

# The dual role of cyclin C connects stress regulated gene expression to mitochondrial dynamics

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**ABSTRACT** Following exposure to cytotoxic agents, cellular damage is first recognized by a variety of sensor mechanisms. Thenceforth, the damage signal is transduced to the nucleus to install the correct gene expression program including the induction of genes whose products either detoxify destructive compounds or repair the damage they cause. Next, the stress signal is disseminated throughout the cell to effect the appropriate changes at organelles including the mitochondria. The mitochondria represent an important signaling platform for the stress response. An initial stress response of the mitochondria is extensive fragmentation. If the damage is prodigious, the mitochondria fragment (fission) and lose their outer membrane integrity leading to the release of pro-apoptotic factors necessary for programmed cell death (PCD) execution. As this complex biological process contains many moving parts, it must be exquisitely coordinated as the ultimate decision is life or death. The conserved C-type cyclin plays an important role in executing this molecular Rubicon by coupling changes in gene expression to mitochondrial fission and PCD. Cyclin C, along with its cyclin dependent kinase partner Cdk8, associates with the RNA polymerase holoenzyme to regulate transcription. In particular, cyclin C-Cdk8 repress many stress responsive genes. To relieve this repression, cyclin C is destroyed in cells exposed to pro-oxidants and other stressors. However, prior to its destruction, cyclin C, but not Cdk8, is released from its nuclear anchor (Med13), translocates from the nucleus to the cytoplasm where it interacts with the fission machinery and is both necessary and sufficient to induce extensive mitochondria fragmentation. Furthermore, cytoplasmic cyclin C promotes PCD indicating that it mediates both mitochondrial fission and cell death pathways. This review will summarize the role cyclin C plays in regulating stress-responsive transcription. In addition, we will detail this new function mediating mitochondrial fission and PCD. Although both these roles of cyclin C are conserved, this review will concentrate on cyclin C's dual role in the budding yeast *Saccharomyces cerevisiae*.

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**Abbreviations:**

PCD - programmed cell death,

Cdks - cyclin dependent kinases,

CWI - cell wall integrity.

## ROLE 1: Cyclin C IS A TRANSCRIPTION FACTOR REPRESSING STRESS-RESPONSIVE GENES

### Cyclin C-Cdk8 kinase is a part of the Mediator complex

The cyclin protein family was initially identified as promoters of cell cycle progression by binding and activating cyclin dependent kinases (Cdks). As indicated by their name, cyclins display a periodic expression pattern with their levels peaking at specific stages during mitotic cell division (reviewed in [1]). However, other cyclin-Cdk kinases were

subsequently discovered that regulate transcription rather than cell cycle progression [2, 3]. This group, cyclin C-Cdk8, cyclin H-Cdk7 and cyclin T-Cdk9 also share a commonality by associating with the RNA polymerase II machinery. Of these, cyclin C-Cdk8 share the most sequence conservation from yeast to man [4]. Structural analysis revealed specific determinants that promote cyclin C-Cdk8 interaction [5, 6]. In addition, unlike other Cdks, Cdk8 does not require phosphorylation of the canonical T-loop for activation. Rather,



*N*-glycosylation is important for Mtl1 function, as mutating the receptor residue (Asn42) or an enzyme required for synthesis of *N*-acetylglucosamine (Gfa1) reduces sensor activity [48]. These results provide a mechanism by which the cell is able to discern high- from low-level ROS damage to mediate cyclin C destruction.

Similar to activation of other transcription factors regulated by this pathway, the route the stress signal takes from Pkc1p to cyclin C is bifurcated at the MAP kinase step. The Slit2 MAPK directly phosphorylates cyclin C at Ser266 [49]. Eliminating this phosphorylation site prevents cyclin C proteolysis while a phosphomimetic mutation enhances its destruction kinetics. Conversely, the pseudokinase Kdx1 interacts with Ask10, a previously identified cyclin C associating factor [50]. Ask10 is required for efficient cyclin C destruction and is phosphorylated in response to H<sub>2</sub>O<sub>2</sub> [49, 50]. Interestingly, Ask10 phosphorylation requires the MEKs Mkk1 and Mkk2, the pseudokinase Kdx1, but not Slit2 [49, 50]. Therefore, these results suggest the activity of another, unknown kinase in modifying Ask10 and controlling cyclin C destruction (Figure 2). Thus, cyclin C regulation is complex, as both Slit2 and Kdx1 are required for cyclin C destruction but do so through direct and indirect mechanisms, respectively. These findings emphasize that the molecular decision to destroy cyclin C is carefully regulated to prevent aberrant derepression of stress response genes.

