Macronutrients and caloric intake in health and longevity

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Abstract

Both lifespan and healthspan are influenced by nutrition, with nutritional interventions proving to be robust across a wide range of species. However, the relationship between nutrition, health and aging is still not fully understood. Caloric restriction is the most studied dietary intervention known to extend life in many organisms, but recently the balance of macronutrients has been shown to play a critical role. In this review, we discuss the current understanding regarding the impact of calories and macronutrient balance in mammalian health and longevity, and highlight the key nutrient-sensing pathways that mediate the effects of nutrition on health and ageing.

Key Words

- calories
- macronutrients
- health
- lifespan
- longevity

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Introduction

Aging is one of the greatest societal challenges in the modern world. Lifestyle choices, improved technology and modern medicine have contributed to a rapidly growing aging population (Partridge 2014). While we live longer on average than our ancestors, increased lifespan is not without its drawbacks. The primary problem with living longer is that with increasing age comes a heightened risk of chronic diseases such as cancer, type 2 diabetes, stroke, dementia and cardiovascular disorders, leading to disability and related mortality (Fontana *et al.* 2010, Piper *et al.* 2011, de Cabo & Le Couteur 2015). Currently, the major focus of modern medicine is treating specific age-related diseases. However, with a growing number of older people encumbered with multiple chronic conditions (Fontana *et al.* 2014), this approach is problematic, e.g. leading to complications arising from multiple medications for different conditions (de Cabo & Le Couteur 2015). Rather than treat the symptoms of aging, a logical alternative approach would be to intervene in the aging process itself (Partridge 2014).

Interventions that slow the rate of aging and increase healthspan and lifespan have been of considerable interest over the past 80 years. While genetic and pharmaceutical interventions have been widely explored in laboratory models (Kenyon *et al.* 1993, Baur *et al.* 2006, Mitchell *et al.* 2014), translating such approaches to humans is difficult (Fontana & Partridge 2015). Nutritional manipulations, however, have proven to be similarly robust across multiple animal models and humans, with profound impacts on reproduction, health and aging. However, the complex relationship between nutrition and age-related health is not fully understood. A growing body of evidence has pointed to dietary restriction as an important mediator of health and lifespan (Masoro 2000, 2003,

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Miller *et al.* 2005, Piper *et al.* 2011). But what does dietary restriction actually mean? Throughout the literature, dietary restriction is often used interchangeably with caloric restriction (CR). Whereas dietary restriction can involve different feeding regimens such as intermittent fasting or alternate day feeding (Ingram & Roth 2015), CR refers more specifically to the reduction of total calorie intake by 20–50% without malnutrition (Weindruch *et al.* 1986, Masoro 2005). Recent evidence suggests that the balance of macronutrients, rather than total energy intake, plays a larger role in lifespan extension than previously attributed (Zimmerman *et al.* 2003, Mair *et al.* 2005, Solon-Biet *et al.* 2014). Whether calories or specific nutrients affect aging is a critically important issue to resolve, with important implications for aging research (Simpson & Raubenheimer 2007). In this review, we discuss the current understanding and impact of both calories and macronutrients on health and lifespan based on studies in invertebrate and mammalian models, and highlight the use of nutritional geometry as a framework to help disentangle the complex relationship between diet and healthy aging.

