Tipping the Energy Balance toward Longevity

William Mair[1,*]
[1]Department of Genetics and Complex Diseases, Harvard School of Public Health, 665 Huntington Avenue, Boston, MA 02115, USA
*Correspondence: wmair@hsph.harvard.edu
http://dx.doi.org/10.1016/j.cmet.2012.11.011

AMPK is a cellular energy sensor conserved across eukaryotes that in *C. elegans* prolongs life span and mimics dietary restriction. Stenesen and colleagues (2012) activate AMPK both directly and indirectly by altering AMP biosynthesis to slow aging in *Drosophila,* highlighting AMPK as a conserved life span modulator that links energy sensing to longevity.

For an organism to survive, it must maintain energy homeostasis by tightly regulating the balance between anabolic processes that generate energy and catabolic ones that eat into reserves. Fine-tuning this balance becomes especially critical when energy intake is low, leaving cells without adequate supply to meet demand. In such cases, organisms from yeast to mammals avoid energy crisis by implementing austerity measures, reallocating limited resources from growth and reproduction toward self-preservation and survival (Fontana et al., 2010). Strikingly, animals in this thrifty state show remarkable resistance to multiple age-onset pathologies, including cancer, metabolic disease, and neurodegenerative disorders. In this issue of *Cell Metabolism*, Stenesen et al. (2012) use genetic approaches to disrupt energy balance and slow aging in the fruit fly *Drosophila melanogaster*, reinforcing the idea that energetics, metabolism and longevity are tightly linked and that altering steady-state energy levels may be a means to treat age-related diseases.

To identify genes linking energy homeostasis to longevity, Stenesen and coworkers performed a two-pronged forward genetics screen in *Drosophila,* seeking mutations that both increased life span and specifically affected genes expressed in metabolically active tissues. Of ten significantly long-lived fly mutants, flies carrying mutations in the gene encoding *Adenylosuccinate Synthetase* (AdSS), a key metabolic enzyme involved in the synthesis of adenosine monophosphate (AMP), showed the strongest effects. AMP can be generated from both de novo synthesis and salvage pathways and is a nucleotide precursor of adenosine triphosphate (ATP), which acts as the critical energy source for most cellular processes. Confirming that the increase in longevity was not specific to AdSS, Stenesen et al. tested the life span of flies harboring mutants in multiple genes involved in AMP biosynthesis, and in each case they saw life span extension.

To determine the effect these prolongevity mutations were having on cellular energetics, Stenesen et al. used high-performance liquid chromatography (HPLC) to measure AMP and ATP availability as a readout of energy balance. Surprisingly, despite disrupting AMP biosynthesis, each long-lived mutant showed increases in both total AMP and the ratio of AMP::ATP, mimicking the effects of energy depletion (Figure 1). Increases to the AMP::ATP ratio are indicative of energy imbalance, with more energy being utilized than is produced. When such imbalance is detected, cells attempt to restore energy homeostasis by inhibiting anabolic processes that use energy and activating catabolic ones that produce it. In eukaryotes, the key orchestrator of this homeostatic process is AMP-activated protein kinase (AMPK), which is activated by increased AMP::ATP and as such acts as a cellular fuel gauge (Hardie et al., 2012). AMPK is activated during energy limiting conditions known to extend life span, and its dysregulation is associated with multiple age-related diseases (Steinberg and Kemp, 2009). As such, targeting AMPK has been suggested as a means of recapitulating the protective effects of energy restriction (Fontana et al., 2010). However, to date the effect of AMPK activation on survival has only been tested in the nematode worm *C. elegans*, the result being long lived animals that mimicked those under energy stress despite being well fed (Apfeld et al., 2004).

Stenesen et al. tested whether AMPK was both necessary and sufficient for the longevity effects of disrupted AMP biosynthesis. As expected, given the rise in AMP::ATP ratios, AMPK activity was indeed increased in the long-lived flies. Further, AMPK activation was required for the longevity effects, as expressing a dominant negative form of AMPK completely suppressed the life span increase of AdSS mutants. In a final tour de force of fly genetics, Stenesen and coworkers used a conditional gene switch system to activate AMPK specifically in metabolic tissues in adult flies. The resulting AMPK gain-of-function animals showed increases in life span comparable to that of AdSS mutants, suggesting that increased AMPK activity is sufficient for the longevity effects of disruptions to AMP biosynthesis pathways.

These data support the theory that targeting AMPK might ameliorate diseases of aging, but also raise further questions. First, what are the identities of downstream mediators responsible for the effects? Life span extension by activating AMPK in *C. elegans* requires both activation of the FOXO transcription factor DAF-16 (Greer et al., 2007) and inactivation of the transcriptional coactivator CRTC-1 (Mair et al., 2011). Whether these AMPK targets work together or separately to mediate longevity remains unclear. Both are well conserved in *Drosophila* and humans, and testing their roles in longevity will yield valuable insight.