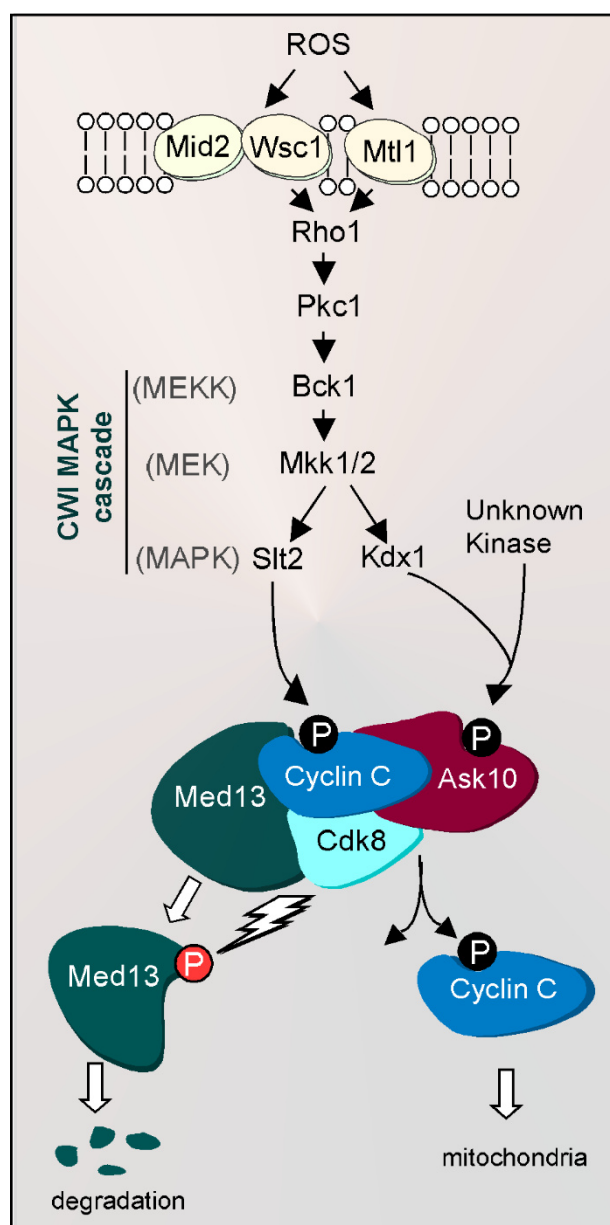
## ROLE 2: Cyclin C MEDIATES STRESS-INDUCED MITOCHONDRIA HYPER-FISSION

### Stress-induced mitochondrial dynamics

Similar to mammalian cells, yeast mitochondria serve as a signaling platform to both receive and send stress signals. Under normal growth conditions, mitochondria are usually observed in a more connected, reticular morphology (fusion) that enables maximum ATP production and the repair of mtDNA or damaged membranes by associating organelles. Conversely, mitochondrial fission allows isolation of defective organelles for removal via autophagy [51] or their efficient segregation at mitosis. However, in response to a variety of cytotoxic agents, the mitochondria undergo extensive fragmentation (Figure 3, see [52, 53] for reviews). This hyper-fission is an important first step in the stress response pathway and observed in all organisms examined. Since the same machinery is utilized to execute normal mitochondrial division and hyper-fission, a stress-induced trigger for this process must be necessary.

### Mitochondrial division machinery

Mitochondrial fission requires the conserved dynamin-like GTPase Dnm1. Dnm1 is recruited to the mitochondria by the outer membrane receptor Fis1 through one of two WD-40 adaptor proteins, Mdv1 [54, 55] or Caf4 [56]. Functionally, Mdv1 acts as a nucleation factor for GTP bound Dnm1, recruiting it to the membrane via its C-terminal domain [57, 58], and promoting Dnm1 to form spirals encircling the mitochondria [59]. GTP hydrolysis causes ring constriction that promotes scission [60]. X-ray structure analysis has revealed that Mdv1 dimerizes in an antiparal-



**FIGURE 2: Regulation of cyclin C relocation by the cell wall integrity pathway following H<sub>2</sub>O<sub>2</sub> stress.** H<sub>2</sub>O<sub>2</sub>-induced damage is recognized by the cell wall sensors Wsc1, Mid2 and Mtl1. These sensors transmit the stress signal via Rho1 to the Cell Wall Integrity (CWI) MAPK pathway resulting in the phosphorylation of Slit2 and Kdx1 (P). Activated Slit2 translocates to the nucleus and phosphorylates cyclin C at serine 266. Activated Kdx1 is also imported into the nucleus where it binds Ask10, which permits Ask10 phosphorylation by an unknown kinase. CWI activation leads to cyclin C translocation to cytoplasmic where it associates with the fission machinery to induce mitochondrial fission. Following fission, cyclin C is ultimately degraded via ubiquitin-mediated proteolysis. In addition, cyclin C-Cdk8 activity is required for ubiquitin-mediated Med13 proteolysis, an event that is required for cyclin C's release from the mediator complex.