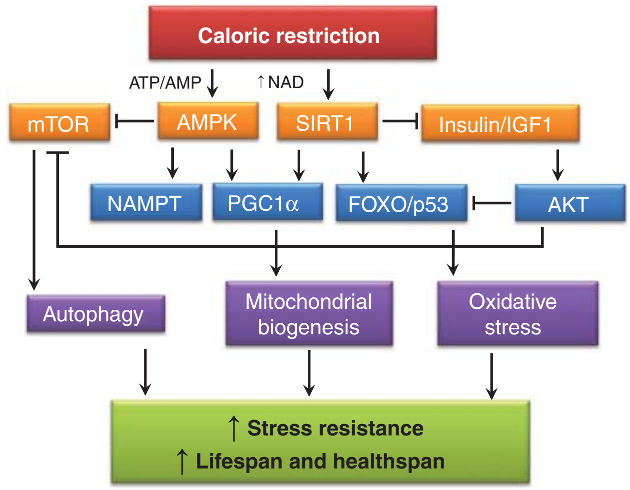

Figure 1
The complex metabolic network of potential players in the mechanism of caloric restriction (CR). A reduction in energy intake influences cellular energy levels, activating the AMPK and SIRT1 pathways. Antagonistic responses include the inhibition of the anabolic pathways mTOR and insulin/IGF1. Downstream effects result in increased stress resistance and improved lifespan and healthspan.

Dietary restriction

There is widespread consensus in aging research that eating fewer calories results in a longer, healthier life. To date, CR has been the primary focus of most non-genetic nutritional interventions (Mattison *et al.* 2003, Ingram *et al.* 2004, Sinclair 2005). Yeasts, nematode worms, fruit flies, rodents and even non-human primates have been used as models for the study of CR and aging, suggesting that these effects must act via evolutionarily conserved mechanisms (Fig. 1; Weindruch *et al.* 1986, Lin *et al.* 2000). Since the first account of the life-extending effects of CR in rats in the early 1930s, there has been a substantial amount of research into the dietary basis of aging (McCay *et al.* 1935). It was not until the early 1980s that the idea of CR as a viable model for aging and the study of age-related diseases really came to fruition (Masoro *et al.* 1982, Masoro 1991, Walford *et al.* 1992). Despite the great strides made towards understanding the mechanisms of CR, much still remains unknown. Initial work exploring CR as a robust nutritional intervention for aging began with yeasts, worms and flies. In yeast (*Saccharomyces cerevisiae*), CR is mediated by reduced glucose levels, extending both overall lifespan and replicative lifespan (Kaeberlein *et al.* 2005, Powers *et al.* 2006, Bonawitz *et al.* 2007) and in the worm *Caenorhabditis elegans* and the fruit fly *Drosophila melanogaster*, some forms of food restriction via nutrient manipulation also successfully extended lifespan (Partridge *et al.* 2005, Taormina & Mirisola 2014). Interestingly, the beneficial effect of CR does not appear to be universal. Although experiments in rodents produces a net beneficial effect to overall metabolic health in laboratory animals (Masoro 2000, Ingram *et al.* 2004, Bordone & Guarente 2005), the effects on lifespan extension are highly dependent on various other factors such as strain and sex (Festing & Blackmore 1971, Yuan *et al.* 2009, Liao *et al.* 2010). On average, 40% CR extends maximal lifespan in male B6D2F1 mice by 20% relative to *ad libitum* fed controls (Wolf *et al.* 1995). However, whether this effect also extends to females remains to be seen. We do know that CR extends lifespan in genetically heterogeneous mice created from four inbred strains (BALB/c, C57BL/6, C3H and DBA2), although more than 90% died of cancer, which may not be representative of the human situation (Miller *et al.* 2011). Translation into longer-lived mammals has continued to show conflicting results (Liao *et al.* 2010, Mattison *et al.* 2012). Two long-term studies in non-human primates were initiated in the early 1980s in order to address this question. Although both studies confirm the findings that CR delays the onset of age-associated diseases, CR monkeys from the National Institute on Aging (NIA) did not live longer than their *ad libitum* fed counterparts, which is in contrast to results obtained in the Wisconsin cohort (Colman *et al.* 2009,

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2014, Mattison *et al.* 2012). These results were attributed to possible discrepancies in diet design and diet composition (Mattison *et al.* 2012). NIA monkeys were fed a diet rich in natural ingredients such as protein derived primarily from plant sources while the Wisconsin monkeys were fed a semi-purified diet with protein derived from lactalbumin (Ingram *et al.* 1990, Ramsey *et al.* 2000). Carbohydrate quality also differed between studies with the NIA diets containing significantly less sucrose than the Wisconsin study (Mattison *et al.* 2012).

