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SIP-ing the Elixir of Youth

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AMP-activated protein kinase (AMPK) is a conserved cellular fuel gauge previously implicated in aging. In this issue, Lu et al. (2011) describe how age-related deacetylation of Sip2, a subunit of the AMPK homolog in yeast, acts as a life span clock that can be wound backward or forward to modulate longevity.

From the age of Hippocrates, medicine has long appreciated the importance of preserving physiological homeostasis for a healthy life. Indeed, the ancient Greeks believed that a failure to maintain proper balance between the four "humors," or liquids of the blood, was at the root of human disease. Despite modern medicine's departure from humorism, the idea that a cellular collapse in homeostasis might underlie late onset diseases still prevails. In this issue, Lu and colleagues (Lu et al., 2011) present new data supporting this ancient theory.

One fundamental cellular process requiring tight homeostatic control during aging is the balance between energy generation and usage. In eukaryotes, a key orchestrator of energy homeostasis is AMPK, a serine/threonine kinase that functions as a cellular energy sensor, activating catabolic processes to generate ATP when energy levels are low while simultaneously shutting down energy requiring anabolic processes (Steinberg and Kemp, 2009). The importance of maintaining energy homeostasis throughout life is underscored by the fact that AMPK activity mediates life span in yeast, worms, and flies. Uncovering a novel mode of AMPK regulation in yeast, the work by Lu et al. (2011) demonstrates that progressive deacetylation of the AMPK subunit Sip2 with age limits replicative life span (defined as the number of times that a single cell can divide) and that blocking this change can slow aging.

The *S. cerevisiae* homolog of AMPK is a heterotrimeric complex made up of both a single α and γ subunit, Snf1 and Snf4 (sucrose *non*fermenting), respectively, and one of three alternative β subunits, *S*nf-*i*nteracting *p*roteins (Sip) 1 and 2 and Gal83. Previous work has shown that one β subunit in particular, Sip2, plays a pivotal role in regulating Snf1 activity with age (Ashrafi et al., 2000). Sip2 inhibits the Snf1 complex by sequestering Snf4 to the plasma membrane. As cells age, Sip2 shuttles from the plasma membrane to the cytosol, progressively activating Snf1, resulting in limited replicative life span. In the current study, Lu et al. (2011) expand upon this model to demonstrate that the acetylation status of Sip2 is the critical mechanism controlling Snf1 activity during aging.

Using tandem mass spectrometry, the authors identify residues on Sip2 that become progressively deacetylated in older cells. This change in Sip2 acetylation status seems causal in yeast replicative aging, as Sip2 mutants that are always deacetylated are short lived, whereas Sip2 acetylation mimics live longer than wild-type cells. Acetylation of Sip2 is antagonistically regulated by the acetyl transferase NuA4 and the deacetylase Rpd3. Strikingly, Sip2 is the primary longevity target of these enzymes; the short life span of NuA4 mutants is rescued by Sip2 acetylation mimics, whereas the extended life span of *RPD3* mutants is not further enhanced by increasing Sip2 acetylation. Together, these data suggest that progressive deacetylation of Sip2 with time acts analogously to a longevity clock that marks the age of the cells and that interventions that drive acetylation or deacetylation of Sip2 can wind the clock backward or forward, respectively (Figure 1).

The mechanism by which the ticking of this clock modulates cellular aging hinges upon changes to Snf1 activity; as Sip2 becomes deacetylated with age, it loses its ability to bind to Snf1 and repress the complex. The resulting hyperactivation of Snf1 leads to accumulation of the stress-associated disaccharide trehalose, increased sensitivity to reactive oxygen species, and limited life span—all of which can be reversed by preserving Sip2 acetylation status.

Changes to energy balance can have profound physiological consequences for the cell and have been shown previously to even alter the rate at which organisms age. In species ranging from yeast to primates, reducing available energy increases organismal life span and protects against age-related diseases (Fontana et al., 2010). Given its role in sensing energy status, AMPK has therefore been suggested to be a central mediator of life span by dietary restriction. However, in the study by Lu et al., the effects of Sip2 acetylation on life span appear to be independent of glucose availability of the cell, and as such, the authors suggest a role for Sip2 in determining the intrinsic rate at which cells age, rather than the ability to change that rate in response to extrinsic factors. Interestingly, however, both the intrinsic aging pathway described by Lu et al. and the dietary restriction-induced "extrinsic" pathway, regulated by *t*arget *o*f *r*apamycin 1 (TORC1) in yeast, converge upon a shared downstream mediator, Sch9.