lel coiled coil [61]. This coiled-coil domain also promotes assembly of Dnm1 oligomers, thus is important for fila-

ment formation. Caf4 also recruits Dnm1 to the mitochondria [56, 62-64]. However, phenotypes associated with loss of Mdv1 function are more severe than in *caf4Δ* strains suggesting that Mdv1 plays a more essential role in fission [55, 65].

### Mitochondrial division machinery and PCD

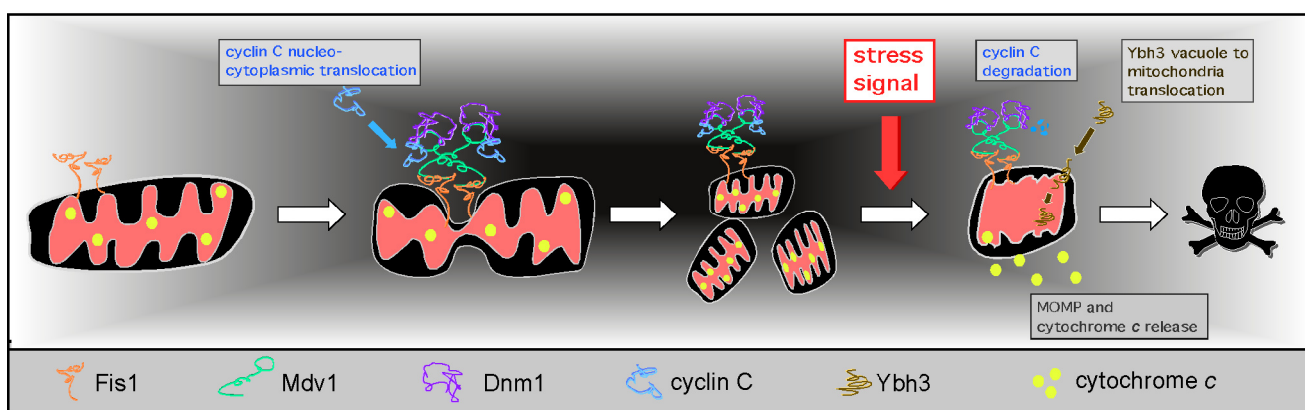
As described above, exposure to adverse environmental conditions shifts the delicate balance between fission and fusion dramatically toward fission [52]. In yeast and higher eukaryotes, hyper-fission is proposed to be part of the process that leads to loss of mitochondrial membrane integrity and subsequent release of pro-apoptotic factors required for PCD execution. Many basic players in the PCD pathway have been conserved from yeast to humans such as caspases (reviewed in [66]), a Bcl-2 family member [67] and the nucleases Nuc1p and Aif1p that are responsible for chromatin cleavage (reviewed in [68, 69]). However, some important mammalian PCD regulators (e.g., p53, SMAC) have not been identified to date in yeast. Consistent with a functional connection between hyper-fission and PCD, inactivating Dnm1 in yeast or its paralog in mammalian cells (Drp1) protects cells from PCD-inducing agents [70, 71]. However, other reports have found that hyper-fission is not required for the release of all pro-apoptotic factors [72, 73] suggesting that there may not be an absolute connection between the two processes.

### Cytoplasmic localization of cyclin C directs stress-induced mitochondrial hyper-fission and programmed cell death

Several observations indicate that cyclin C directs stress-induced mitochondrial fission. First, before it is destroyed, cyclin C (but not Cdk8) translocates to the cytoplasm [31] where it associates with the mitochondria [74]. This latter study found that cyclin C is both necessary and sufficient for inducing extensive mitochondrial fragmentation. A

mechanism to explain the role of cyclin C in mediating stress-induced fission is suggested by co-immunoprecipitation studies revealing that cyclin C associates with the fission machinery and is required for enhanced association of Dnm1 and Mdv1 in stressed cultures [74]. In addition, it was shown that cyclin C-Dnm1 association does not require mitochondrial association as the interaction was detected in *fis1Δ* mutant strains. In addition, Dnm1 forms large, non-functional aggregates in cyclin C mutants. These findings indicate that cyclin C is required for normal assembly of functional Dnm1 filaments in stressed cells.

