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Chapter 14 ThermoTRPs

Role in Aging

Authors

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14.1. Introduction

An organism's health depends on the integrity of molecular and biochemical networks responsible for ensuring homeostasis within its cells and tissues. However, upon aging, a progressive failure in the maintenance of this homeostatic balance occurs in response to various insults, allowing the accumulation of damage, the physiological decline of individual tissues, and susceptibility to diseases. Despite the complex nature of the aging process, simple genetic and environmental alterations can cause an increase in healthy lifespan or "healthspan" in laboratory model organisms. Genetic manipulations of model organisms including yeast, worms, flies, and mice have revealed signaling elements involved in DNA damage, stem cells maintenance, proteostasis, energy, and oxidative metabolism (Riera et al., 2016).

However, one of the most intriguing discoveries made in these models resides in the ability of environmental factors to profoundly alter the aging process by remodeling some of the genetic programs mentioned above (Riera and Dillin, 2016). The first line of evidence that an external cue could powerfully regulate longevity was obtained by performing dietary restriction in rodents, a reduction in food intake without malnutrition. Dietary restriction is the most robust intervention to increase lifespan in model organisms including rodents and primates, and delays the emergence of age-related diseases (Mair and Dillin, 2008). How dietary restriction extends lifespan remains an open question, but decades of research are evidencing molecular pathways embedded in the response to reduce energy availability, resulting in the emergence of an altered metabolic state that promotes health and longevity. Nonetheless, the discovery of dietary restriction opened a new avenue of research in the aging field, and in particular in the understanding of how animals deal with fluctuating energy levels in their natural environment, and how their longevity is affected by such factors. This is particularly relevant for the nematode *Caenorhabditis elegans*, which survives in a changing environment and must be able to coordinate energy-demanding processes including basal cellular functions, growth, reproduction, and physical activity with available external resources. In order to sense their environment, *C. elegans* possess ciliated sensory neurons located primarily in sensory organs in the head and tail regions. Cilia function as sensory receptors, expressing many G protein-coupled receptors (GPCRs) and transient receptor potential (TRP) channels, and mutants with defective sensory cilia have impaired sensory perception (Bargmann, 2006). Cilia are membrane-bound microtubule-based structures and in *C. elegans* are only found at the dendritic endings of sensory neurons.

Sensory neurons provide nematodes with a remarkable form of developmental plasticity, allowing them to assess food availability, temperature, and crowding information (worm density) in order to arrest their development if required, thus forming long-lived and stress-resistant dauer larvae (Bargmann, 2006; Golden and Riddle, 1982). When favorable times return, worms assess the same cues to recover and resume normal development. As the entry and exit of the dauer larval stage suggest, worm sensory neurons truly function as neuroendocrine organs, being implicated in many physiological functions in addition to their behavioral role (Bargmann, 2006). Much information on these neurons has been gathered from laser ablation experiments and analysis of mutants presenting defects in sensory cilia. A seminal discovery in the aging field was achieved when the laboratory of Cynthia Kenyon showed in 1999 that mutations that cause various defects in cilia formation, including the absence of cilia, deletion of middle and distal segments, or impair chemosensory signal transduction increase longevity profoundly (Apfeld and Kenyon, 1999). Later, this group also demonstrated that laser ablation of specific pairs of gustatory and olfactory chemosensory

neurons was sufficient to extend lifespan (Alcedo and Kenyon, 2004). What is the role of TRP channels in modulating these neuroendocrine processes, and what kind of stimuli are these receptors detecting to control aging? This chapter summarizes relevant discoveries that clarify some of the roles of TRP channels in the aging process.

14.2. *C. Elegans* trpa1 in the regulation of longevity at low temperatures

14.2.1. Core Body Temperature and Aging

In 1916, Loeb and Northrop asked whether the duration of life depends on a definite temperature coefficient for each species. Their work demonstrated that lower temperatures could dramatically extend the lifespan of the fruit fly, *Drosophila* (Loeb and Northrop, 1916). Other poikilothermic animals, whose internal temperature varies considerably, including *C. elegans* and the fish *Cynolebias adloffi*, also present increased lifespan upon modest temperature reduction (Conti, 2008). Additionally, lowering the core body temperature of homeothermic animals, such as mice, also increases lifespan (Conti et al., 2006), highlighting a general role of temperature reduction in lifespan extension in both poikilotherms and homeotherms. Reduction in core body temperature has been proposed to mediate the longevity benefits of dietary restriction (Lane et al., 1996). Conversely, raising the culturing temperature (e.g., to 25°C) greatly shortens nematode lifespan (Lee and Kenyon, 2009). This phenomenon is mediated by a pair of amphid thermosensory neurons with finger-like ciliated endings termed *AFD neurons*, which allow the animals to migrate toward temperatures previously associated with food or thermotaxis (Hedgecock and Russell, 1975; Mori and Ohshima, 1995).

