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Energetic Interventions for healthspan and resiliency with aging

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Abstract

Several behavioral and pharmacological strategies improve longevity, which is indicative of delayed organismal aging, with the most effective interventions extending both life- and healthspan. In free living creatures, maintaining health and function into old age requires resilience against a multitude of stressors. Conversely, in experimental settings, conventional housing of rodents limits exposure to such challenges, thereby obscuring an accurate assessment of resilience. Caloric restriction (CR) and exercise, as well as pharmacologic strategies (resveratrol, rapamycin, metformin, senolytics), are well established to improve indices of health and aging, but some paradoxical effects have been observed on resilience. For instance, CR potentially retards the onset of age-related diseases, and improves lifespan to a greater extent than exercise in a variety of models. However, exercise has proven more consistently beneficial to organismal resilience against a broad array of stressors, including infections, surgery, wound healing and frailty. CR can improve cellular stress defenses and protect from frailty, but also impairs the response to infections, bed rest and healing. How an intervention will impact not only longevity, health and function, but also resiliency, is critical to better understanding translational implications. Thus, organismal robustness represents a critical, albeit understudied aspect of aging, which needs more careful attention in order to better inform on how putative age-delaying strategies will impact preservation of health and function in response to stressors with aging in humans.

Introduction

A growing list of genetic, behavioral and pharmacologic strategies have shown the ability to improve longevity in pre-clinical models (Barzilai and others 2012). Moreover, these approaches have proven effective at delaying the onset of age-related diseases and preserving healthspan across multiple domains, including cognitive, cardiovascular, neuromuscular and metabolic function (Barzilai and others 2012). Interestingly, the vast majority of these interventions, including caloric restriction, exercise, rapamycin, resveratrol and metformin, are involved in modulating features of energetic, metabolic and inflammatory pathways. Similarly, acarbose, 17- α -estradiol and nordihydroguaiaretic

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acid all modulate key aspects of metabolism and cellular signaling, and preferentially extend male longevity (Harrison and others 2014). More recently, senolytic drugs, which selectively kill senescent cells, have emerged as a new class of agents that delay the onset of aging-related conditions (Zhu and others 2015a; Zhu and others 2015b).

The evaluation of lifespan, which is the time from birth until death of an organism (Tissenbaum 2012), and healthspan, which can be defined as the length of healthy lifespan prior to onset of age-related decline (Tissenbaum 2012), remain a cornerstone of evaluating intervention efficacy in aging research. However, it is becoming increasingly appreciated that housing rodents in conventional, unprovoked conditions, rather than exposed to the same variety of stressors normally encountered by free-living humans, fails to adequately assess resiliency, and introduces uncertainty about translational potential. In ecology, resilience has been defined as the capacity of an ecosystem to respond to a perturbation or disturbance by resisting damage and recovering quickly (Holling 1994). Similarly, physiologic resiliency, can be broadly defined as the ability of an organism to cope with a challenge, and return to normal baseline function following the perturbation. Common challenges to physiologic human resiliency include surgical stress, burns, bone fractures, metabolic duress (e.g. obesity, metabolic syndrome), chemotherapeutic regimens, toxins, infections, immobility and bed rest, among others.

The concept of physiologic resiliency as it relates to aging, has been proposed by a number of groups in a variety of contexts (Ferrucci and others 2008; Sorrell 2008; Varadhan and others 2008; Whitson and others 2008; Wook Yoo and others 2015), and is recognized to decline with age due in part to a progressive accumulation of molecular and cellular damage and weakening of interactions among multiple physiologic regulatory functions, leading to a loss of physiologic reserves and impaired ability to restore homeostasis and function. Importantly, the gradual loss of resiliency with age contributes to, and may underlie the onset of aging-related conditions, including chronic disease, multimorbidity, frailty syndrome, and death (Bergman and others 2007; Fabbri and others 2015; Ferrucci and others 2008; Fried and others 2001; Piggott and others 2015; St Sauver and others 2015) (Figure 1). Robust early life resilience may also be inherently related to healthy aging and longevity in experimental models. For instance, long-lived mice (*i.e.*, mutant dwarf and calorie restricted mice) exhibit increased immune, stress, and defense responses, at least at the level of transcription (Schumacher and others 2008), while fibroblasts from dwarf mice (Salmon and others 2005) are also more resistant to a variety of stressors. Collectively, these traits favor somatic maintenance over growth and may underlie their more robust health- and lifespan (Panici and others 2010). However, as will be discussed in more detail, physiologic resilience of calorie-restricted mice to a variety of extrinsic stressors has not always produced beneficial effects. Therefore, it will be critical that the field consider resiliency to stressors as an essential component in the evaluation of age-delaying interventions.

This review will mainly focus on current evidence, gaps and limitations in what is known about energetic and metabolic interventions on resilience, and provide future directions to consider in advancing this important domain in aging research. In particular, much of what we know about resiliency with these strategies is gleaned from studies in young animals, often in only one sex, suggesting that the purported impact of these regimens will likely

need to be revisited in aged rodents (and humans when possible) of both sexes. Furthermore, the extent to which these interventions can acutely and preemptively promote resiliency (i.e. anticipated surgery), and/or attenuate the age-related decline in resilience with chronic use, is an issue that has not been well studied. A resolution to these matters will undoubtedly help in guiding appropriate ways forward to broadly and strategically boost resiliency in the aging population.