Such studies highlight the question of whether CR *per se* is solely responsible for extended longevity or if particular macronutrients or a balance of macronutrients is more important (Table 1). While the effect of CR on human lifespan is yet to be determined, CR has been shown to improve several markers of health (Heilbronn *et al.* 2006, Fontana *et al.* 2010). But despite these benefits, a central limitation is that compliance to lifetime CR is challenging in humans and the risk of missing essential nutrients can be detrimental to reproduction, bone structure and overall metabolic health (Fontana & Partridge 2015, Ingram & Roth 2015). Hence, dietary interventions involving *ad libitum* access to diets designed to prolong healthspan would be of greater utility than CR.

CR or protein restriction?

Recent studies have suggested that the beneficial effects of CR on lifespan may be due to the reduced intake of specific dietary components such as proteins, rather than total energy intake (Zimmerman *et al.* 2003, Mair *et al.* 2005, Piper *et al.* 2005, Pamplona & Barja 2006) with these effects acting largely through the same evolutionarily conserved signaling pathways (Fig. 2). The restriction of protein intake, rather than energy, may offer a more feasible nutritional intervention in humans. Work by McCay as early as 1929 reported that a low protein diet extended the lifespan of trout (McCay *et al.* 1929). Since then, it has been shown that the restriction of essential amino acids can increase lifespan in honeybees (Paoli *et al.* 2014), and the restriction of particular amino acids, such as methionine, can extend lifespan in mice (Sun *et al.* 2009) and rats (Orentreich *et al.* 1993, Richie *et al.* 1994), and lower the levels of serum insulin-like growth factor 1 (IGF1), insulin, glucose and thyroid hormone in (BALB/cJ × C57BL/6J) F1 mice (Miller *et al.* 2005). Recently, the restriction of essential amino acids (Robertson *et al.* 2015) and the sulfur amino acids methionine and cysteine (Robertson *et al.* 2015) have been shown to protect against hepatic ischemia reperfusion injury by preconditioning against oxidative stress, complications of cardiovascular surgery (Robertson *et al.* 2015) and mediating hydrogen sulfide (H_2S) production (Hine *et al.* 2015). H_2S production under protein restriction exerts a hormetic response, acting on brain signaling and the vascular system to reduce blood pressure and trigger the same signaling response cascade observed in animals fed protein-restricted diets via activation of GCN2, eIF2α and ATF4 and repression of mechanistic target of rapamycin (mTOR; Fig. 2; Hine *et al.* 2015, Robertson *et al.* 2015). Moreover, a meta-analysis of animal studies of CR and aging conclude that the restriction of protein, rather than CR, appeared to have the greatest effect on delaying aging (Nakagawa *et al.* 2012). Data in humans indicate that reduced protein intake may become an important component of anticancer and anti-aging dietary interventions (Fontana *et al.* 2008, Levine *et al.* 2014).

Macronutrient balance

While both CR and protein restriction have been shown to impact aging, a fundamental limitation of these two one-variable-at-a-time approaches is that they cannot disentangle the interactive effects of nutrients and calories (Simpson *et al.* 2015). Recent studies have begun to tackle these interactions and show the importance of the balance of macronutrients on health and aging. Such evidence has been derived using the Geometric Framework (GF) for nutrition (Simpson & Raubenheimer 2009, 2012). In the GF, nutrition is represented in an *n*-dimensional space, in which the components of *n* represent focal dietary components (e.g. macronutrients). Various phenotypic responses (e.g. lifespan) can be modelled onto this *n*-dimensional space, providing a detailed landscape of the effects of nutrition. Using this framework allows the use of nutritional geometry to simultaneously interpret the effects of energy, individual macronutrients (or other focal dietary components) and the interactions within and between nutrients (Piper *et al.* 2011, Simpson & Raubenheimer 2012). This framework has helped to resolve conflicting ideas about the nutritional determinants of health and aging, and to reconcile views on resource-mediated trade-offs between reproduction and longevity (Lee *et al.* 2008, Tatar *et al.* 2014, Jensen *et al.* 2015, Solon-Biet *et al.* 2015*a*).