14.2.2. Molecular Basis of Lifespan Extension upon Reduced Core Body Temperature

How is the cold-dependent lifespan extension mediated? One prominent model assumes that lowering the body temperature would reduce the rate of chemical reactions, thereby leading to a slower pace of living. This model suggests that the extended lifespan observed at low temperatures is simply a passive thermodynamic process. It takes a longer time for worms to develop from embryos to adults at lower temperatures, a phenomenon seemingly consistent with this model. However, a more attractive hypothesis suggests that specific genetic programs might be engaged to actively promote longevity at cold temperatures, as observed upon dietary restriction or other paradigms. Xiao et al. reasoned that a cold sensor of the TRP channel family might be recruited in this process (Xiao et al., 2013). The best-known mammalian cold sensors are TRPA1 and TRPM8; however, TRPM8 does not have a *C. elegans* homolog (Peier et al., 2002; Story et al., 2003; McKemy et al., 2002), thus ruling this receptor out of the candidate-based approach. But, TRPA1 has one ortholog in *C. elegans* referred to as TRPA-1, which becomes active under 20°C (Chatzigeorgiou et al., 2010) and therefore constitutes an attractive candidate to mediate the longevity extension observed under cold temperature.

Three temperatures (15°C, 20°C, and 25°C) are common laboratory conditions for culturing worms. If TRPA-1 is involved in promoting longevity at low temperatures, one would expect that mutant worms lacking TRPA-1 should have a shorter lifespan at 15°C and 20°C than wild-type worms, but not at 25°C. This is because this cold-sensitive channel is expected to be functional at 15°C and 20°C but remains closed at 25°C. Consistent with this prediction, *trpa-1* null mutant worms showed a significantly shorter lifespan than wild-type worms at 15°C and 20°C but not 25°C (Xiao et al., 2013). Similarly, transgenic expression of TRPA-1 under its own promoter increased lifespan at 15°C and 20°C but not at 25°C (Xiao et al., 2013).

Lifespan extension at cold temperatures depends on the Ca^{2+} permeability of TRPA-1, as point mutants E1018A, which are Ca^{2+} impermeable but retain Na^{+} or K^{+} permeability, fail to extend lifespan at low temperature (Xiao et al., 2013). Calcium signaling is therefore critical to mediate the effects of TRPA-1, and suggest that canonical signaling cascades function downstream of the channel to regulate lifespan. Mutation of the Ca^{2+}-sensitive kinase protein kinase C-2 (PKC-2), which is the sole classical PKC in *C. elegans*, fully suppressed the long-lived phenotype of TRPA-1 transgenic animals, indicating that PKC-2 is required for the function of TRPA-1 in the pathway (Xiao et al., 2013). Using genetic epistasis, Xiao et al. showed that TRPA-1 acts specifically upstream on the transcription factor daf-16, a FOXO longevity master regulator (Xiao et al., 2013). How are Ca^{2+} signals transmitted to DAF-16?

Mutation of the Ca^{2+}-sensitive kinase PKC-2, which is the sole classical PKC in *C. elegans*, fully suppressed the long-lived phenotype of TRPA-1 transgenic animals, indicating that PKC-2 is required for the function of TRPA-1 in the pathway. More specifically, these authors were able to show using genetic evidence that PKC-2 acts upstream of SGK-1, a serine/threonine kinase that directly phosphorylates DAF-16, and is linked to increased DAF-16 nuclear activity in these conditions (Figure 14.1, Xiao et al., 2013). Analysis of tissue specificity revealed that both the nervous and intestine systems were required for the low temperature–dependent longevity increase observed in TRPA-1–overexpressing worms, but the specific function of each of these tissues remains to be determined. Both tissues are critical for lifespan extension in insulin/IGF-1-pathway mutants, with the classical view being that the intestine integrates anti-aging cues provided by the neurons and also signals to other tissues to propagate a body-wise response (Kenyon, 2010; Libina et al., 2003).

14.3. Role of the trpvs OCR-2 and OSM-9 in aging

14.3.1. Sensory Function of the TRPV OCR-2 and OSM-9

In nematodes, many amphid sensory neurons signal through channels encoded by the TRPV *osm-9* and *ocr-2* genes (Colbert et al., 1997; Tobin et al., 2002). OCR-2 and OSM-9 are coexpressed in the sensory cilia and plasma membrane of four pairs of chemosensory neurons: ADF, AWA, ASH, and ADL (Colbert et al., 1997; Tobin et al., 2002).

