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Snf1 Dependent Destruction of Med13 is Required for Programmed Cell Death Following Oxidative Stress in Yeast

Stephen D Willis
Rowan University School of Osteopathic Medicine

David C Stieg
Rowan University School of Osteopathic Medicine

R. Shah
Rowan University

Randy Strich
Rowan University School of Osteopathic Medicine

Katrina F Cooper
Rowan University School of Osteopathic Medicine

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Snf1 dependent destruction of Med13 is required for programmed cell death following oxidative stress in yeast.

S.D. Willis[1], D.C. Stieg[1], R. Shah[1], A.K. Strich[1], K.F. Cooper[1];
[1]Molecular Biology, Rowan University, Stratford, NJ

All eukaryotic cells, when faced with unfavorable environmental conditions have to decide whether to mount a survival or cell death response. The conserved cyclin C and its kinase partner Cdk8 play a key role in this decision. Both are members of the Cdk8 kinase module that, along with Med12 and Med13, associate with the core mediator complex of RNA polymerase II. In *S. cerevisiae*, oxidative stress triggers Med13 destruction[1], which thereafter releases cyclin C into the cytoplasm. Cytoplasmic cyclin C associates with mitochondria where it induces hyper-fragmentation and programmed cell death[2]. This suggests a model in which oxidative stress mediated destruction of Med13 represents a key molecular switch which commits the cell to programmed cell death. Thus it is important to decipher the precise molecular mechanisms that control Med13 destruction following exposure to oxidative stress.
Previous studies have revealed that both cyclin C/Cdk8 and Slt2, the MAPK of the cell wall integrity pathway, are required for the SCF^{Grr1} mediated destruction of Med13 following oxidative stress[3]. Here we show that the conserved AMP kinase Snf1 is also required for this event[4]. Deletion of Snf1 results in stable Med13 protein levels and predominantly reticular mitochondria morphology following H_2O_2 treatment. Consistent with this, deletion of Sak1, a Snf1 activating kinase or using the inactive snf1K84R mutant as the only source of Snf1 results in the same phenotypes. Deletion analysis has revealed that the Snf1 degron lies adjacent to the Slt2 degron and contains a potential Snf1 phosphorylation site. Taken together, these results suggest that ubiquitin mediated destruction of Med13 is very tightly controlled, requiring the action of 3 different kinases. As Med13 destruction results in cyclin C nuclear translocation these results support a model in which Med13 degradation plays a key role in controlling a molecular switch that dictates cell fate following exposure to adverse environments.

[1]Mol. Biol. Cell (2014) 25:2807, [2]Dev. Cell. (2014), 28:161, [3]Mol. Biol. Cell . (2017) *submitted*, [4]Oxid Med Cell Longev. (2017) *submitted.*

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