As indicated earlier, mitochondrial fission is associated with the initial stages of PCD. If there is causation between the two events, cyclin C would be predicted to be required for normal PCD execution. This is indeed the case as yeast strains lacking cyclin C are more resistant to ROS-induced programmed cell death [75]. However, ectopically inducing extensive fission by overexpressing cyclin C does not induce PCD [74] indicating that fission itself is not a commitment point for PCD execution in yeast. These findings suggest a two-step model for cyclin C-induced PCD. First, cyclin C localization to the mitochondria induces extensive fragmentation of this organelle. However, another cellular damage signal is required for the cell to commit to the cell death pathway. The nature of this signal is unknown at present. Interestingly, these results are different than those obtained with other PCD inducers that function at the mitochondria. For example, ectopically targeting p53 or bax to the mitochondria in non-stressed cells is sufficient to induce cell death [76, 77]. Likewise, overexpression of the yeast BH3 domain protein (Ybh3) is also sufficient to induce cell death [66]. Therefore, cyclin C appears to represent a different class of regulator that is necessary and sufficient for hyper-fission but only necessary for efficient PCD.



**FIGURE 3: Cyclin C regulation of mitochondrial morphology and PCD following ROS stress.** Upon release from the mediator complex, cyclin C enters the cytoplasm where it associates with Mdv1 promoting Mdv1-Dnm1 complex formation and extensive mitochondrial fragmentation. Thereafter, cyclin C disassociates from the fission complex and is destroyed by ubiquitin-mediated degradation. An additional stress signal, in combination with hyper-fission and Ybh3 localization to the mitochondria, is needed to complete the PCD pathway (represented by MOMP and cytochrome c release).

### Med13p anchors cyclin C in the nucleus in unstressed cells.

As stated above, in the nucleus, cyclin C-Cdk8 are components of a subcomplex of the mediator composed of Med12 and Med13. Recent studies have revealed that Med13 functions as an anchor protein that retains cyclin C in the nucleus in unstressed cultures [78]. Deleting *MED13* allows constitutive cytoplasmic localization of cyclin C resulting in continuously fragmented mitochondria. The consequence of constant mitochondrial fragmentation is a loss of organelle function due to mtDNA deletions and a hypersensitivity to oxidative stress. To dissolve cyclin C-Med13 interaction, Med13 is subjected to ubiquitin-mediated destruction that is dependent on Cdk8 activity. In yeast strains expressing a kinase dead derivative of Cdk8, Med13 destruction is abrogated and cyclin C fails to leave the nucleus or nucleolus (Figure 2). Therefore, cyclin C release from the nucleus requires Slt2 phosphorylation and Med13 destruction, perhaps mediated by Cdk8 phosphorylation. These findings elaborate a complicated biochemical switch controlling cyclin C release that involves multiple signal transduction pathways and proteins that interact directly with cyclin C.

### CONCLUSIONS AND FUTURE PERSPECTIVES

In response to stress, the cell must sense cellular damage, transmit this signal to the nucleus to alter gene expression programs, then finally alert the remainder of the cell to the damage. In the case of cyclin C, the cell has utilized relocalization strategies to solve this problem. Following the upstream and downstream components of this regulatory system, we observe an example of how the cell has been able to integrate multiple functions into a single protein. Being a single cell organism, yeast routinely encounters cytotoxic compounds that alter membrane fluidity, generating a signal that is transduced to the nucleus (Figure 3). In the nucleus, cyclin C phosphorylation induces its release from the nucleus resulting in derepression of stress response genes through inactivation of Cdk8p. In addition, its relocalization to the mitochondria represents an intracellular signal inducing extensive remodeling of the organelle that may result in cell death. This dual role for cyclin C allows the cell to couple gene expression with organelle dy-

namics to produce a coordinated response. In addition, both roles for cyclin C have been conserved in human cells (our unpublished results). These observations indicate that cyclin C-dependent control of transcription and mitochondrial dynamics is a very ancient process. It is clear that as metazoans developed, additional regulatory layers were applied to both transcriptional and PCD control. However, using yeast as a model has allowed the field to peel back the years to distill the basic regulatory and mechanistic threads of these diverse processes. Such knowledge will be important not only to provide a basic understanding of how these critical events are orchestrated, but also will help identify new players in these pathways that may provide new strategies to attack diseases such as cancer. For example, the ability to manipulate cyclin C localization affects cellular sensitivity to cytotoxic agents. Therefore, only a detailed knowledge of how this system works in normal cells will allow rational designs of potential therapeutics to be realized.

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### CONFLICT OF INTEREST

The authors declare no conflict of interest.

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