Osm-9 and *ocr-2* mutants are defective in all forms of AWA olfaction and ASH nociception, and may play additional roles in other amphid sensory neurons that do not contain the cyclic nucleotide–gated (CNG) channels TAX-4/TAX-2 (Colbert et al., 1997; Tobin et al., 2002). OSM-9 and OCR-2 proteins are localized to the AWA and ASH cilia and are mutually required for each other's cilia localization, suggesting that the two proteins assemble into a single channel complex (Tobin et al., 2002). These channels are also coexpressed in the ADF and ADL amphid neurons, where less is known about their sensory functions. Loss of function of this channel complex results in downregulation of the gene encoding the serotonin (5HT) synthesis enzyme tryptophan hydroxylase (tph-1) in serotonergic ADF neurons through cell autonomous regulation of *tph-1* transcription (Zhang, 2004). The nature of the sensory cues and activation mechanisms of OCR-2/OSM-9 in ADF neurons is not yet determined.

14.3.2. Molecular Basis of Lifespan Extension Downstream of OCR-2/0SM-9

Loss of OCR-2/OSM-9 in the worm results in increased longevity (Riera et al., 2014). Null mutants of either *osm-9(ky4)* or *ocr-2(ak47)* yield to a modest increase in longevity, consistent with the functional redundancy of this receptor pair (Colbert et al., 1997; Tobin et al., 2002). Lifespan extension by *ocr-2(ak47)* mutation has previously been shown to depend on daf-16, and to extend larval starvation survival (Lee and Ashrafi, 2008). However, loss of both *osm-9* and *ocr-2* resulted in a robust longevity extension up to 32% compared to control animals. The lifespan extension observed in worms lacking OCR-2/OSM-9 channels relies on reduced Ca^{2+} signaling within affected cells, and utilize one of the major transponders of Ca^{2+} flux in the cell, the phosphatase calcineurin (Mellstrom et al., 2008). The worm calcineurin ortholog, the Ca^{2+}-activated calcineurin catalytic A subunit, *tax-6*, plays an intricate role in the aging process (Dong et al., 2007; Mair et al., 2011). Loss of *tax-6* results in long-lived animals, and hyperactivation results in short lifespan (Dong et al., 2007). One essential target of *tax-6* to regulate the aging process in worms is the highly conserved CRTC1 (CREB-regulated transcriptional coactivator 1). Dephosphorylation of CRTC1 on serines 76 and 179 by *tax-6* results in nuclear localization, modulation of CREB transcriptional targets, and increased longevity (Mair et al., 2011). Opposing *tax-6*, AMP-activated protein kinase (AMPK) monitors energy sources and phosphorylates CRTC1, retaining CRTC1 in the cytoplasm (Mair et al., 2011). Consistent with loss of *tax-6* resulting in increased longevity, increased activity of AMPK results in increased longevity through phosphorylation of CRTC1 at serines 76 and 179, sites counteracted by *tax-6* (Mair et al., 2011).

Upon tricaine treatment, a drug that increases intracellular Ca^{2+} in cells, CRTC1 shuttles to the nucleus in wild-type animals but remains strictly cytoplasmic in *tax-6(ok2065)* mutants (Mair et al., 2011). Similarly to *tax-6* mutant worms, *trpv* mutants (*osm-9; ocr-2* double mutant animals) retained cytoplasmic localization of CRTC1 upon tricaine

treatment, suggesting that OCR-2/OSM-9 function within the tax-6/CRTC pathway (Riera et al., 2014). The increased longevity caused by loss of OCR-2/OSM-9 in the worm is completely dependent on the CRTC1 longevity pathway. Inactivating *tax-6*, which extends lifespan in wild-type animals, did not further increase the lifespan of the *trpv* mutants, suggesting that *tax-6* and *osm-9/ocr-2* function in the same pathway. Concordant with *tax-6* modulating longevity through post-translational modifications of CTRC1, the increased longevity of the *trpv* mutants was abrogated when CRTC1 is mutated at the calcineurin dephosphorylation sites S76A, S179A, making it constitutively nuclear (Riera et al., 2014). Therefore, the lifespan extension caused by loss of *trpv* signaling depends on nuclear exclusion of the CREB-regulated transcriptional coactivator CRTC1 at the same phosphorylation sites used for regulation by AMPK and calcineurin (Riera et al., 2014). Taken together, these results indicate that a subset of chemosensory neurons utilizes a TRPV Ca^{2+} signaling cascade to adjust the worm metabolism with environmental conditions by modulating CREB activity that ultimately dictates longevity of the animal (Figure 14.2).

14.4. Role of TRPV1 in mammalian aging

The ability to affect aging by manipulation of TRP channels in invertebrate models such as *C. elegans* provides evidence for evolutionary conservation and argues for the investigation of homologous and analogous circuits in mammalian models. Recently, evidence of the conserved function of chemosensory neurons in the regulation of longevity has been provided through the study of the capsaicin receptor TRPV1 (Riera et al., 2014).

