Die Another Day: A Painless Path to Longevity

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Riera et al. identify a neuroendocrine circuit that controls longevity and the age-dependent onset of metabolic decline via the pain-transducing channel TRPV1. Thus, pharmacological inhibition of TRPV1 may provide a new approach to treat not only metabolic disorders but also a broader range of age-related pathologies.

Societies are currently facing a dramatic demographic change with an ever-increasing life expectancy. This is associated with a steady rise in age-related diseases, such as type 2 diabetes mellitus, neurodegenerative disorders, and malignancies. The recent identification of molecular pathways that control the aging process and thus lifespan provides new therapeutic targets for the prevention and treatment of these diseases. In particular, metabolic signaling pathways, such as the insulin/IGF-1/FOXO signaling cascade, offer an evolutionary conserved target to regulate aging and the onset of aging-associated diseases. In this line, the work of Riera et al. (2014) in this issue of *Cell*, sheds light on a new mechanism that relays the crosstalk between aging and metabolism. The authors unravel a new role for the capsaicin receptor (the transient receptor potential cation channel subfamily V member 1, TRPV1) in the regulation of health- and lifespan. TRPV1 predominantly resides on sensory neurons of the "pain pathway," where it senses noxious stimuli such as heat, extracellular acidification, and capsaicin, the pungent component of chili peppers. Along with its key function as a molecular integrator of pain signaling, TRPV1-deficient mice display an impairment of nociception and pain sensation (Caterina et al., 2000). In addition to hypoalgesia, TRPV1 deficiency also protects from diet-induced obesity (Motter and Ahern, 2008), pointing toward a dual role of TRPV1 in pain sensitivity as well as in metabolic regulation.

The implication of sensory perception in longevity has previously been reported in both worms and flies (Alcedo and Kenyon, 2004; Libert et al., 2007). Alterations of both olfactory and taste perception affect lifespan in *C. elegans* and *Drosophila*. Riera et al. (2014) reveal an evolutionary conserved role for sensory perception via the TRPV1 channel in the regulation of lifespan, metabolic disease, and cognition. They demonstrate that mutation of the *trpv1* gene in mice or of its orthologs *osm-9/ocr-2* in *C. elegans* increases longevity in both species. The only limitation of the longevity study in mice stems from the use of isogenic controls rather than control littermates for the TRPV1 conventional knockout. The authors do, however, provide convincing support, based on SNP genotyping, that the controls are 100% genetically identical to the knockout animals.

The authors further reveal that TRPV1 activation limits lifespan via calcium-dependent activation of calcineurin/CRTC1/CREB signaling in worms and TRPV1-dependent CREB regulation is conserved in dorsal root ganglia neurons of mice (Figure 1). Given the previous demonstration that CRTC1-dependent CREB signaling controls lifespan in *C. elegans* (Mair et al., 2011), the present study reveals a (patho)-physiologically relevant upstream regulator of this pathway.

While the majority of studies investigating the interplay between longevity and metabolism reveal an important role of impaired action of GH/IGF-1 (growth hormone/insulin-like growth factor) in promoting longevity, the lifespan-extending effect of TRPV1 deficiency appears to be GH- and IGF-1-independent. Thus, the TRPV1-deficient mice provide a rare example of extended longevity in the presence of normal somatic growth. Instead, Riera and coworkers elegantly describe a new neuroendocrine pathway in control of age-related deterioration of metabolism and longevity. They demonstrate that TRPV1 receptors control the release of the insulin-secretion-antagonizing peptide CGRP (calcitonin-gene-related peptide) (Figure 1). Thus, TRPV1 deficiency prevents the age-related decline in insulin secretion to improve metabolism. Notably, as direct proof for the detrimental impact of increased CGRP on metabolic health, the authors show that chronic infusion of CGRP receptor antagonist in aged mice is sufficient to restore the age-related loss of circadian rhythm regulation of respiratory exchange. Further studies will have to address whether CGRP antagonism also improves glucose metabolism during aging and whether it can confer longevity.