Studies in both invertebrates and mice show that reproduction and longevity do not trade-off against one another, rather these responses have different nutritional requirements. In the field cricket *Teleogryllus commodus* and fruit fly *D. melanogaster*, the macronutrient blend that

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Table 1 Experiments on a range of organisms exploring CR, protein restriction and macronutrient balance

Animal	Lifespan increase	Beneficial health effects	Reproductive effects	References
Caloric restriction				
Yeast	Increase in mean and maximum lifespan with glucose depletion	Increased mitochondrial respiration	Biomass production impaired on low glucose treatments	Lin *et al.* (2004), Bonawitz *et al.* (2007) and Wu *et al.* (2013)
Worms	Up to 50% with bacteria-free media	Increase oxidative and thermal stress resistance	Number of eggs laid per worm increased	Hosono *et al.* (1989) and Houthoofd *et al.* (2002)
Flies	Up to 50% at 40% CR	Not reported	Egg production decreased with CR	Partridge *et al.* (2005)
Rhesus monkeys	Trend seen. Conflicting results about lifespan extension	Delay in age-related disease, improved metabolic health and decrease in cancer. Reduction in cardiovascular disease and brain atrophy	Unknown	Colman *et al.* (2009) and Mattison *et al.* (2012)
Humans	Unknown	Reduced risk of age-related disease such as diabetes, stoke, cardiovascular disease, obesity, metabolic disorders and cancer	Late reproductive maturity, suppressed ovarian function and impaired fecundity	Heilbronn & Ravussin (2003), Fontana & Klein (2007) and Mercken *et al.* (2012)
Protein restriction				
Flies	Yeast-restricted flies also show median and maximal lifespan extension	Not reported	CR reduces lifetime fecundity	Mair *et al.* (2005) and Grandison *et al.* (2009)
Mice	Maximal lifespan extended by methionine restriction	Reduced IGF1, insulin, glucose and thyroid hormone levels. Delayed immune impairment and cataracts	Not reported	Miller *et al.* (2005)
Rats	Mean and maximal lifespan extended by methionine restriction	Reduced body weight	Not reported	Richie *et al.* (1994)
Humans	Decreased mortality by 25% in people aged 50–65. Higher protein intake associated with reduced mortality in people over 65	Fourfold decrease in cancer death risk in people aged 50–65. Fivefold decrease in diabetes overall	Not reported	Levine *et al.* (2014)
Macronutrient balance				
Flies	Threefold on diets with a low protein:carbohydrate ratio	Increased triglyceride storage on low protein diets	Higher protein:carbohydrate ratios optimized reproduction	Lee *et al.* (2008), Skorupa *et al.* (2008), Fanson *et al.* (2009), Bruce *et al.* (2013) and Jensen *et al.* (2015)
Crickets	Up to 3.5-fold on diets with a low protein:carbohydrate ratio	Not reported	Responses vary by sex. Reproduction optimized at higher protein: carbohydrate ratios females only	Maklakov *et al.* (2008)
Mice	~30% on diets with a low protein:carbohydrate ratio	Improved blood pressure, lipid profiles, mitochondrial function, insulin sensitivity, HOMA and immune function	Reproduction optimized in diets with a higher protein: carbohydrate ratio compared to lifespan	Le Couteur *et al.* (2014) and Solon-Biet *et al.* (2014, 2015*a*,*b*)

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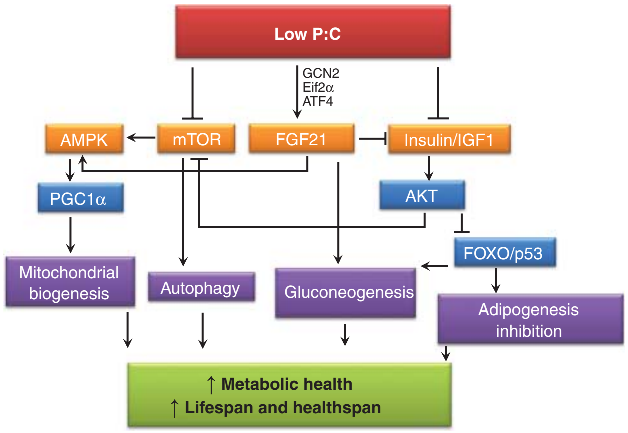