14.4.1. TRPV1 Mutation Increases Mouse Lifespan

Impairment of TRPV1 sensory receptors is sufficient to extend mouse lifespan and improve many aspects of health in aging mice such as metabolic decline, cognitive impairment, and cancer incidence (Riera et al., 2014). Under normal fed ad libitum conditions, the TRPV1 mutation is not sex specific in its effects: longevity in both genders was extended to a similar extent, with 11.9% increase in male TRPV1 mutants and 15.9% increase in median female lifespan compared to wild-type, isogenic C57BL/6 controls (WT). The longevity increase observed in these animals is not due to previously established mouse longevity paradigms such as reduced growth hormone (GH) and/or insulin growth factor (IGF-1) signaling, often resulting in delayed growth and small adult animals (Bluher, 2003; Ortega-Molina et al., 2012; Selman et al., 2008). TRPV1 mutants show no growth delay and do not differ in body composition compared to control animals. TRPV1 mutant mice also do not present core body temperature differences with controls, arguing that their long lifespan is not due to a dietary restriction mimetic mechanism.

14.4.2. Visceral Role of TRPV1 in Lifespan

How can a mutation in a sensory TRPV result in increased lifespan? TRPV1 is highly expressed in sensory nerves innervating the abdominal viscera (such as stomach, pancreas, small intestine) arising from the vagus and spinal nerves with cell bodies (NG) and dorsal root ganglia (DRG) (Christianson and Davis, 2010). In particular, DRG afferents innervating the pancreas, stomach, duodenum, and jejunum are largely peptidergic, expressing calcitonin gene-related peptide (CGRP) and substance P (Christianson and Davis, 2010). A fundamental output of activating TRPV1 receptors in spinal nerves from the DRG is the secretion of multiple neuropeptides from the terminals of primary sensory neurons including the tachynins, CGRP, neurokinin A (NKA), and substance P (SP), involved in neurogenic inflammation (Benemei et al., 2009). Among these substances, CGRP is the main neurotransmitter in the nociceptive C sensory nerves and a potent vasodilator and hypotensive agent implicated in chronic pain and migraines (Springer et al., 2003). Unmyelinated C-fibers of spinal afferents form a dense meshwork innervating the pancreas, as observed in retrograde labeling studies from the pancreas 75% of these DRG afferents are positive for TRPV1, among them 65% reacting for CGRP (Fasanella et al., 2008). In contrast, very few NG afferent innervating the same viscera are peptidergic and the TRPV1/CGRP-positive neurons represent only 35% of the NG population (Fasanella et al., 2008). The secretion of CGRP and substance P occurs in a TRPV1-dependent manner and has been associated with neurogenic inflammation (Noble et al., 2006) and insulin release inhibition in animal models, respectively (Ahrén et al., 1987; Akiba et al., 2004; Asahina et al., 1995; Gram, 2005; Gram et al., 2007; Kogire et al., 1991; Lewis et al., 1988; Pettersson et al., 1986; Tanaka et al., 2011; Melnyk and Himms-Hagen, 1995).

Consistent with a role of TRPV1 and CGRP in antagonizing insulin secretion, mice presenting TRPV1 mutation display a greater ability to secrete insulin upon glucose challenge coupled to enhanced beta cell mass at an advanced age (Riera et al., 2014). Very strikingly, TRPV1 mutant mice present improved glucose tolerance throughout life, as well as increased oxygen consumption as measured in metabolic cages. The respiratory exchange ratio (RER), obtained by indirect calorimetry, compares the volume of carbon dioxide an organism produces to the volume of oxygen consumed over a given time and varies inversely with lipid oxidation. In young and healthy wild-type mice, the RER displays a youthful circadian shift from night to day reflecting the daily transition between carbohydrates to lipid metabolism. Old mice, however, develop a substrate preference toward lipids, losing the capacity to switch between fuel sources also known as metabolic inflexibility (Riera and Dillin, 2015). Old TRPV1 mutants maintain a youthful RER with age, and are protected from age-associated disease, presenting both reduced cancer incidence and delayed onset of cognitive decline with age.