Intriguingly, despite an improvement of glucose tolerance and of glucose-stimulated insulin secretion, TRPV1 deficient mice are already less sensitive to insulin

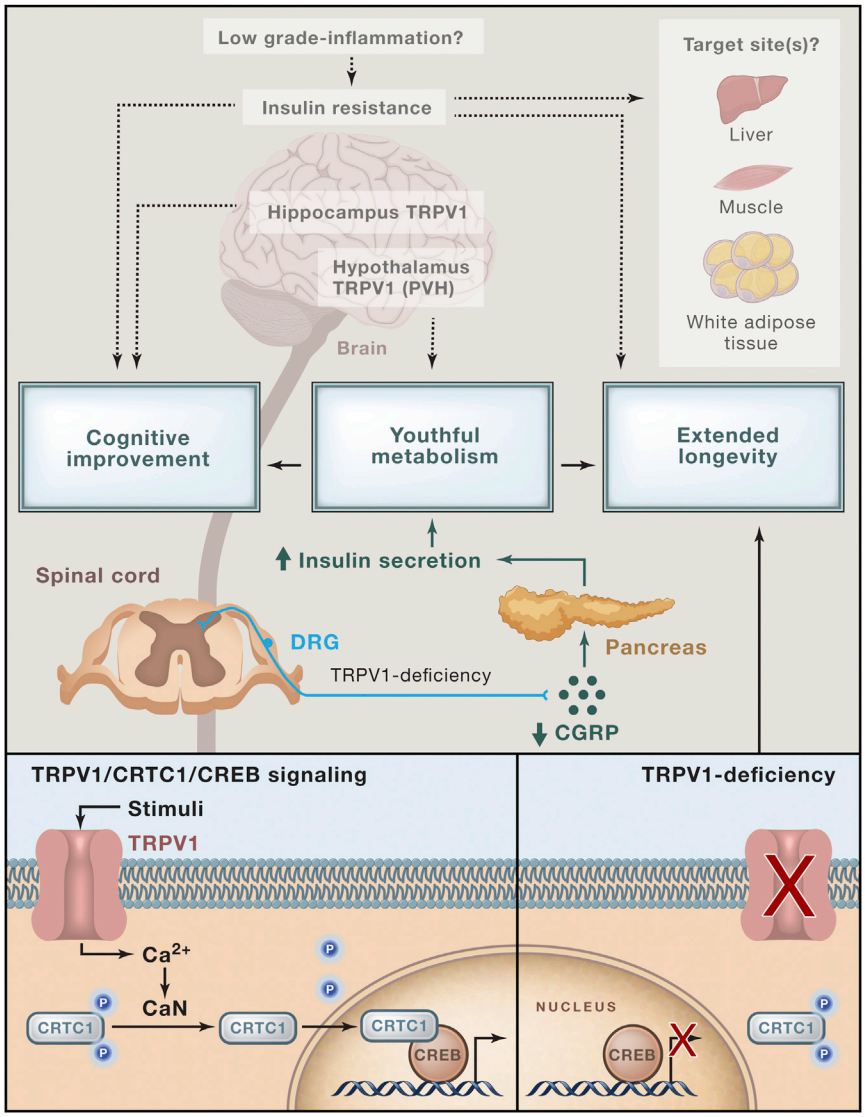

Figure 1. Disrupting a Pain Pathway Promotes Longevity

The work of Riera et al. (2014) reveals that deficiency in TRPV1, an ion channel involved in sensing pain, leads to a decrease in circulating levels of calcitonin gene-related peptide (CGRP) and to an increase in insulin secretion with aging. Improvement of insulin release from pancreatic beta cells is associated with a youthful metabolism at old age as well as an extension of longevity and an improvement of cognition. In both *C. elegans* and in the dorsal root ganglion (DRG) of mice, calcium influx secondary to TRPV1-activation initiates calcineurin (CaN)-dependent dephosphorylation of CREB-regulated transcription coactivator 1 (CRTC1). Subsequent to its dephosphorylation, CRTC1 translocates to the nucleus where it initiates the transcription through activation of the cAMP response element-binding protein (CREB). Inactivation of the CRTC1/CREB pathway, as occurs in the absence of TRPV1, has been previously shown to directly increase lifespan. In addition to the neuroendocrine circuitry demonstrated, further studies will need to address the specific involvement of insulin resistance and of reduced inflammation reported in TRPV1-deficient mice in their long-lived phenotype. Additionally, the specific role of TRPV1 within the hypothalamus and the hippocampus in the regulations of metabolism and cognition, respectively, requires further investigation.

at a young age, and this insulin-resistance worsens with age. This resistance to the glucose regulatory effects of insulin is not associated with detectable alterations of insulin-stimulated AKT activation in key insulin-sensitive tissues such as skeletal muscle and liver. Thus, further studies will have to reveal the exact site(s) where insulin resistance develops in the absence of TRPV1 and whether this insulin resistance may also contribute to the longevity observed in these mice independent from CGRP-mediated control of insulin secretion (Figure 1).