Dietary Strategies

Caloric restriction (CR) remains the most robust dietary intervention for the extension of lifespan and delay of age-related diseases in diverse species (Barzilai and others 2012). However, it has become increasingly clear that this response is not universal (Austad 2012; Liao and others 2010), and the extent to which CR will prove efficacious in humans remains an issue of debate (Cava and Fontana 2013). Nevertheless, CR consistently retards the development of cancer (Longo and Fontana 2010; Weindruch 1992), cardiovascular disease (Fontana and others 2004; Meyer and others 2006), metabolic syndrome (Larson-Meyer and others 2006) (Ravussin and others 2015), and cognitive decline (Halagappa and others 2007; Sridharan and others 2012). In addition, animals on CR are also more insulin sensitive, and harbor less adiposity, systemic inflammation, and signs of oxidative and cellular stress (Barzilai and others 2012). Methodologically, CR is often implemented at a very early age, and is either studied in the context of youth, or after life-long treatment. Less is known about the effects of imposing CR at later ages, but evidence suggests diminishing benefits on lifespan with increasing age of onset (Speakman and Hambly 2007).

In regard to resiliency, both short and long-term CR have been studied in a variety of contexts. One major domain of interest is its effects on immunity and resistance to infections. CR can extend lifespan of rodents (Weindruch 1996), and slows the decline of some features of immunosenescence with aging (Yang and others 2009). However, while CR of short and moderate duration (3–11 wks) has proven mostly beneficial to immune response (Kristan 2008), other reports where caloric-restricted rodents were challenged with infectious agents, such as West Nile virus (Goldberg and others 2015), influenza (Gardner 2005) or intestinal parasites (Kristan 2007), demonstrated an impaired ability to cope with these stressors (Gardner 2005; Gardner and others 2011; Kristan 2007; McCaskey and others 2012). The adverse effects of CR further extend to decreases in Natural Killer (NK) cell maturation and cytotoxicity (Clinthorne and others 2013), as well as alterations in T-cell development and function (Goldberg and others 2015). However, re-feeding previously energy restricted mice restores NK function (Clinthorne and others 2010), demonstrating that this phenotype is transiently modulated and reversible by restoration of energy availability. Therefore, these data highlight an important adverse consequence of CR on immune function that is not detectable in animals housed in conventional, unprovoked conditions.

In contrast to some of the apparently detrimental effects of CR on immunity, short-term restriction regimens appear to confer protection from some features of surgical stress. Utilizing an ischemia-reperfusion model of injury, a preemptive CR regimen (dietary preconditioning) mitigated liver and renal organ damage in young mice (Mitchell and others

2010; Robertson and others 2015), while fasting of the donor improved outcomes of liver transplantation as well as hepatic regeneration following partial hepatectomy. CR was also shown to mitigate weight loss following implantation of a jugular canula in F344 rats (Masoro 1998), though concerns have been raised regarding CR in the context of wound healing (Robertson and Mitchell 2013), which is a time when energy demands are increased. Indeed, wound healing has been shown to be adversely impacted by CR (Hunt and others 2012; Reiser and others 1995), but these effects could be mitigated by a short-term refeed of CR animals prior to wounding. An additional concern with long-term CR involves effects on the musculoskeletal system as CR may increase propensity for age-related loss of bone (osteopenia) and skeletal muscle (sarcopenia), potentially contributing to the development of frailty. Indeed, a 24 mo CR regimen in humans reduced bone density in regions vulnerable to fracture (Villareal and others 2015), a finding corroborated by some (Devlin and others 2010), but not all animal studies (Hepple and others 2005). However, while a characteristic change with CR is a reduction in lean body mass, long-term CR has been shown to oppose age-related sarcopenia and preserve skeletal muscle in aged rhesus monkeys (McKiernan and others 2012). Likewise, long-term CR in rodents has been shown to protect against declines in mitochondrial function, oxidative capacity and proteostasis (Baker and others 2006; Hepple and others 2005; Hepple and others 2006; Hepple and others 2008). Furthermore, it was recently demonstrated that lifelong CR reduced the frailty index score in aged C57BL/6J mice (Kane and others 2015).

While CR has proven to be a valuable tool to understand mechanisms involved in slowed or accelerated aging phenotypes, it has not proven to be a sustainable, practical intervention for most individuals over the long term. Thus, alternative strategies, including short-term fasting, as well as alternate day feeding regimens (Castello and others 2011; Heilbronn and others 2005) and manipulation of macronutrients (Levine and others 2014; Solon-Biet and others 2014) and micronutrients (Miller and others 2005; Sun and others 2009) have been explored and found to recapitulate at least some of the beneficial effects of CR. Work from the Longo Laboratory has found that nutrient deprivation in yeast as well as short-term fasting regimens in rodents (3 days) can dramatically improve both cellular and whole organismal stress resistance (Longo and Fabrizio 2002). In *in vivo* studies, fasting was elegantly shown to improve resiliency in response to chemotherapeutic stress in mice by simultaneously protecting normal cells, while sensitizing malignant cells to treatment. Moreover, short-term fasting (Lee and others 2012a; Lee and others 2010; Safdie and others 2012), but not acute bouts of reduced protein or CR (Brandhorst and others 2013), conferred protection against chemotoxicity and enhanced treatment efficacy. A modified version of this protocol is under investigation in humans as a strategy to improve chemotherapy outcomes (Safdie and others 2009).

In summary, while CR has proven to be a robust strategy to improve multiple domains of healthspan and longevity in captive laboratory animals, its ability to promote resiliency and confer protection against a variety of environmental stressors has been mixed. CR has clearly favorable effects on preventing metabolic duress linked to overnutrition (Kitada and others 2013) and age-related metabolic decline, as well as promoting cellular stress resistance. Surprisingly, CR also confers protection against age-related sarcopenia, but adversely affects resiliency against a variety of infections, the rate of wound healing and

closure, and preservation of bone mass in some studies. Interestingly, short-term fasting regimens, which is able to induce many of the same cellular pathways as CR, but without many of the 'side effects' associated with chronic energy restriction, appear well suited to enhance chemotherapy outcomes. Furthermore, it seems plausible that combining CR with increased physical activity, which is discussed in more detail below, could oppose many of the adverse effects linked to CR alone, and improve resiliency. Nevertheless, additional studies are needed, particularly in aged animals, to definitively determine the effect of short versus long-term CR, the optimal dose and duration of CR, as well as combinatorial strategies with re-feeding or exercise, to strategically improve outcomes in humans.