The insulin antagonizing capacity of TRPV1 fibers appears to rely on the neuropeptide CGRP, which locally inhibits insulin secretion from the pancreatic β-cells microenvironment as presented in many *in vitro* and *in vivo* assays (Riera et al., 2014; Ahrén et al., 1987; Akiba et al., 2004; Asahina et al., 1995; Gram, 2005; Gram et al., 2007; Kogire et al., 1991; Lewis et al., 1988; Pettersson et al., 1986; Tanaka et al., 2011; Melnyk and Himms-Hagen, 1995), whereas *in vitro* assays show that substance P does not affect glucose-dependent insulin secretion (Riera et al., 2014). Additionally, CGRP levels appear to fluctuate with age and become elevated in aging animals (Riera et al., 2014; Melnyk and Himms-Hagen, 1995), whereas they remain youthful in old TRPV1 mutant animals (Riera et al., 2014). Similarly, obese and diabetic rodent models show sustained CGRP levels associated with impaired insulin secretion, and reduction of CGRP through TRPV1 inhibition or sensory denervation improved metabolic function in these animals (Gram, 2005; Tanaka et al., 2011). Taken together, these findings suggest that sustained TRPV1 activation and corresponding high CGRP levels are detrimental to metabolic health in aged animals (Figure 14.3). To test this directly, 22-month-old mice were implanted with osmotic pumps diffusing the CGRP receptor antagonist $CGRP_{8–37}$ (Poyner et al., 1998). After 6 weeks of treatment, pharmacologic inhibition of CGRP receptors restores the RER in old mice as observed upon genetic deletion of TRPV1 (Riera et al., 2014), thus improving these animals' age-induced metabolic inflexibility.

14.4.3. TRPV1 and CREB Transcriptional Activity with Age

The lifespan extension of mice lacking TRPV1 appears to be regulated by inactivation of the CRTC1/CREB pathway in DRG sensory neurons, conserved with results in the worm (Riera et al., 2014). Application of capsaicin to cultured DRG neurons provoked accumulation of CRTC1 in the nuclei of CGRP-positive cells of WT DRGs cultures. Capsaicin-induced CRTC1 shuttling is abolished in TRPV1 mutant DRG neurons or in the presence of SB-366791, a selective TRPV1 antagonist (Riera et al., 2014). The ability of CRTC1 to shuttle to the nucleus under TRPV1 activity demonstrates the existence of a plastic transcriptional mechanism adapting rapidly to external outputs. The nuclear exclusion of CRTC1 in TRPV1 mutant DRG neurons suggests that CREB transcriptional activity is likely to be altered in the DRG neurons of TRPV1 mutant mice. Under inflammatory conditions, TRPV1 expressing DRG neurons utilize a CREB signaling cascade to induce neurogenic inflammation through the release of CGRP, by the binding of CREB onto the CGRP promoter (Nakanishi et al., 2010). CREB transcriptional activity is downregulated due to the nuclear exclusion of CRTC1 in the TRPV1 mutant mice, and results in downregulation of many CREB target genes including calcitonin-related polypeptide α (calca) and tachykinin 1 (tac1) transcripts, precursors of two TRPV1 secreted neuropeptides, CGRP and substance P.

14.4.4. TRPV1 and Metainflammation with Age

These findings raise the question as to which potential age-dependent factors may cause increased TRPV1 activation and lead to sustained CGRP secretion during aging. Accumulation of systemic low-grade inflammation is a hallmark of aging, and increased levels of multiple inflammatory cytokines including tumor necrosis factor-α (tnf-α), interleukin-6 (IL-6), IL-1β, cytokine antagonists, and acute phase proteins such as C-reactive protein (CRP), may underlie the activation of pathological senescence processes (Bruunsgaard et al., 2000). The accumulation of these

proinflammatory agents or “inflammaging” characterizes multiple age-induced pathologies, such as sarcopenia, neurodegeneration, arthritis, atherosclerosis, and insulin resistance (Salvioli et al., 2013). Both age-derived adipose tissue expansion and macrophage recruitment in inflamed tissues ramp up the levels of proinflammatory cytokines, which contribute to chronic insulin resistance and metabolic inflexibility (Riera and Dillin, 2015). The presence of low-grade chronic inflammation, common of obesity-associated diseases, has been termed “metainflammation” (Lumeng and Saltiel, 2011). Because TRPV1 is a polymodal receptor activated by many reagents in the inflammatory milieu (Suri and Szallasi, 2008), it is plausible that the low-grade inflammation observed during obesity, diabetes, and aging sustains TRPV1 activation and exacerbates CGRP release, thus impacting negatively on metabolic health. Mutation of α-CGRP protects against diet-induced obesity by increasing energy expenditure, as observed in the TRPV1 mutant mice (Walker et al., 2010). Similarly, TRPV1 mutant animals present reduced metainflammation in the brain and skeletal muscle tissues (Riera et al., 2014), both shown to be critically involved in aging and insulin resistance upon inflammatory activation (Zhang et al., 2008, 2013). In addition to the regulation of insulin secretion from β-cells, CGRP mediates distinct pro- and anti-inflammatory immune activities that implicate this peptide in neuroimmunological communication (Assas et al., 2014; Harzenetter et al., 2007). The broad distribution of CGRP fibers and their association with immune cells including dendritic cells, mast cells, and T cells places CGRP as a key mediator of neuroimmune communication with the sensory fibers participating in both the mediation of sensory signals as well as a controller of immune function (Assas et al., 2014). Future studies investigating the neural-immune interaction involving TRPV1 fibers and CGRP secretion will uncover key mechanisms to understand age-dependent metainflammation.