Figure 2
The complex metabolic network of potential players in the mechanism of low protein:carbohydrate (P:C) diets. Low P:C diets activate GCN2 and FGF21 and inhibit activation of mTOR and insulin/IGF1. Inhibition of these pathways activate AMPK and AKT, resulting in improved metabolic health, lifespan and healthspan.

maximized lifespan was markedly different from diets which maximized reproductive variables (Maklakov *et al.* 2008, Jensen *et al.* 2015). Maximal longevity occurred on low protein (P), high carbohydrate (C) diets in both males and females, while a higher P:C ratio was better for reproduction in females only. Consuming a low proportion of protein in the diet relative to carbohydrate, not total calories, extended lifespan in *ad libitum*-fed flies (Lee *et al.* 2008, Bruce *et al.* 2013), while diets with a higher proportion of protein shortened lifespan but improved reproduction (Lee *et al.* 2008). This result has been replicated in several other insect species (Lee *et al.* 2008, Dussutour & Simpson 2009, Fanson *et al.* 2009, Grandison *et al.* 2009, Piper *et al.* 2011) and consistently indicates that the balance of macronutrients is the chief nutritional cue that directs metabolism towards longevity or reproduction (Wilder *et al.* 2012). A recent study in mice showed that *ad libitum* low protein, high carbohydrate diets fed short-term improved several markers of health including insulin, homeostatic model assessment (HOMA), glucose tolerance and triglycerides to a level comparable to CR, but without at 40% reduction in total calorie intake (Solon-Biet *et al.* 2015*b*). Long-term investigations in *ad libitum*-fed mice across 25 different diets varying in macronutrient composition support these findings, showing that latelife health and longevity were optimized not by reducing energy intake, but by low P:C diets (Solon-Biet *et al.* 2014). In an attempt to stabilize protein intake, mice displayed a compensatory increase in food intake on low protein diets, resulting in increased energy intake and greater adiposity, but experienced a significant increase in lifespan, improved blood pressure, lipid profiles, mitochondrial function, insulin sensitivity (Solon-Biet *et al.* 2014) and immune function (T and B cell populations) measured at 15 months (Le Couteur *et al.* 2014). These health and longevity consequences were shown to be related to circulating branched chain amino acid (BCAA) levels, which, interestingly, were the only amino acids to be positively correlated to protein intake under chronic feeding conditions. BCAA levels were the lowest in mice on the low protein, high carbohydrate diets correlating to diet treatments that yielded the longest health and lifespan.

Reports about the role of BCAAs in aging and health are seemingly divergent. Some suggest that elevated BCCAs are harmful because they are linked with obesity and diabetes, while others suggest that BCAAs should be supplemented to increase mitochondrial biogenesis (D'Antona *et al.* 2010). For example, in a major review, Newgard (2012) noted that human epidemiological studies and animal studies show that elevated BCAAs are associated with and predict diabetes, obesity and heart disease, while animal and cell studies show that BCAA supplementation increases activation of certain nutrient signaling pathways which are detrimental for aging (Chotechuang *et al.* 2009). In another review, Valerio *et al.* (2011) argue that BCAAs increase mitochondrial biogenesis and muscle function, thus BCAA supplementation should be considered as a treatment for older people. While the exact roles of BCAAs in health and lifespan are yet to be determined, evidence suggests that BCAAs may be an important mediator of key molecular pathways that link nutrition with aging.