Exercise

Physical activity is a robust energetic intervention that reduces mortality rates in humans (Moore and others 2012; Samitz and others 2011). In Rodents, voluntary wheel running has been shown to improve survival in male rats, but fails to extend lifespan (Holloszy and others 1985; Navarro and others 2004). However, exercise has been strongly linked to the extension of healthspan and preservation of function, delayed onset of age-related diseases (Garcia-Valles and others 2013). Indeed, physical activity significantly lowers the risk of numerous age-related conditions, including heart disease, stroke, cancer, dementia, and frailty (Pedersen and Saltin 2006). Conversely, sedentary behavior is now recognized as a key modifiable risk factor and cause of chronic disease (Booth and others 2012). In a systematic review, the greatest sedentary time compared to the lowest, was associated with 112% increase in the relative risk of diabetes, a 147% increase in the RR of cardiovascular events, and a 90% increase in the risk of cardiovascular mortality (Wilmot and others 2012). Thus, physical activity interventions provide a safe, effective, inexpensive, and scalable means to reduce chronic disease risk, extend healthspan, (O'Gorman and others 2006) and potentiate resilience (Singh and others 2013).

Structured exercise is a tractable approach to increase moderate-to-vigorous physical activity. Benefits arising from both aerobic and resistance exercise occur through adaptation. Bouts of exercise are associated with mechanical, humoral, and metabolic stimuli, which drive transient pulses in transcriptional and translational activation that return to basal levels during rest and recovery (Kraemer and Ratamess 2005; Pilegaard and others 2000). The net effect of temporal activity repetition is a gradual accumulation of cellular protein and organelle material to support increased energy demands (Fluck 2006). The phasic bolus-recovery principle underlying exercise-mediated tissue remodeling is also responsible for the adaptive stress-resistance benefits of exercise. Central to this notion is the concept of hormesis—the theory that chronic or interval exposure to a low-grade negative stress affords enhanced resilience over the long term and in response to large doses of a similar stimuli (Radak and others 2008). Upregulation of oxidative energy metabolism to meet increased ATP requirements results in inexorable production of reactive oxidative species (ROS) (Davies and others 1982). ROS activates intracellular signaling, including antioxidant pathways, necessary for adaptation, with the magnitude and temporal induction of ROS being essential factors dictating the hormetic response (Radak and others 2008).

The adaptive changes that occur with regular physical activity appear to provide rejuvenative benefits by augmenting stochastic and deterministic processes that govern cellular aging, including genomic damage, dysregulated proteostasis, telomere erosion, dysfunctional nutrient sensing and metabolic response, cellular senescence, inflammation, altered cell signaling and stem cell exhaustion (Lopez-Otin and others 2013). The effect of exercise on these aging hallmarks is remarkable. Exercise training increases antioxidant capacity and reduces markers of DNA damage in lymphocytes (Soares and others 2015), skeletal muscle (Radak and others 2002) and liver (Nakamoto and others 2007). Proteostasis enhancements are mediated, in part, by the autophagy–lysosomal system, and aerobic exercise induces systemic autophagy (He and others 2012b), which may be requisite for activity-related metabolic improvements (He and others 2012a; Liu and others 2015). Longer leukocyte telomere length is associated with greater physical activity (Denham and others 2016). Likewise, metabolic reprogramming is strongly associated with exercise, and is driven in part by altered amino acid sensing through mTOR and low-energy sensing through AMPK signaling pathways, ultimately leading to improved insulin sensitivity, lipid and glucose handling (Liu and others 2012). Indeed, even metabolic changes associated with short-term exercise are sufficient to improve insulin sensitivity (Koopman and others 2005). Exercise also results in reduced levels of cellular senescence markers in hepatic (Huang and others 2013) and vascular (Werner and others 2009) tissue, concordant with reduced inflammatory activity and increased telomerase, respectively.

Bouts of physical activity drive production of pro-inflammatory factors, such as interleukin-6 (IL-6), which is compulsory for the hypertrophic, angiogenic and insulin sensitizing effects of exercise (Ellingsgaard and others 2011; Pedersen and Febbraio 2012), but regular physical activity is widely accepted as an effective means to reduce systemic inflammation and associated chronic disease (Abramson and Vaccarino 2002). Thus, reminiscent of context-dependent ROS functions, exercise-mediated induction of inflammatory markers serves to coordinate adaptive, intracellular signaling-mediated changes with the ultimate effect being activation of anti-inflammatory cytokines and systemic suppression of pro-inflammatory processes (Petersen and Pedersen 2005).

Physical activity prevents dysregulation of cellular signaling corresponding to a wide range of outcomes, but a powerful example pertains to trophic factor signaling in the hippocampus, a brain sector responsible for coordinating learning and memory. Brain-derived neurotrophic factor (BDNF) mediates synaptic transmission and plasticity to oppose hippocampal neurodegeneration and cognitive decline (Petersen and Pedersen 2005). Indeed, exercise increases BDNF signaling, which enhances hippocampal plasticity and improves learning and memory (Erickson and others 2011; Vaynman and others 2004). Exercise may also attenuate stem cell exhaustion. Within muscle, a single bout of high intensity activity is sufficient to induce muscle satellite cell activation (Cramer and others 2004), and within the brain, exercise promotes adult neurogenesis (Kronenberg and others 2006). The array of aging hallmarks that are mitigated by exercise, therefore, emphasizes the multifaceted, systemic alterations underlying its ability to promote survival.