Sch9, itself a kinase, has homology to Akt and functions analogously to mammalian S6 kinase. No stranger to the

aging field, inhibition of S6K increases longevity in yeast, worms, flies, and mammals (Fontana et al., 2010). Although Sch9 is perhaps best known as a substrate for TORC1, Lu et al. show that the Snf1 complex can phosphorylate Sch9 independently and that the short life span of Sip2 acetylation mutants can be rescued by deleting *SCH9*. Sch9 is known to regulate many cellular processes that influence aging, including autophagy and translation, both central nodes in the maintenance of cellular homeostasis. The data presented by Lu et al. indicate that, at least in yeast, Sch9 may be crucial for modulating both intrinsic and extrinsic aging, emphasizing the importance of identifying the downstream targets of Sch9-mediated longevity.

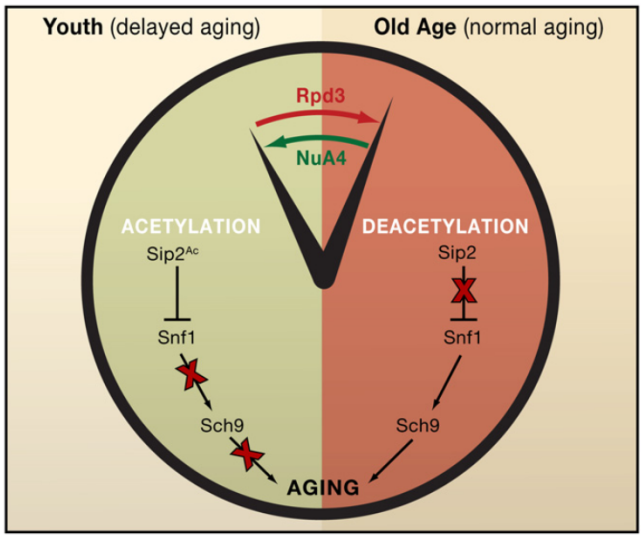

Figure 1. The Deactylation Life Span Clock
Deacetylation of the yeast AMPK subunit Sip2 with time acts as an intrinsic aging clock, which drives cellular aging by a mechanism that is distinct from the effects of dietary restriction. As yeast cells age, Sip2 becomes deacetylated, removing its repression of the AMPK homolog Snf1 and inducing cellular aging via Sch9 phosphorylation. The life span clock can be wound backward via Sip2 acetylation mimics or by inactivating the deacetylase Rpd3, promoting longevity. These findings describe a novel level of AMPK regulation with age and pose new questions about the links between energy homeostasis and longevity and the potential of AMPK as a target to treat age-related disease.

The study by Lu and colleagues describes a novel role for acetylation of a nonhistone protein in mediating yeast life span and provides an exciting link between AMPK and S6K that may be critical for mediating intrinsic cellular aging. However, it also leaves some questions unanswered. Foremost of these is the extent to which this mechanism will translate to higher organisms. Indeed, several lines of evidence suggest that, despite a high degree of conservation between Snf1 and AMPK, there has been divergence in their regulation. Whereas mammalian AMPK senses cellular energy status via nucleotide binding to its γ subunit, this does not seem to be the case for Snf1 (Steinberg and Kemp, 2009). Furthermore, unlike yeast, mammals only have two AMPK β subunits, and as yet, neither has been shown to antagonize AMPK. Finally, little is currently known about the relationship between AMPK and S6K in mammals, but in at least one cancer model, stimulation of AMPK results in reduced, rather than enhanced, phosphorylation of S6K (Taliaferro-Smith et al., 2009).

The effects of yeast AMPK activity on life span also contrast with what is known in multicellular organisms. In yeast, inhibiting AMPK activity is beneficial for life span, whereas inhibiting AMPK shortens life span in both *C. elegans* (Apfeld et al., 2004) and *Drosophila melanogaster* (Tohyama and Yamaguchi, 2010). Conversely, activating AMPK increases *C. elegans* life span (Apfeld et al., 2004), dependent upon downstream transcriptional regulators FOXO (Greer et al., 2007) and CRTC-1 (Mair et al., 2011). However, as is the case in yeast (Zhang et al., 2010), different heterotrimeric combinations of AMPK have alternating functions in mammals (Steinberg and Kemp, 2009), and which of these might be involved in life span modulation is yet to be investigated.

If the work from Lu et al. in yeast does translate to mammals, perhaps dysregulation of this ancestral energy homeostasis control mechanism represents a conserved basis for aging, the prevention of which will take us one step closer to the elixir of life.

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