Nutrient-sensing pathways

Nutrient-sensing pathways that mediate the effects of nutrition on health and aging have been explored in many experimental models (Fontana *et al.* 2010, Hubbard & Sinclair 2014, Chantranupong *et al.* 2015). These include the evolutionarily conserved key regulators mTOR, AMP-activated protein kinase (AMPK), insulin/IGF1 and sirtuins. Both calories and macronutrients influence these pathways which have evolved to respond to periods of famine by switching cells and organism from their focus on growth and reproduction, towards survival and resilience (Fig. 3; Kapahi *et al.* 2010, Speakman & Mitchell 2011, Le Couteur *et al.* 2012). Although there are at least four key nutrient-sensing pathways implicated in longevity, these interact and share many downstream targets

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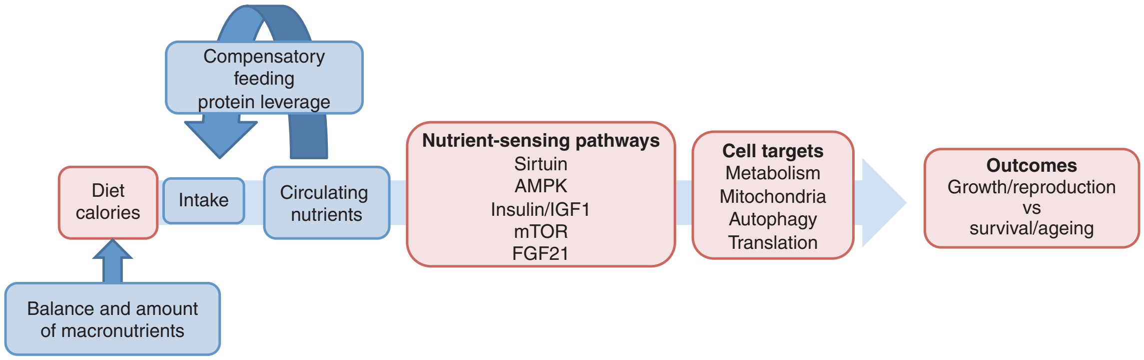

Figure 3
Schema showing the mechanism for the beneficial effects of caloric restriction on aging. The red boxes show the standard view based on energy intake. The impact of the balance of macronutrients and compensatory feeding in *ad libitum* diets in relation to this pathway (blue boxes). This more closely approaches real-life feeding in animals and humans that have unlimited access to food across a wide range of macronutrient compositions.

that regulate cell processes involved in aging, including mitochondrial biogenesis, cellular metabolism, autophagy, DNA repair and expression, and translation.

Mechanistic target of rapamycin

In eukaryotic cells, mTOR is highly conserved and acts as a central regulator of growth and metabolism in response to nutrient and growth factor cues (Stanfel *et al*. 2009). This pathway is involved in anabolic processes including protein and lipid synthesis (Efeyan *et al*. 2015). mTOR integrates input from various pathways, including insulin and IGF1, and responds to dietary protein, particularly BCAAs (Chotechuang *et al*. 2009, Solon-Biet *et al*. 2014). In addition, mTOR responds to changes in cellular energy levels, altered genetic makeup, gene manipulations and pharmacological interventions that affect lifespan (Arsham *et al*. 2003, Wang & Proud 2009, Tato *et al*. 2011). In mammals, mTOR has two structurally and functionally distinct multiprotein complexes: mTORC1 and mTORC2 which are differentiated by their accessory proteins, Raptor and Rictor (Jacinto *et al*. 2004). mTORC1 is the only complex sensitive to amino acids (Yuan *et al*. 2013) and is the primary modulator of protein, lipid, nucleotide synthesis and autophagy while mTORC2 is involved in cell proliferation and survival (Chantranupong *et al*. 2015). In animal models, it has been demonstrated that inhibition of mTOR protects against metabolic dysfunction, obesity, cancer and neurodegeneration (Stanfel *et al*. 2009) which can be achieved through pharmaceutical interventions such as rapamycin (Harrison *et al*. 2009, Miller *et al*. 2011) or nutritional interventions such as alterations in the ratio of dietary P:C (Solon-Biet *et al*. 2014). In mice, mTOR was activated most strongly by the ratio of circulating BCAA to glucose (i.e. the P:C), providing a key mechanistic link from the longevity and health impacts of low P:C diets to the mTOR pathway. Reducing mTOR signaling is critical for improved health and lifespan.