In addition to attenuating central mechanisms of aging to maintain tissue quality, exercise exerts robust hypertrophic and hyperplastic effects. Atrophy is a fundamental feature of age-

related systemic decline, and the positive impact of activity-mediated preservation of tissue quantity on total body homeostasis cannot be understated, particularly regarding muscle and brain. Sarcopenia begins in the third decade of life (Janssen and others 2000). The consequence of progressive atrophy in older adults is increased risk for disability, hospitalization, morbidity and mortality (Rolland and others 2008). Reduced muscle mass throughout aging corresponds to a diminished number of muscle fibers (Lexell and others 1988) and cross sectional area (Aniansson and others 1986). The mechanisms attributed to age-related skeletal muscle loss include reduced hormonal signaling, denervation and aberrant ROS- and inflammatory-activated catabolic processes (Vinciguerra and others 2010); inactivity is a potent mediator of all of these processes (Evans 2010). In cardiac muscle, exercise training increases mass by expanding cardiomyocyte size, which is associated with enhanced cardiac output (Weeks and McMullen 2011). The signaling events and remodeling that occur in physiological hypertrophy are distinct from pathological hypertrophic changes, associated with reduced cardiac efficiency, resulting from chronic occlusion or hypertension (Heineke and Molkentin 2006). Volumetric reductions are also observed in the brain throughout aging and are a primary predictor of cognitive decline (Apostolova and others 2010). Although the brain is largely believed to be postmitotic, several studies have identified increased total brain or hippocampal volume concordant with improved memory in humans (Colcombe and others 2006; Erickson and others 2011) and mice (Yuede and others 2009).

Exercise confers resistance to stress and injury. Accordingly, prescribing exercise in the context of 'prehabilitation' to enhance reserve prior to a major stress, such as surgery, is emerging as an important means to improve resilience in older adults (Jack and others 2011). A range of preoperative exercise strategies have shown efficacy in reducing negative postoperative outcomes. Delay of surgery is often impractical, but several studies utilizing prehabilitation have identified significant benefits resulting from training during the natural waiting period prior to surgery. For example, exercise intervention prior to coronary artery bypass graft surgery reduces time spent in intensive care and overall duration of hospital stay, while improving self-reported quality of life (Arthur and others 2000). Similarly, prehabilitative aerobic and resistance exercise initiated one month prior to colorectal resection for cancer has been shown to improve post-operative gait speed, an important indicator of frailty, and overall recovery rate, relative to counterparts that received post-surgical rehabilitation alone (Gillis and others 2014). In addition, limited evidence also supports exercise promoting resiliency by mitigating the cardiotoxicity effects of chemotherapy (Yu and Jones 2015).

In summary, physical activity enhances longevity by attenuating multiple hallmarks of aging. Cellular and physiological changes are largely driven by adaptive processes that drive tissue remodeling, as well as enhanced hormetic stress response. Exercise counteracts natural atrophy of muscle and other tissues, which is central to prevention of age-related frailty and systemic decline. The multifaceted nature of exercise challenges the notion of 'exercise mimetics'. However, interventions that replicate some of the effects of exercise may confer clinically meaningful benefits. The potent ability of exercise to enhance resilience, even in older adults with reduced systemic reserve, is demonstrated by

prehabilitation prior to surgery, as well as across several other challenges, and suggests that exercise is uniquely capable of promoting and preserving human resiliency.

Pharmacologic Strategies

Rapamycin

Over the past decade, the NIA-supported Intervention Testing Program (ITP) has uncovered multiple agents capable of extending rodent lifespan, most notably rapamycin—an immunomodulating drug commonly given to transplantation patients. Regardless of whether it is provided early or later in life, rapamycin robustly improves survival in male and especially female mice, and delays many features of aging (Halloran and others 2012; Zhang and others 2014), although one report suggested that these benefits were largely independent of aging *per se* (Neff and others 2013).

Although rapamycin has proven to be an effective age-delaying drug, presumably due to its immunomodulating effects and reduction in mTOR signaling, known side effects, including insulin resistance and dyslipidemias, preclude its chronic use as an age-delaying drug in humans (Barzilai and others 2012; Lamming and others 2012). For this reason, ongoing efforts to identify so-called 'rapalogs', as well as modified doses of rapamycin, to maximize the 'benefit-cost ratio', is an area of active investigation (Arriola Apelo and others 2015; Lamming and others 2013).

Several studies have linked rapamycin treatment to improved stress resistance at the cellular level and in lower organisms (Robida-Stubbs and others 2012), but its effect on resiliency in mammals is less clear. Concerns have been raised that rapamycin treatment, particularly in older individuals, may compromise an already declining immune system, and accelerate age-related sarcopenia, due to its interference with mTOR signaling in skeletal muscle (Markofski and others 2015). However, administration of the rapamycin derivative, RAD001, rejuvenated the immune response to influenza in elderly subjects (Mannick and others 2014), and young female mice treated with rapamycin responded more effectively to an influenza challenge than controls (Keating and others 2013), suggesting that this immunomodulatory strategy may have therapeutic potential for infections and immunosenescence. The definitive effects of rapamycin and related derivatives on age-related sarcopenia in humans is not yet clear, but short-term administration of rapamycin in young mice did not impair exercise endurance (Ye and others 2013), while long-term rapamycin treatment improved neuromuscular performance (Zhang and others 2014). However, rapamycin led to a delay in bone fracture healing (Holstein and others 2008) and wound repair (Brewer and others 2008; Nashan and Citterio 2012), and also increased mortality in obese, type 2 diabetic mice (Sataranatarajan and others 2015), suggesting that caution should be taken with rapamycin and related derivatives in response to certain stressors.

