where it recruits and activates Parkin to initiate mitophagy, eliminating the damaged mitochondria. If membrane potential is decreased to a lesser extent, PINK1 continues to be imported, proteolytically clipped and degraded. However, the inner membrane bound protease Oma1, that is normally inactive under normal inner membrane potential, becomes activated by partially reduced membrane potential. Oma1 then cleaves Opa1 to prevent mitochondrial fusion isolating impaired mitochondria from the larger network. Activated Oma1 also cleaves the inner membrane space protein Dele1, which then relocalizes to the cytosol where it activates the integrated stress response and transcriptionally increases mitochondrial chaperones to address the stress. Oma1 also acts as a backup protease to eliminate PINK1 from partially impaired mitochondria.

Another form of mitochondrial stress stems from the plugging of the TOM or TIM import channels. In yeast several mechanisms have been identified depending on how mitochondrial import is prevented. We find a distinct mechanism that mammalian cells use to deal with plugged import complexes. Plugging the import channel does not activate PINK1 or the integrated stress response, but alters the import complex itself to decrease protein import.