AMP-activated protein kinase

AMPK regulates cellular uptake of glucose, β-oxidation of fatty acids, the glucose transporter 4 (GLUT4) and mitochondrial biogenesis. Activation of AMPK has been proposed as one of the mechanisms through which CR has beneficial effects on lifespan and healthspan (Cantó & Auwerx 2011). AMPK is a serine/threonine protein kinase, which is activated by cellular stresses that alter the AMP:ATP ratio resulting in depletion of ATP. As a consequence, ATP-consuming pathways are turned off, while ATP generation is turned on (Dagon *et al*. 2006). AMPK is a heterotrimeric protein comprised of one catalytic (α) and two regulatory (β and γ) subunits containing the kinase domain which when phosphorylated results in increased AMPK activity (Dagon *et al*. 2006). Recently, Mair *et al*. (2011) showed that CREB protein-regulated transcriptional co-activator (CRTC1) is an essential target for AMPK-mediated lifespan extension in *C. elegans*. Longevity via transcriptional regulation of AMPK occurred through CRTC1 downregulation, with neuronal CRTC1 playing a primary role in regulating

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longevity and mitochondrial metabolism in peripheral tissues (Mair *et al.* 2011, Burkewitz *et al.* 2015). In mammals, hepatic AMPK activation acts to slow gluconeogenesis and downregulate key genes such as G6Pase and PEPCK, while in the muscle, it stimulates glucose uptake by increasing expression of glucose transporters such as GLUT4 (McCarty 2004). The cardioprotective effects of short-term CR are thought to be mediated through AMPK activation (Shinmura *et al.* 2007). Administration of the drug metformin enhances lifespan in mice and this is accompanied by an increase in AMPK activity (Martin-Montalvo *et al.* 2013), hence AMPK modulation represents an attractive target for inducing CR-like benefits. By activating this nutrient sensor, AMPK can extend healthspan and lifespan by restoring energy balance via catabolic responses such as fatty acid oxidation, proteolysis and inhibiting processes not essential for survival such as cell growth and proliferation (Cantó *et al.* 2009). These responses have been shown to underlie the beneficial effects of CR. Whether AMPK activation reflects the balance of dietary macronutrients as well as measures of energy status remains to be seen, but has been postulated (Simpson & Raubenheimer 2009).

Sirtuin pathway: SIRT1

Sirtuins have been shown to regulate the aging process and mediate CR-induced longevity in organisms including *S. cerevisiae*, *C. elegans* and *D. melanogaster* (Guarente & Kenyon 2000). Sirtuins are class III histone deacetylases that require NAD^+ as a cosubstrate. CR increases cellular NAD^+ as a consequence of reduced energy intake, thereby activating sirtuins. In mammals, there are seven homologs (SIRT1–7) that have been identified. SIRT1 remains perhaps the best and most studied, which is likely due to it sharing the most sequence similarity with the yeast Sir2 (Frye 2000, Allard *et al.* 2009). SIRT1 has multiple functions, some of which are outlined in Fig. 1, and include deacetylation of a large number of transcription factors (Guarente 2006, Longo & Kennedy 2006, Boily *et al.* 2008), and regulation of PGC1α (Rodgers *et al.* 2005, Gerhart-Hines *et al.* 2007, Sun *et al.* 2007). In middle-aged rats, CR has been reported to increase the expression of SIRT1 protein in brain, fat, kidney and liver (Cohen *et al.* 2004, Nisoli *et al.* 2005). In young CR mice, SIRT1 protein expression was increased in muscle and fat but markedly reduced in the liver (Chen *et al.* 2008). The SIRT1 protein, but not its increased expression, is essential for lifespan extension in CR mice (Mercken *et al.* 2013). There is a number of pharmacological agents that allosterically activate SIRT1 and delay aging, including resveratrol and SRT2014 (Howitz *et al.* 2003, Baur *et al.* 2006, Milne *et al.* 2007, Mercken *et al.* 2014, Sinclair & Guarente 2014). Notably, resveratrol increased lifespan in mice fed a high fat diet but not in mice on standard chow where only health benefits were observed (Baur *et al.* 2006, Pearson *et al.* 2008). This suggests that activation of the SIRT1 pathway may have its greatest effect on aging where there is high energy intake and greatest inhibition of SIRT activity.