Resveratrol

The dietary polyphenol, resveratrol, represents another widely-studied compound which has shown beneficial effects on survival and features of aging in some (Baur and others 2006;

Bernier and others 2016; Fiori and others 2013; Jimenez-Gomez and others 2013; Mattison and others 2014), but not all studies (Strong and others 2013). In animal studies, resveratrol has proven effective at protecting against the detrimental effects of obesity on insulin resistance and fatty liver, while improving mitochondrial function and survival (Barger and others 2008; Baur and others 2006). Administration of resveratrol has also been linked to preserved cognitive function (Kodali and others 2015), cardiovascular and cerebrovascular benefits (Petrovski and others 2011; Toth and others 2015; Ungvari and others 2007), including under conditions of high fat and high sucrose feeding in non-human primates (Mattison and others 2014). Resveratrol may also confer protection against cancer (Jang and others 1997; Lee-Chang and others 2013) and chemotherapeutic stress (Lou and others 2015), while preserving bone (Kim and others 2015) and expediting recovery of muscle mass after disuse (Bennett and others 2013). Reports of negative consequences of resveratrol use are few in the literature, but one study suggests it may impair wound healing in young mice (Brakenhielm and others 2001) while others reported beneficial effects on healing (Cakmak and others 2009; Yaman and others 2013).

Human studies in relation to resveratrol, have focused heavily on type 2 diabetes, cancer and cardiovascular health, with beneficial effects demonstrated in some, but not all reports (Crandall and others 2012; Pollack and Crandall 2013). One study observed a reduction in frailty syndrome in individuals consuming high amounts of dietary resveratrol (Rabassa and others 2015), a finding which was corroborated by a reduction in the frailty index score of aged mice fed resveratrol, albeit to a more limited extent than was observed with CR animals (Kane and others 2015). In summary, since the initial report by Baur et al (Baur and others 2006), an extensive literature now exists on resveratrol, aging and stress resistance in animal models. However, less is certain regarding the implications of resveratrol on aging and resiliency in humans. Determining the correct dosing, timing, duration and source of resveratrol, along with targeting the optimal population(s) and endpoint(s) for evaluating effects, remains an obstacle in optimally assessing the potential of resveratrol as an age-delaying and resiliency promoting agent in humans.

Metformin

The commonly prescribed drug, metformin, which has proven to be a safe and cost-effective first-line therapy for type 2 diabetes, has generated renewed and increased interest among basic and clinical investigators due to its potential age-delaying effects. Metformin is a biguanide, whose mechanism of action has historically been attributed to activation of AMPK in liver (Zhou and others 2001), though recent data have revealed that the likely mode(s) and site(s) of action are far more complex than originally suggested (Andrzejewski and others 2014; Foretz and others 2014). Metformin improves lifespan in most (Anisimov and others 2010; Martin-Montalvo and others 2013), but not all rodent studies thus far (Smith and others 2010). More important, an observational study from the UK in more than 78,000 subjects reported that type 2 diabetes patients treated with metformin had improved survival, as compared to those not receiving metformin, as well as matched, non-diabetic patients (Bannister and others 2014). Consistent with these putative effects on survival, accumulating observational and pre-clinical data have revealed benefits of metformin use that extend far beyond type 2 diabetes, and include protection against cardiovascular disease

(Forouzandeh and others 2014), dyslipidemias in mice (Geerling and others 2014), certain cancers (Morales and Morris 2015; Sehdev and others 2015) infections (Joven and others 2013) and frailty syndrome (Sumantri and others 2014). Further, while metformin was shown to have no effect on bone mass and fracture healing time in young rodents (Jeyabalan and others 2013) or surgical stress in humans (Duncan and others 2007), it was found to reduce prolonged tracheal intubation and overall morbidities following surgery (Duncan and others 2007). However, conflicting reports regarding the effects of metformin on wound healing exist and should be investigated further (Inouye and others 2014; Jian and others 2013; Ochoa-Gonzalez and others 2016). Overall, early indications suggest that metformin has either proven beneficial or at least without negative consequences against a host of common challenges to robustness making it a promising agent to target many aspects of human aging.

Therefore, given the safety, efficacy and feasibility of metformin as a drug to treat human aging, an interdisciplinary consortium of leading scientists are currently pursuing a large-scale clinical trial (TAME; Targeting Aging with MEtformin), with the goal of achieving US Food and Drug Administration (FDA) approval to prescribe metformin with aging as the indication (Check Hayden 2015). If proven successful, this effort will undoubtedly pave the translational pathway forward for additional drugs aimed to treat not only human aging, but also to selectively improve domains of resiliency in older adults.

Senolytics

Considerable evidence implicates cellular senescence, a state of stable growth arrest in response to various forms of molecular and cellular damage, in the biology of aging. Widely appreciated as a tumor suppressive mechanism, senescent cells also accumulate with advancing age and compromise the structure and function of a tissue (Herbig and others 2006; Krishnamurthy and others 2004; van Deursen 2014; Waaaijer and others 2012). In part, this is due to the factors they secrete, including cytokines, chemokines, and matrix remodeling proteins, collectively referred to as the senescent associated secretory phenotype (SASP)(Coppe and others 2010; Coppe and others 2008; Tchkonina and others 2013). Several reviews have highlighted the potential role of senescent cells and the SASP in aging-related conditions (LeBrasseur and others 2015; Munoz-Espin and Serrano 2014; Palmer and others 2015; Tchkonina and others 2013). Thus, pharmacological interventions that target senescent cells and/or the SASP may combat disease, improve resilience, and extend healthspan.

