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A Radical Signal Activates the Epigenetic Regulation of Longevity

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Hormesis is an adaptive stress response implicated in longevity regulation. Schroeder et al. (2013) have now connected stress, epigenetic changes, and aging in yeast by showing that mitochondria-derived reactive oxygen species modulate the chromatin binding capacity of the histone demethylase Rph1p at subtelomeres, resulting in lifespan extension.

Reactive oxygen species (ROS), including superoxide and other free radicals, byproducts of mitochondrial respiration (mtROS), and also products of extramitochondrial enzymes, are central culprits in the macromolecular damage associated with aging in virtually every organism studied. Hormesis, the adaptive response to moderate levels of stress caused by ROS, has long been implicated in the induction of cellular protection, and several recent reports demonstrate that these protective effects are sufficient to delay aging in model organisms (Pan et al., 2011). An increase in mtROS, produced during the early growth and survival phases, was shown to reduce mtROS at later stages of survival, and extends longevity (Pan et al., 2011), in agreement with a central role for ROS in promoting yeast aging (Fabrizio et al., 2001). This early mtROS signal was suggested to be one of the mechanisms by which reduced activity of Tor, a conserved protein that promotes aging in many organisms, extends yeast chronological lifespan (Pan et al., 2011). A growing body of evidence also implicates epigenetic alterations in the aging process in both mammalian cells and model organisms (Dang et al., 2009). The epigenetic control of lifespan in worms was shown to be long lasting and transgenerational (Greer et al., 2011), and in mammals, alteration of the DNA methylation pattern has been repeatedly associated with gene expression modification during the aging process (Hannum et al., 2013).

In this issue of *Cell Metabolism*, Schroeder and coworkers provide clear evidence linking hormesis to the epigenetic regulation of aging by defining a pathway in which ROS modulate the activity of the Rph1 demethylase specifically at subtelomeres to remodel chromatin and extend lifespan (Schroeder et al., 2013). The authors first analyzed two published microarrays reporting gene expression changes in response to mtROS and identified two promoter motifs enriched in the affected genes, implicating the usual suspects, stress resistance transcription factors Gis1 and Msn2/Msn4, which are known to play central roles in the lifespan extension mediated by both calorie restriction (CR) and inactivation of antiaging pathways (Fabrizio et al., 2001) (Figure 1). Two of these pathways, Ras-cAMP-PKA, activated by glucose, and Tor-Sch9, activated by both amino acids and glucose, promote aging by causing the inactivation of the serine threonine kinase Rim15 and of transcription factors Msn2/Msn4 and Gis1, which in turn control many stress resistance genes, including the mitochondrial antioxidant enzyme superoxide dismutase 2 (SOD2) (Figure 1). However, Schroeder et al. found that Gis1 and Msn2/Msn4 together accounted for only 50% of the mtROS-dependent longevity extension. The search for other genes responsible for the hormesis effect resulted in the identification of a novel Rph1 demethylase-dependent coregulation of lifespan extension. mtROS were linked to Rph1 and longevity extension via the DNA damage response proteins Rad53 and Tel1, the yeast orthologs of mammalian ATM and Chk2. Tel1 phosphorylates Rad53, which in turn phosphorylates Rph1 to cause subtelomeric transcriptional repression (Figure 1). Deletion of Rad53 or Tel1 erased the mtROS-dependent effect on lifespan in agreement with the increased expression of Tel1 in the major yeast long-lived mutants lacking Tor, Sch9, or Ras2 (Madia et al., 2009). Notably, analysis of the Tel1 phosphorylation site in Rad53 indicated that the ROS hormesis effect did not match that caused by a DNA damaging agent and that the transcriptional effects of ROS were distinct from those caused by DNA damage. These findings led the authors to conclude that the hormetic effect of ROS does not require, nor is it initiated by, DNA damage.