Along the same line, the authors report a tendency toward a beneficial effect of TRPV1 deletion on the aging-associated activation of a low-grade inflammatory tone, both in the brain and in skeletal muscle, whereas inflammatory gene expression increases in white adipose tissue. Given the link between activated inflammation and insulin resistance, this may actually point to the possibility that TRPV1 deficiency might cause insulin resistance in adipose tissue. Moreover, considering the emergence of inflammatory signals in aging and its associated disorders (Steculorum et al., 2014), it is likely that this improvement of inflammatory tone may also contribute to the regulation of longevity. To what extent insulin-resistance and decreased inflammation contribute to the long-lived phenotype of TRPV1 deficiency, still needs to be investigated.

Interestingly, in addition to increasing lifespan and metabolism, TRPV1 inactivation also improves cognitive functions. However, these experiments are performed in aged animals, leaving open the possibility that TRPV1 deficiency improves cognition already in young animals. Notably, in the central nervous system, TRPV1 is highly expressed in various brain areas controlling cognitive functions such as the cortex and the hippocampus (Mezey et al., 2000). Although the authors state an indistinguishable gross anatomy of the hippocampus between TRPV1 knockout and control mice, based on the known ability of TRPV1 to directly modulate hippocampal synaptic plasticity including long-term potentiation (Marsch et al., 2007), it is likely that the improved cognition of the TRPV1-deficient mice may not only be secondary to the metabolic youthfulness but also to a direct effect of TRPV1 on the cellular mechanisms controlling learning and memory.

Similarly, although the authors have elegantly described a pathway by which TRPV1 acts on dorsal root ganglia to regulate insulin secretion and control metabolism, TRPV1 expression is also dense in the hypothalamus (Mezey et al., 2000). Here, it is particularly expressed on preautonomic neurons located in the

paraventricular nucleus of the hypothalamus (PVH) that are providing projections to the liver and those liver-related PVH neurons are activated by the TRPV1-activator capsaicin (Gao et al., 2012). Thus, in addition, TRPV1 may also regulate glucose homeostasis by a direct TRPV1-dependent modulation of the brain-liver autonomic circuitry. Thereby, the present study opens numerous new research avenues focusing on the interplay between aging and metabolic health through the pleiotropic actions of TRPV1 in various target sites.

Another aspect of TRPV1 signaling that requires further attention is their endovanilloid-dependent activation. Indeed, considering the critical implication of lipids in low-grade inflammation and in the resultant neuronal and peripheral insulin-resistance as well as cognitive impairment, one could speculate that activation of TRPV1 by endovanilloid lipids could be a mechanism at the crossroads of aging-associated decline in cognition and metabolic health. Regardless of the endogenous ligand through which TRPV1 limits lifespan, the availability of potent TRPV1 antagonists opens new therapeutic possibilities to improve longevity and forestall the onset of age-related disease.

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Focusing in on T Cell Cross-Reactivity

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To provide broad immunity to a vast array of foreign antigens with a limited number of T lymphocytes, each cell has to recognize many targets. By implementing a strategy to identify T cell receptor (TCR) ligands and investigating at a fine granularity their structure and sequence relationship, Birnbaum et al. demonstrate the surprisingly tight focus of such T cell cross-reactivity.

The immune system must mount specific host-protective responses to a large variety of pathogens. $CD4^+$ and $CD8^+$ T cells contribute to host defense by employing clonally distributed heterodimeric ($\alpha\beta$) receptors (TCRs) to recognize pathogen-derived peptides presented on host cells by major histocompatibility complex-encoded molecules (pMHCs). As a result of nucleotide insertions and somatic recombination of gene segments, the potential combinatorial diversity of the TCR repertoire exceeds 10^{20} (Zarnitsyna et al., 2013). This staggering theoretical diversity is tempered, however, by the fact that each individual can only possess at one time a tiny subset of possible TCRs—at most equal to the total number of T cells, $\sim 10^{11}$ for humans and $\sim 10^{8}$ for mice. Nevertheless, the actual diversity is sufficient to respond to at least one antigen expressed by any of a universe of pathogens, avoiding repertoire holes that pathogens could exploit. The obvious implication is that every TCR must recognize many distinct pMHC ligands (Mason, 1998). This notion is consistent with a large body of experimental evidence involving studies of individual T cell clones, analysis of T cell development in the thymus that requires selection by self-peptides, and responses of T cells to modified versions of their nominal agonist peptide ligands (Morris and Allen, 2012).

Although cross-reactivity in TCR recognition is widely accepted, answers to two key questions have eluded the field (Figure 1): what is the actual extent of such cross-reactivity for any particular TCR, and is there a pattern to such cross-reactivity? In this issue of *Cell*,