Recent studies have garnered support for this premise. In particular, Zhu and colleagues leveraged the unique transcriptional profiles of senescent cells to identify druggable targets (Zhu and others 2015b). A screen was then performed for agents that selectively killed senescent cells, but not proliferating, quiescent or differentiated cells. The tyrosine kinase inhibitor, dasatinib, and the flavonol, quercetin, were selected as candidate senolytics and tested *in vivo*. In 24-month-old mice, a single dose of dasatinib and quercetin lowered the abundance of senescent cell biomarkers in several tissues, and improved parameters of cardiovascular function. In progeroid *Ercc^{-/-}* mice, the senolytic cocktail cleared senescent cells and delayed the onset of several aging-related phenotypes, including kypohosis, dystonia, tremors, weakness, ataxia and incontinence. Additional compounds with senolytic

activity have since been identified, but effects on healthspan have not been described. Chang et al. reported that ABT263, an inhibitor of the anti-apoptotic proteins Bcl-2 and Bcl-xL, is also a potential senolytic agent (Chang and others 2016). ABT263 was shown to reduce the number of senescent hematopoietic stem cells in bone marrow and senescent progenitor cells in skeletal muscle in both irradiated and conventionally aged mice, compared to vehicle. Moreover, in a follow-up study, Zhu et al. demonstrated that navitoclax, a BCL-2 family inhibitor, has senolytic activity in specific human cell types, including umbilical vein epithelial cells and lung fibroblasts (Zhu and others 2015a). Additional work is needed to determine the safety of these agents and their ability to prevent or treat age-related conditions.

Recent data also supports efficacy in suppression of the SASP, a plausible contributor to aging-associated chronic sterile inflammation. Xu and colleagues demonstrated that inhibition of the JAK pathway using RNAi or pharmacological inhibitors, diminished the SASP of pro-inflammatory senescent preadipocytes (Xu and others 2015b). Delivery of a JAK 1/2 inhibitor to 24-month-old mice reduced systemic inflammation and the pro-inflammatory state of adipose tissue. Moreover, treatment of aged mice with the JAK 1/2 inhibitor improved clinical parameters of frailty, including grip strength, habitual physical activity and gait speed (Xu and others 2015a). Collectively, these data add further support to the concept that cellular senescence and the SASP can be targeted therapeutically as a means to potentially improve function and resilience.

A summary on the impact of energetic interventions on resilience discussed here is provided in Table 1. It should be noted that as metformin, resveratrol, rapamycin, senolytics and other candidates continue to be interrogated in pre-clinical and human aging studies, investigators should strongly consider the impact on resiliency with these diets and drugs and whether effects require chronic use or can be acutely implemented. Furthermore, there is a need to develop better standard operating procedures for comprehensively evaluating potential benefits (and detriments) to the molecular, cellular and organ-system integrated response across resiliency sub-domains in pre-clinical and human trials. Collectively, advancing this field promises to provide a more accurate assessment of the potential risks and benefits of specific interventions, which should enable a more informed and targeted strategy to broadly and selectively improve human health.

Summary

Understanding the role of energetic interventions, not only in the context of lifespan and disease, but also in promoting resiliency to stressors with aging, represents an emerging frontier in aging research, with important translational implications. Studies on behavioral strategies, including diet and exercise, have historically shown that CR trumps exercise in its ability to retard some age-related diseases, such as cancers, and improve mean and maximum lifespan. However, endurance and strength resistance exercise paradoxically appear better adept at improving stress resistance and robustness across multiple sub-domains, highlighting the importance of resiliency in providing a more comprehensive understanding of how these interventions may translate to older adults. More recently, the pursuit of pharmacologic strategies to treat aging, which has resulted in several candidates

that predominantly target energetic and metabolic pathways (i.e. AMPK, mTOR, sirtuins, insulin/IGF-1 signaling, mitochondrial metabolism etc), have demonstrated effects on lifespan and disease onset, but less is known about their impact on resilience. It is important to mention that a consensus battery of tests for measuring robustness in rodents across sub-domains of resilience has not yet been clearly established, but is a growing area of interest across several laboratories and the NIA. It is also recommended that resiliency studies include aged rodents of both sexes, with interventions of short and long duration, in order to increase the translational implications. Continued validation and inclusion of resilience as a predictive component of intervention efficacy will undoubtedly provide a more comprehensive understanding as to how these approaches are likely to impact human health.

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References

- Abramson JL, Vaccarino V. Relationship between physical activity and inflammation among apparently healthy middle-aged and older US adults. *Arch Intern Med*. 2002; 162:1286–1292. [PubMed: 12038947]
- Andrzejewski S, Gravel SP, Pollak M, St-Pierre J. Metformin directly acts on mitochondria to alter cellular bioenergetics. *Cancer Metab*. 2014; 2:12. [PubMed: 25184038]
- Aniansson A, Hedberg M, Henning GB, Grimby G. Muscle morphology, enzymatic activity, and muscle strength in elderly men: a follow-up study. *Muscle Nerve*. 1986; 9:585–591. [PubMed: 3762579]
- Anisimov VN, Egormin PA, Piskunova TS, Popovich IG, Tyndyk ML, Yurova MN, Zabezhinski MA, Anikin IV, Karkach AS, Romanyukha AA. Metformin extends life span of HER-2/neu transgenic mice and in combination with melatonin inhibits growth of transplantable tumors in vivo. *Cell Cycle*. 2010; 9:188–197. [PubMed: 20016287]
- Apostolova LG, Mosconi L, Thompson PM, Green AE, Hwang KS, Ramirez A, Mistur R, Tsui WH, de Leon MJ. Subregional hippocampal atrophy predicts Alzheimer's dementia in the cognitively normal. *Neurobiol Aging*. 2010; 31:1077–1088. [PubMed: 18814937]
- Arriola Apelo SI, Neuman JC, Baar EL, Syed FA, Cummings NE, Brar HK, Pumper CP, Kimple ME, Lamming DW. Alternative rapamycin treatment regimens mitigate the impact of rapamycin on glucose homeostasis and the immune system. *Aging Cell*. 2015
- Arthur HM, Daniels C, McKelvie R, Hirsh J, Rush B. Effect of a preoperative intervention on preoperative and postoperative outcomes in low-risk patients awaiting elective coronary artery bypass graft surgery. A randomized, controlled trial. *Ann Intern Med*. 2000; 133:253–262. [PubMed: 10929164]
- Austad SN. Ageing: Mixed results for dieting monkeys. *Nature*. 2012; 489:210–211. [PubMed: 22932269]
- Baker DJ, Betik AC, Krause DJ, Hepple RT. No decline in skeletal muscle oxidative capacity with aging in long-term calorically restricted rats: effects are independent of mitochondrial DNA integrity. *J Gerontol A Biol Sci Med Sci*. 2006; 61:675–684. [PubMed: 16870628]
- Bannister CA, Holden SE, Jenkins-Jones S, Morgan CL, Halcox JP, Scherthaner G, Mukherjee J, Currie CJ. Can people with type 2 diabetes live longer than those without? A comparison of mortality in people initiated with metformin or sulphonylurea monotherapy and matched, non-diabetic controls. *Diabetes Obes Metab*. 2014; 16:1165–1173. [PubMed: 25041462]
- Barger JL, Kayo T, Vann JM, Arias EB, Wang J, Hacker TA, Wang Y, Raederstorff D, Morrow JD, Leeuwenburgh C, Allison DB, Saupe KW, Cartee GD, Weindruch R, Prolla TA. A low dose of