14.5. Conclusion

In light of the evidence reviewed here, multiple members of the TRP channel superfamily have already been implicated in processes that drive the aging process. TRPA-1 functions as a cold sensor in nematodes in which activation drives daf-16 transcriptional activity, activating a genetic program associated with increased lifespan. Additionally, TRPV channels that are recruited for sensory perception of the environment appear to be tightly connected with regulation of neuroendocrine processes that affect aging in both nematodes and mice. TRPV1 afferent fibers secrete the neuropeptide CGRP, a natural inhibitor of insulin secretion with age. However, TRPV1 mutation results in enhanced insulin secretion with age and a youthful metabolic profile that leads to increased lifespan in mice. In accordance with these findings, the insulin secretion capacity of the beta cell, but not insulin resistance, has been shown to be the limiting factor that predicts the onset of diabetes (Goldfine et al., 2003) and appears to be a major gatekeeper of metabolic health in humans (Ahrén and Larsson, 2002). Remarkably, if the causal role of CGRP in regulating longevity remains unknown, considerable lifespan extension is observed in a rodent naturally lacking CGRP, the naked mole rat, an exceptionally long-lived rodent, with a lifespan that can reach 30 years. In comparison, mice that are of a similar size have a maximum lifespan of 4 years. Naked mole rats are fully resistant to cancer, which is reduced in TRPV1 knockout mice (Riera et al., 2014). However, whether CGRP plays a role in the extreme longevity of the naked mole-rat is unknown, and other mediators of this exceptional lifespan have been suggested. For example, naked mole-rat fibroblasts secrete extremely high-molecular-mass hyaluronan, which is over five times larger than the human or mouse homologs, and prevents tumorigenesis in this species (Seluanov et al., 2009; Tian et al., 2013). Nonetheless, these preliminary discoveries established a strong role for TRP channels in the regulation of aging, leading to the mobilization of intracellular Ca^{2+} within target cells to affect different transcriptional profiles associated with aging. Whether other TRP channels also play a role in the control of age-dependent health in sensory or nonsensory tissues remains unknown and will provide an exciting avenue of research for future studies.