Insulin/IGF1

Lower levels of insulin and IGF1 induced by CR or low P:C diets are associated with improved health and increased lifespan across taxa including humans (Fontana *et al.* 2010, Miller *et al.* 2011, Levine *et al.* 2014). Mice with mutations along the growth hormone–IGF1–insulin pathway have been shown to be long-lived (Flurkey *et al.* 2001, Hsieh *et al.* 2002) and low IGF1 levels in humans can predict survival in people with exceptional longevity (Milman *et al.* 2014). The balance of macronutrients, namely low P:C, reduces insulin levels and HOMA in mice (Solon-Biet *et al.* 2014) supporting findings that inhibiting this pathway through diet is important for healthspan and lifespan extension. Moderating insulin secretion either by diet or administration of metformin can reduce insulin/IGF1 signaling via activation of AMPK (McCarty 2004), facilitating glucose uptake into the cell, reducing glucose, insulin and IGF1 levels, leading to the prevention, or even reversal, of insulin resistance (Minor *et al.* 2010).

Fibroblast growth factor 21: an emerging key regulator?

A recent potential addition to these four classical nutrient sensing pathways is fibroblast growth factor 21 (FGF21), which is emerging as an endocrine signal associated with metabolic control. It is increased in response to acute starvation but also in the obese/diabetic condition, with a recent study showing that low protein intake is the major stimulant for its expression in liver and subsequent increase in the circulation (Laeger *et al.* 2014). FGF21 regulates several metabolic functions (gluconeogenesis, mitochondrial activity, ketogenesis, lipid metabolism and energy expenditure), which would be expected to be beneficial for age-related health. Similar effects have been reported in response to dietary methionine restriction (Lees *et al.* 2014, Stone *et al.* 2014). Although circulating FGF21 derives primarily from liver, it is also expressed in other metabolically important tissues, including white

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and brown adipose tissue, skeletal muscle, heart and pancreas (exocrine and β cells). Such a pattern of expression is indicative of a role for this hormone in metabolic control. Just as for the four other nutrient sensing pathways previously discussed are highly interconnected, FGF21 too, plays a communicated role in nutrient signaling and has been shown to activate AMPK and SIRT1 (Chau *et al*. 2010), suggesting a role for FGF21 in linking nutrition and aging.

Outlook

This review has focused primarily on the relationships between calories and macronutrients and their effects on health and aging. Although both CR and macronutrient balance have profound impacts on health and lifespan, it is important to note that other dietary regimens such as intermittent fasting and time-restricted feeding, also have beneficial effects in both mice and humans (Mattson *et al*. 2014, Fontana & Partridge 2015). The fact that results of Solon-Biet *et al*. (2014) show that limiting energy intake by dilution under *ad libitum* conditions has no benefit, yet under CR protocols it does, must suggest that it is not just the restriction *per se* that matters, but also the timing of intake (Simpson *et al*. 2015). Exactly how the complex network of nutrient signaling pathways interact to mediate the effects of various feeding regimens remains to be investigated. Although considerable research has gone into understanding these underlying mechanisms, none have yet studied it as a function of multiple nutrient dimensions. As highlighted in a recent review (Simpson *et al*. 2015), different nutritional interventions will have different effects on these pathways and understanding exactly how multiple nutrient dimensions affect these pathways can only be done using a framework that integrates these components simultaneously. The GF is such a tool. Exactly how calories and macronutrients, and the interplay of both, influence these pathways is a fundamental question to resolve. A better understanding can have important implications for diet management, disease prevention and pharmaceutical interventions.

Declaration of interest
The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of this review.

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