- dietary resveratrol partially mimics caloric restriction and retards aging parameters in mice. *PLoS One*. 2008; 3:e2264. [PubMed: 18523577]
- Barzilai N, Huffman DM, Muzumdar RH, Bartke A. The critical role of metabolic pathways in aging. *Diabetes*. 2012; 61:1315–1322. [PubMed: 22618766]
- Baur JA, Pearson KJ, Price NL, Jamieson HA, Lerin C, Kalra A, Prabhu VV, Allard JS, Lopez-Lluch G, Lewis K, Pistell PJ, Poosala S, Becker KG, Boss O, Gwinn D, Wang M, Ramaswamy S, Fishbein KW, Spencer RG, Lakatta EG, Le Couteur D, Shaw RJ, Navas P, Puigserver P, Ingram DK, de Cabo R, Sinclair DA. Resveratrol improves health and survival of mice on a high-calorie diet. *Nature*. 2006; 444:337–342. [PubMed: 17086191]
- Bennett BT, Mohamed JS, Alway SE. Effects of resveratrol on the recovery of muscle mass following disuse in the plantaris muscle of aged rats. *PLoS One*. 2013; 8:e83518. [PubMed: 24349525]
- Bergman H, Ferrucci L, Guralnik J, Hogan DB, Hummel S, Karunanathan S, Wolfson C. Frailty: an emerging research and clinical paradigm--issues and controversies. *J Gerontol A Biol Sci Med Sci*. 2007; 62:731–737. [PubMed: 17634320]
- Bernier M, Wahl D, Ali A, Allard J, Faulkner S, Wnorowski A, Sanghvi M, Moaddel R, Alfaras I, Mattison JA, Tarantini S, Tucsek Z, Ungvari Z, Csizsar A, Pearson KJ, de Cabo R. Resveratrol supplementation confers neuroprotection in cortical brain tissue of nonhuman primates fed a high-fat/sucrose diet. *Aging (Albany NY)*. 2016
- Biolo G, Ciochi B, Stulle M, Bosutti A, Barazzoni R, Zanetti M, Antonione R, Lebenstedt M, Platen P, Heer M, Guarnieri G. Calorie restriction accelerates the catabolism of lean body mass during 2 wk of bed rest. *Am J Clin Nutr*. 2007; 86:366–372. [PubMed: 17684207]
- Booth FW, Roberts CK, Laye MJ. Lack of exercise is a major cause of chronic diseases. *Compr Physiol*. 2012; 2:1143–1211. [PubMed: 23798298]
- Brakenhielm E, Cao R, Cao Y. Suppression of angiogenesis, tumor growth, and wound healing by resveratrol, a natural compound in red wine and grapes. *FASEB J*. 2001; 15:1798–1800. [PubMed: 11481234]
- Brandhorst S, Wei M, Hwang S, Morgan TE, Longo VD. Short-term calorie and protein restriction provide partial protection from chemotoxicity but do not delay glioma progression. *Exp Gerontol*. 2013; 48:1120–1128. [PubMed: 23454633]
- Brewer JD, Otley CC, Christenson LJ, Phillips PK, Roenigk RK, Weaver AL. The effects of sirolimus on wound healing in dermatologic surgery. *Dermatol Surg*. 2008; 34:216–223. [PubMed: 18093198]
- Brooks N, Cloutier GJ, Cadena SM, Layne JE, Nelsen CA, Freed AM, Roubenoff R, Castaneda-Sceppa C. Resistance training and timed essential amino acids protect against the loss of muscle mass and strength during 28 days of bed rest and energy deficit. *J Appl Physiol* (1985). 2008; 105:241–248. [PubMed: 18483167]
- Cakmak GK, Irkorucu O, Ucan BH, Tascilar O, Emre AU, Karakaya K, Bahadir B, Acikgoz S, Pasaoglu H, Ankarali H, Ugurbas E, Demirtas C, Comert M. The effects of resveratrol on the healing of left colonic anastomosis. *J Invest Surg*. 2009; 22:353–361. [PubMed: 19842890]
- Calvert JW, Condit ME, Aragon JP, Nicholson CK, Moody BF, Hood RL, Sindler AL, Gundewar S, Seals DR, Barouch LA, Lefer DJ. Exercise protects against myocardial ischemia-reperfusion injury via stimulation of beta(3)-adrenergic receptors and increased nitric oxide signaling: role of nitrite and nitrosothiols. *Circ Res*. 2011; 108:1448–1458. [PubMed: 21527738]
- Campbell BA, Richardson R. Effect of chronic undernutrition on susceptibility to cold stress in young adult and aged rats. *Mech Ageing Dev*. 1988; 44:193–202. [PubMed: 3172863]
- Casarin RC, Casati MZ, Pimentel SP, Cirano FR, Algayer M, Pires PR, Ghiraldini B, Duarte PM, Ribeiro FV. Resveratrol improves bone repair by modulation of bone morphogenetic proteins and osteopontin gene expression in rats. *Int J Oral Maxillofac Surg*. 2014; 43:900–906. [PubMed: 24530035]
- Castello L, Maina M, Testa G, Cavallini G, Biasi F, Donati A, Leonarduzzi G, Bergamini E, Poli G, Chiarpotto E. Alternate-day fasting reverses the age-associated hypertrophy phenotype in rat heart by influencing the ERK and PI3K signaling pathways. *Mech Ageing Dev*. 2011; 132:305–314. [PubMed: 21741396]