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Figures

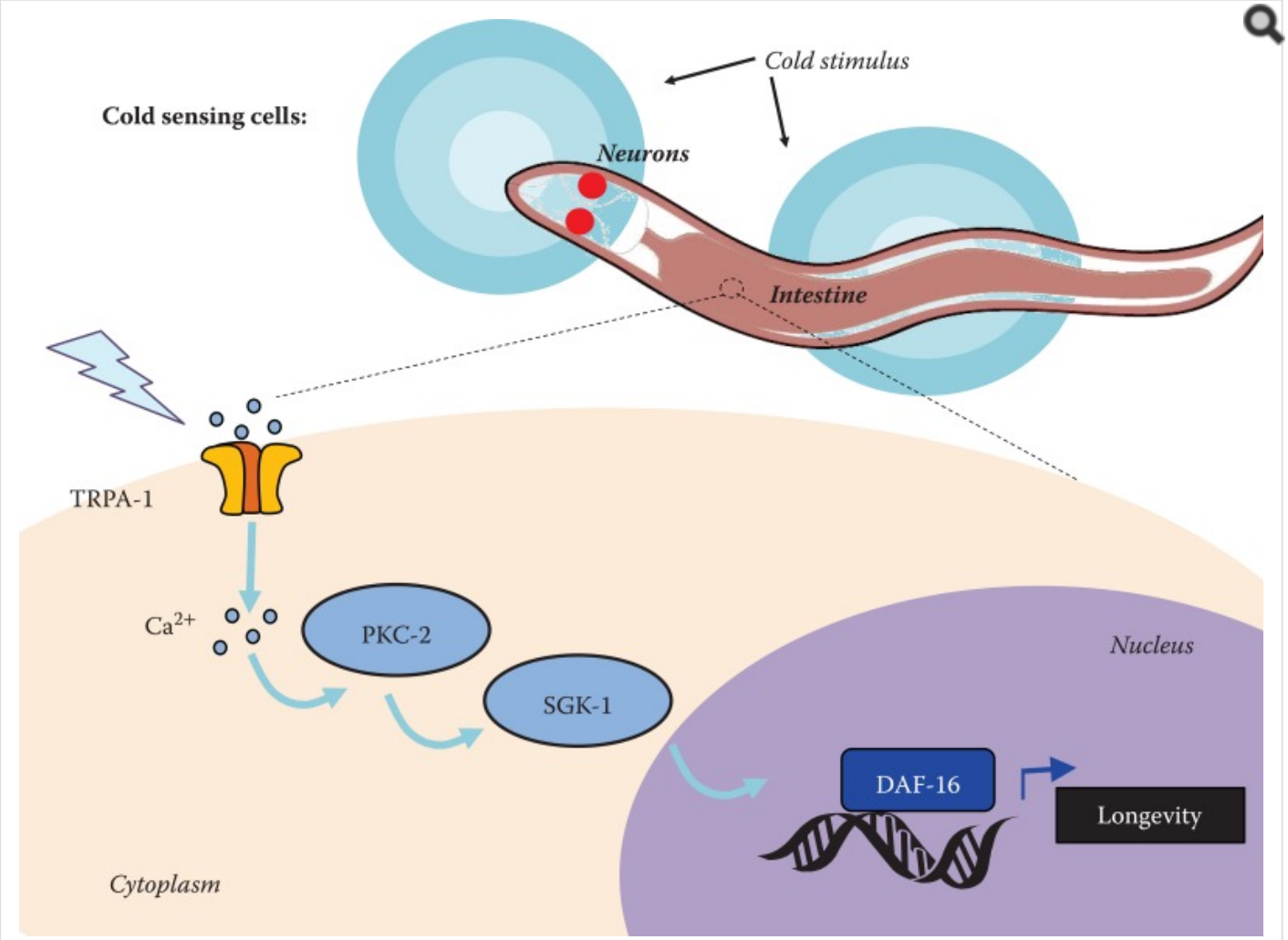

Figure 14.1

A genetic pathway that promotes longevity at cold temperatures in *C. elegans* upon TRPA-1 activation in cold sensing tissues (neurons and intestine). Calcium signaling triggers canonical Ca^{2+}-signaling cascade leading to the FOXO transcription factor DAF-16 to promote transcriptional programs that repress aging.

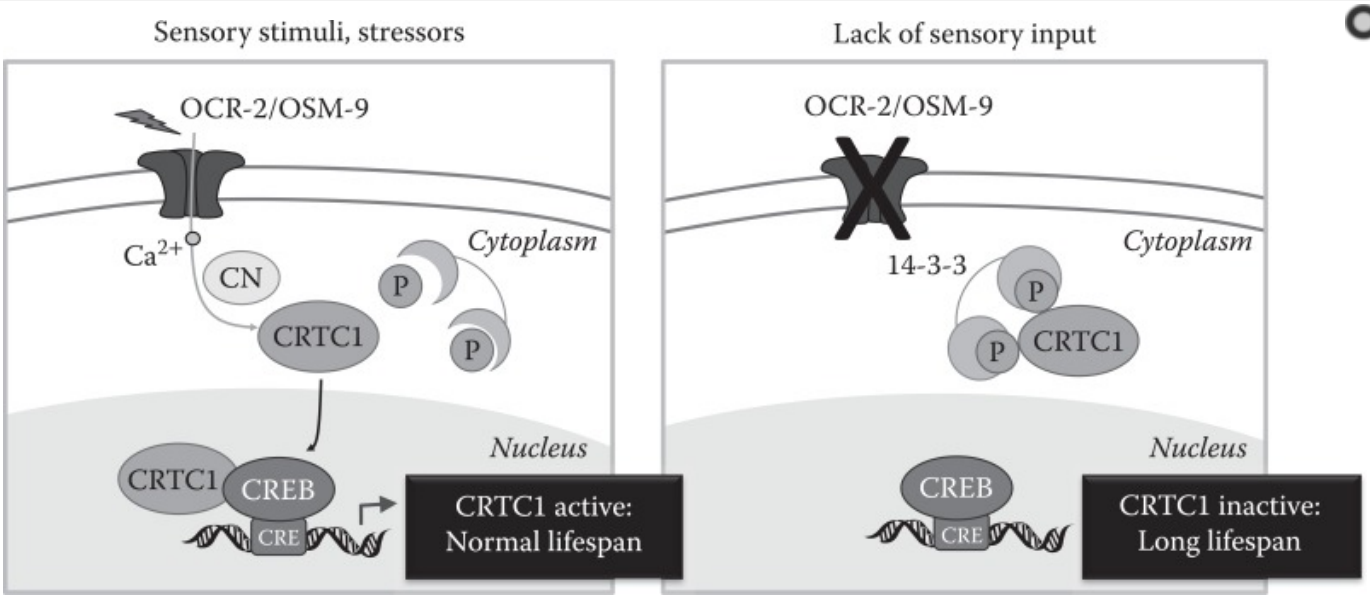

Figure 14.2

Model for the sensory regulation of aging by OCR-2/OSM-9–expressing neurons. Stimulation of OCR-2/OSM-9 by external stimuli results in Ca^{2+} influx and activation of the calcineurin TAX-6 (CN), allowing dephosphorylation of CRTC1 and release from 14-3-3 proteins, resulting in nuclear internalization of CRTC1 and transcription of its targets, resulting in normal lifespan. In contrast, loss of OCR-2/OSM-9 promotes lifespan extension through inactivating of the CRTC1/CREB signaling cascade.