One of the epigenetic mechanisms connecting Rph1 inactivation and longevity described by Schroeder et al. is the recruitment of the Sir silencing complex to the subtelomeric regions. In yeast, the Sir2 NAD^+-dependent histone deacetylase has been implicated in subtelomeric silencing and longevity regulation. However, the role of Sir2 in aging is not clear, since Sir2 deficiency shortens replicative lifespan but extends chronological lifespan when combined with calorie restriction or mutations in the Tor-Sch9 pathway (Bitterman et al., 2003; Fabrizio et al., 2005). Schroeder et al. performed ChIP experiments revealing that ROS treatment enhances the association of the Sir2-binding protein

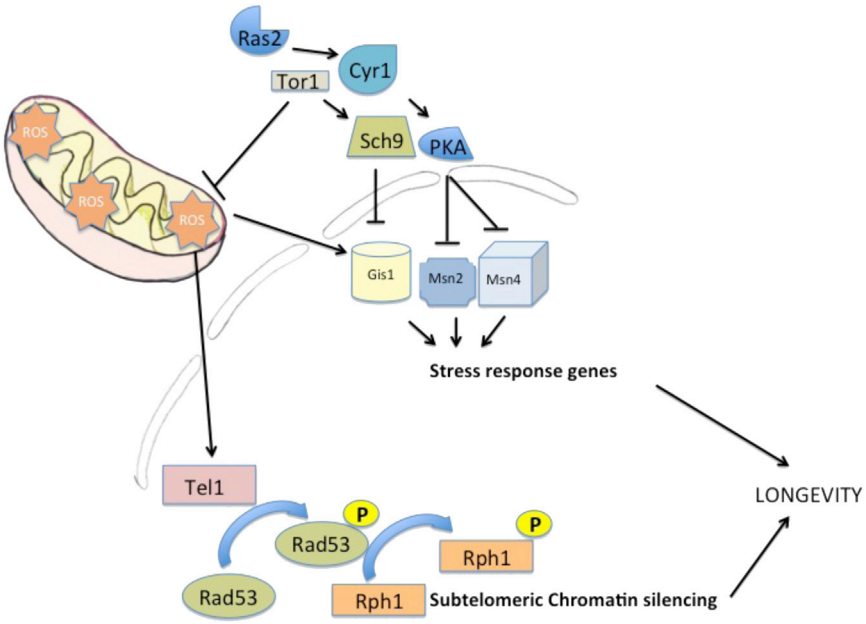

Figure 1. ROS-Dependent Activation of the Epigenetic Regulation of Aging
A model for the effects of ROS generated during the growth/early survival phases in the activation of an epigenetic mechanism that results in longevity extension, which is in part dependent on stress resistance transcription factors Msn2/Msn4 and Gis1 and in part on DNA damage response genes Tel1 and Rad53 and the histone demethylase Rph1. Note that Tor and Sch9 reduce respiration and ROS generation in the early phases of survival, but are known to promote ROS generation in the later stages of survival. Thus, the early ROS-dependent stress appears to stimulate a hormesis effect leading to epigenetic modifications and long-term protective effects including resistance to oxidative stress.

Sir3 with subtelomeric regions in a Rph1-dependent manner and that Sir3 is necessary for subtelomeric silencing.

To gain further insights into the connection between epigenetic modifications and longevity, it will be important in future studies to identify the mechanisms connecting the Rph1 demethylase and subtelomeric silencing to longevity extension. One avenue of investigation would be to determine the effect of Rph1 and epigenetic modifications on the expression and/or stability of nutrients signaling proteins, for instance in the Ras-cAMP-PKA and Tor-Sch9 pathways, which could explain both the Gis1/Msn2/Msn4-dependent and -independent effects of ROS (Figure 1). Another possibility is that the Rph1-dependent epigenetic changes affect unknown genes and antiaging mechanisms downstream of these nutrient signaling pathways in agreement with their role in repressing Tel1 expression. Since genetic alterations and other interventions beneficial for longevity, such as CR, can be associated with enhanced mitochondrial activity and possibly increased ROS production during growth and the initial stages of survival (Ocampo et al., 2012), it will be interesting to investigate whether the effect of CR on longevity may involve epigenetic alterations analogous to those described by Schroeder and colleagues.

In conclusion, this study not only sheds light on the role of epigenetics on lifespan extension but provides a mechanism for a poorly explained connection between hormesis and longevity. It also links both hormesis and epigenetics to the well-established genes known to regulate aging. This represents the first mechanism linking ROS to the epigenetic control of chronological longevity extension in *S. cerevisiae*. The identification of mechanism and/or intervention, which have the potential to switch the epigenome of aging cells to a more youthful mode, is of great interest, since it may identify strategies leading to the rejuvenation of the cell machineries without the need for extreme and chronic interventions such as CR. Together with drugs such as the mTOR inhibitor rapamycin or inhibitors of the growth hormone-IGF-I axis, external stimuli that mimic those caused by mtROS have the potential to promote long-lasting protective states that delay aging and prevent diseases.

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