That disruptions to pathways generating AMP results in increased AMP levels is counterintuitive. Given that AMP can be generated by de novo and salvage pathways, and as a byproduct of the conversion of ADP to ATP ($2ADP \rightleftharpoons AMP + ATP$), it is possible that inhibiting one branch of AMP biosynthesis feeds

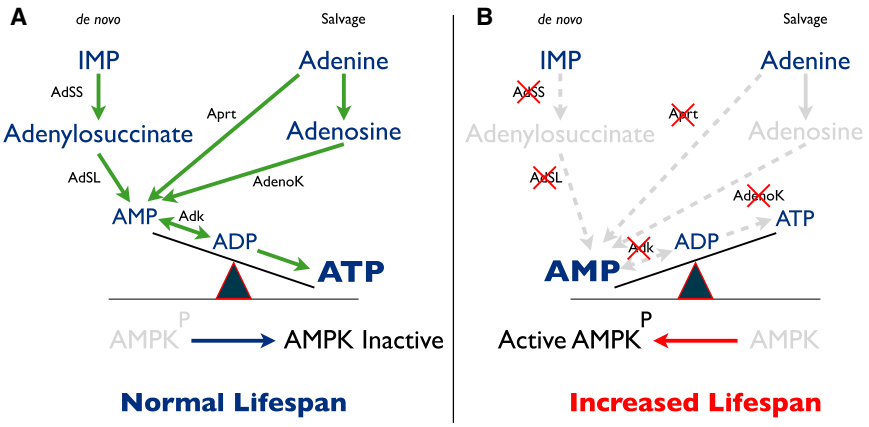

Figure 1. Tipping the Energy Balance: Mutations in AMP Biosynthesis Pathways Increase the AMP::ATP Ratio to Increase Longevity

(A) Under normal conditions, de novo and salvage pathways are active, synthesizing AMP, which is converted to ATP, resulting in a low AMP::ATP ratio and normal life span.

(B) Mutations in genes involved in AMP biosynthesis swing the energy balance to mimic a low-energy state. AMP::ATP ratios are increased, promoting longevity via activation of AMPK.

back to upregulate compensation in another. How this results in an increase in AMP::ATP ratios warrants further investigation.

Ultimately the goal of the aging field is to generate small molecules that promote healthy aging in order to treat age-onset disease, and here again the new data raise interesting questions. Metformin is the most widely prescribed treatment for type II diabetes and a known potent activator of AMPK (Hardie et al., 2012). High doses of Metformin have been shown to increase life span in *C. elegans* in an AMPK dependent manner (Onken and Driscoll, 2010), yet recent data show that this effect is not conserved in *Drosophila* (Slack et al., 2012). That activating AMPK can increase life span in fruit flies, yet Metformin supplementation does not, suggests that either feeding Metformin does not activate AMPK in the relevant tissues for life span extension in *Drosophila*, or that off target effects of Metformin might be limiting longevity in spite of its effects on AMPK. Alternatively, perhaps activating AMPK in all tissues in *Drosophila* is detrimental to health. Ubiquitous expression of the active AMPK used by Stenesen et al. would determine whether AMPK promotes longevity non-cell autonomously when expressed in one tissue or whether tissue-specific activation simply recapitulates a fraction of what might be achievable if AMPK were active in multiple tissue types.

The data of Stenesen et al. show that AMPK can promote healthy aging in organisms beyond *C. elegans*. As such, they add life span extension to the growing list of conserved physiological effects mediated by AMPK (Hardie et al., 2012). The role of AMPK in sensing resources and maintaining energy balance is conserved from worm to fly to mouse to humans. If the longevity data presented by Stenesen et al. in this issue represent the first step on a similar conservation ladder, targeting AMPK to tip the energy balance toward healthy aging in humans might provide protection against the ever-growing burden of age-related pathologies.

REFERENCES

Apfeld, J., O'Connor, G., McDonagh, T., DiStefano, P.S., and Curtis, R. (2004). Genes Dev. *18*, 3004–3009.

Fontana, L., Partridge, L., and Longo, V.D. (2010). Science *328*, 321–326.

Greer, E.L., Dowlatshahi, D., Banko, M.R., Villen, J., Hoang, K., Blanchard, D., Gygi, S.P., and Brunet, A. (2007). Curr. Biol. *17*, 1646–1656.

Hardie, D.G., Ross, F.A., and Hawley, S.A. (2012). Nat. Rev. Mol. Cell Biol. *13*, 251–262.

Mair, W., Morantte, I., Rodrigues, A.P.C., Manning, G., Montminy, M., Shaw, R.J., and Dillin, A. (2011). Nature *470*, 404–408.

Onken, B., and Driscoll, M. (2010). PLoS ONE *5*, e8758.

Slack, C., Foley, A., and Partridge, L. (2012). PLoS ONE *7*, e47699.

Steinberg, G.R., and Kemp, B.E. (2009). Physiol. Rev. *89*, 1025–1078.

Stenesen, D., Suh, J.M., Seo, J., Yu, K., Lee, K.-S., Kim, J.-S., Min, K.-J., and Graff, J.M. (2012). Cell Metab. *17*, this issue, 101–112.