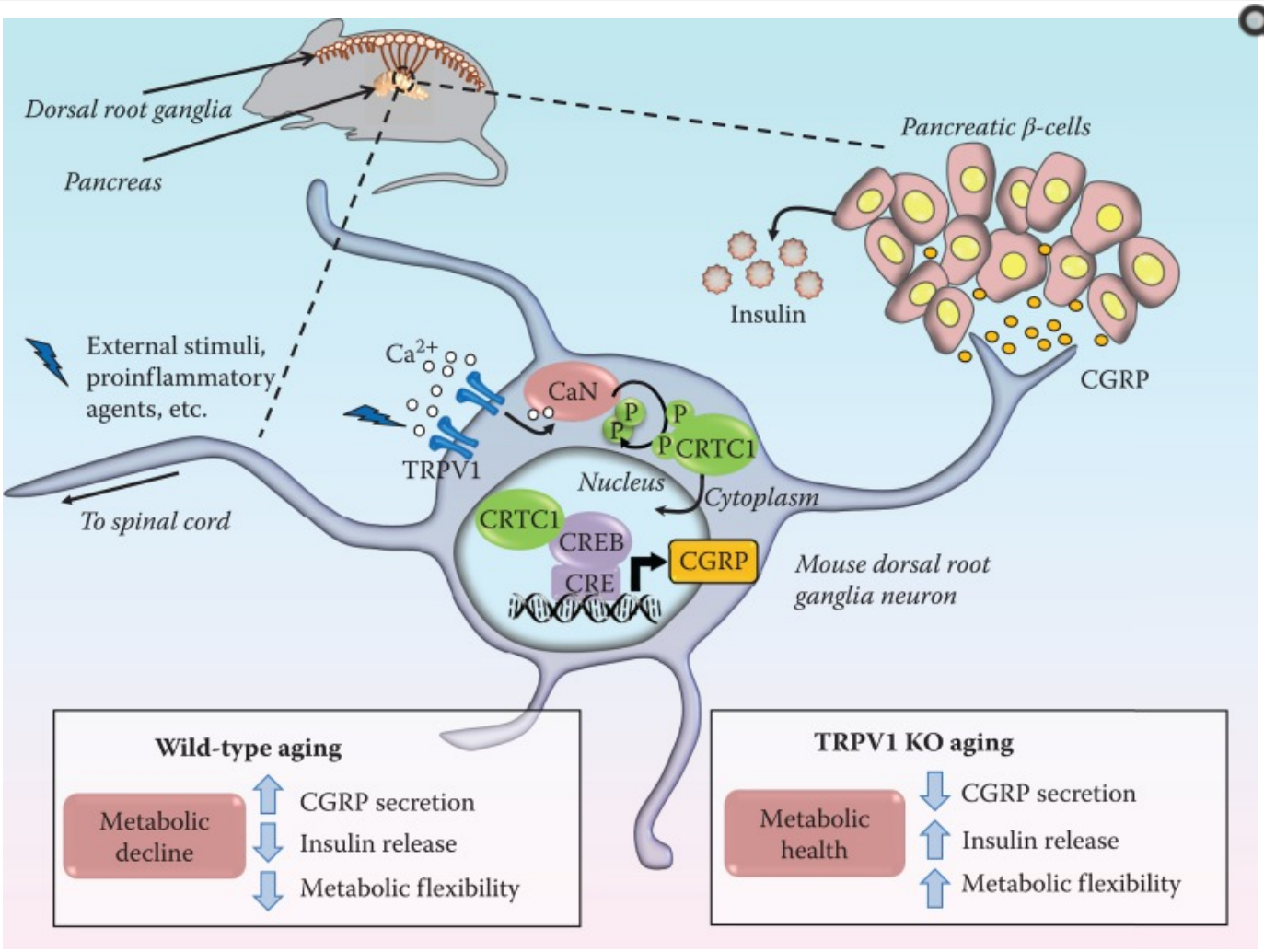

Figure 14.3

Model for the neuroendocrine regulation of metabolism by TRPV1-expressing neurons. Stimulation of TRPV1 by external stimuli promotes CGRP secretion from DRG neurons onto the pancreatic β-cells and inhibition of insulin release. TRPV1 activation results in Ca^{2+} influx and activation of calcineurin, allowing dephosphorylation of CRTC1 and release from 14-3-3 proteins, resulting in nuclear internalization of CRTC1 and transcription of its targets, such as CGRP. CGRP accumulation has detrimental effects on energy expenditure, glucose tolerance, and aging. In contrast, loss of TRPV1 promotes lifespan extension through increased insulin secretion, metabolic health by inactivation of the CRTC1/CREB signaling cascade.

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