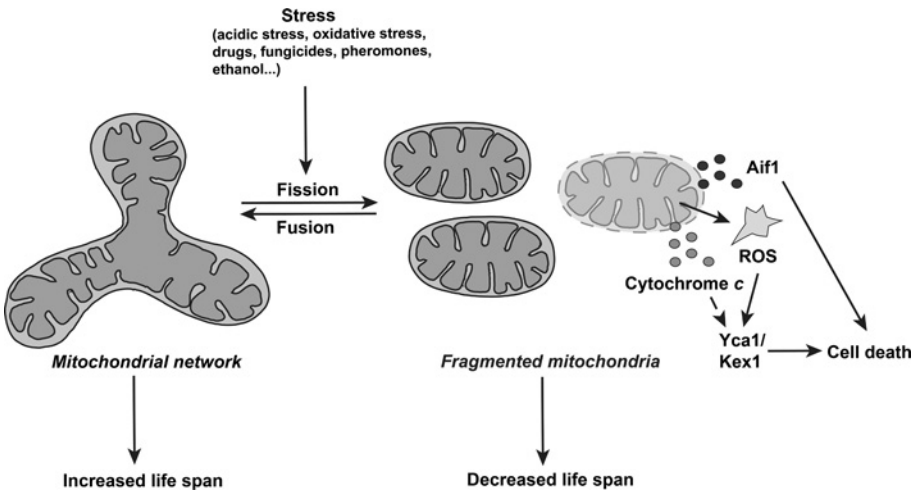
Figure 1 | **Mitochondrial fragmentation and aggregation during programmed cell death and aging in yeast**
See the main text for details.



the adaptor proteins Mdv1 or Caf4 to the outer membrane receptor Fis1 and forms a contractile ring that eventually promotes outer membrane division [25–27]. An increasing number of accessory and regulatory components are being identified to regulate the fusion and fission processes. These include the rhomboid-related membrane protease Pcp1, which processes Mgm1 [28], and the F-box protein Mdm30, a ubiquitin ligase subunit mediating the turnover of Fzo1 [29].

In the present review, we summarize abnormal mitochondrial morphologies that were observed in yeast models for programmed cell death and that link these morphologies with different cell death pathways. We focus on the effect of the mitochondrial fusion and fission balance on yeast cell death and aging, and we outline how these processes may be relevant under deleterious conditions.

Changes in mitochondrial morphology during yeast cell death and aging

Fragmentation of the mitochondrial network into multiple small organelles has been observed on treatment of yeast cells with multiple different stressors inducing programmed cell death (Figure 1; Table 1). Mitochondrial fragmentation occurs on (i) acidic stress, including acetic acid [16,30,31], propionic acid [16] and formic acid [32], (ii) oxidative stress (H_2O_2) [33], (iii) treatment with drugs and fungicides (amiodarone [9,15,16], bostrycin [34] and trichothecene [35]), (iv) yeast pheromones (α-factor) [9] and (v) ethanol [36]. A stringent correlation between mitochondrial fragmentation and yeast cell death was further observed in a variety of mutant yeast strains (Table 1), including strains with mutations in (i) rRNA genes (HsTnII) [37], (ii) mRNA turnover genes (*lsm4*) [38,39], (iii) genes involved in glycoprotein biosynthesis (*wbp1-1*) [14] and (iv) stress response genes (Δ*whi2*) [40]. Furthermore, cell death concomitant with mitochondrial fragmentation was observed in yeast cells overexpressing signalling kinases (*TPK3*) [41], sphingolipid-metabolizing enzymes (*YDC1*) [42] or overexpressing human proteins, including the pro-apoptotic protein BAX [43], and a Huntington's disease-causing variant of huntingtin [44]. Finally, yeast cells that enter the stationary phase and undergo chronological aging contain fragmented mitochondria [22,45]. The wide variety of death-inducing conditions that correlate with disruption of the mitochondrial network indicates that mitochondrial morphology is strongly influenced by the state of health of the cell. Conversely, conditions that trigger mitochondrial fragmentation frequently result in a decreased chronological lifespan [37–39,42].

In some of the cell death scenarios described above, mitochondrial fragmentation is superimposed by aberrant mitochondrial aggregation [40,41,44], which is an active process requiring the actin cytoskeleton [31,40,41]. Aggregated mitochondrial fragments accumulate on disruption of the mitochondrion degradation pathway [31,43], suggesting that most of these organelles are damaged and destined for degradation. Indeed, fragmented and/or aggregated mitochondria were found to be physically and functionally impaired during cell death (Figure 1; Table 1). Mitochondrial deterioration during cell death is characterized by the following events: loss of the mitochondrial membrane potential [32,37], which can be preceded by a strong increase [9], permeabilization of the mitochondrial outer membrane [31], release of cytochrome *c* [9,31] and loss of mtDNA [40]. As a consequence, cells undergoing cell death frequently become respiratory deficient [37,41]. Notably, the accumulation of ROS appears to be a general hallmark of cell death in cells with fragmented and/or aggregated mitochondria [9,14–16,32,34,36,38,39,41,44]. This suggests that damaged mitochondria are a major source of ROS during cell death and thereby actively contribute to the cellular demise (Figure 1).

Cell death correlated with mitochondrial fragmentation either depends on the activity of the yeast cell death protease