- Cava E, Fontana L. Will calorie restriction work in humans? *Aging* (Albany NY). 2013; 5:507–514. [PubMed: 23924667]
- Chang J, Wang Y, Shao L, Laberge RM, Demaria M, Campisi J, Janakiraman K, Sharpless NE, Ding S, Feng W, Luo Y, Wang X, Aykin-Burns N, Krager K, Ponnappan U, Hauer-Jensen M, Meng A, Zhou D. Clearance of senescent cells by ABT263 rejuvenates aged hematopoietic stem cells in mice. *Nat Med*. 2016; 22:78–83. [PubMed: 26657143]
- Check Hayden E. Anti-ageing pill pushed as bona fide drug. *Nature*. 2015; 522:265–266. [PubMed: 26085249]
- Chilton WL, Marques FZ, West J, Kannourakis G, Berzins SP, O'Brien BJ, Charchar FJ. Acute exercise leads to regulation of telomere-associated genes and microRNA expression in immune cells. *PLoS One*. 2014; 9:e92088. [PubMed: 24752326]
- Clinthorne JF, Adams DJ, Fenton JJ, Ritz BW, Gardner EM. Short-term re-feeding of previously energy-restricted C57BL/6 male mice restores body weight and body fat and attenuates the decline in natural killer cell function after primary influenza infection. *J Nutr*. 2010; 140:1495–1501. [PubMed: 20534876]
- Clinthorne JF, Beli E, Duriancik DM, Gardner EM. NK cell maturation and function in C57BL/6 mice are altered by caloric restriction. *J Immunol*. 2013; 190:712–722. [PubMed: 23241894]
- Colcombe SJ, Erickson KI, Scalf PE, Kim JS, Prakash R, McAuley E, Elavsky S, Marquez DX, Hu L, Kramer AF. Aerobic exercise training increases brain volume in aging humans. *J Gerontol A Biol Sci Med Sci*. 2006; 61:1166–1170. [PubMed: 17167157]
- Coppe JP, Patil CK, Rodier F, Krtolica A, Beausejour CM, Parrinello S, Hodgson JG, Chin K, Desprez PY, Campisi J. A human-like senescence-associated secretory phenotype is conserved in mouse cells dependent on physiological oxygen. *PLoS One*. 2010; 5:e9188. [PubMed: 20169192]
- Coppe JP, Patil CK, Rodier F, Sun Y, Munoz DP, Goldstein J, Nelson PS, Desprez PY, Campisi J. Senescence-associated secretory phenotypes reveal cell-nonautonomous functions of oncogenic RAS and the p53 tumor suppressor. *PLoS Biol*. 2008; 6:2853–2868. [PubMed: 19053174]
- Cramer RM, Langberg H, Magnusson P, Jensen CH, Schroder HD, Olesen JL, Suetta C, Teisner B, Kjaer M. Changes in satellite cells in human skeletal muscle after a single bout of high intensity exercise. *J Physiol*. 2004; 558:333–340. [PubMed: 15121802]
- Crandall JP, Oram V, Trandafirescu G, Reid M, Kishore P, Hawkins M, Cohen HW, Barzilai N. Pilot study of resveratrol in older adults with impaired glucose tolerance. *J Gerontol A Biol Sci Med Sci*. 2012; 67:1307–1312. [PubMed: 22219517]
- Danz ED, Skramsted J, Henry N, Bennett JA, Keller RS. Resveratrol prevents doxorubicin cardiotoxicity through mitochondrial stabilization and the Sirt1 pathway. *Free Radic Biol Med*. 2009; 46:1589–1597. [PubMed: 19303434]
- Davies KJ, Quintanilha AT, Brooks GA, Packer L. Free radicals and tissue damage produced by exercise. *Biochem Biophys Res Commun*. 1982; 107:1198–1205. [PubMed: 6291524]
- Davis JM, Murphy EA, Brown AS, Carmichael MD, Ghaffar A, Mayer EP. Effects of moderate exercise and oat beta-glucan on innate immune function and susceptibility to respiratory infection. *Am J Physiol Regul Integr Comp Physiol*. 2004; 286:R366–372. [PubMed: 14551169]
- de Araujo CC, Silva JD, Samary CS, Guimaraes IH, Marques PS, Oliveira GP, do Carmo LG, Goldenberg RC, Bakker-Abreu I, Diaz BL, Rocha NN, Capelozzi VL, Pelosi P, Rocco PR. Regular and moderate exercise before experimental sepsis reduces the risk of lung and distal organ injury. *J Appl Physiol* (1985). 2012; 112:1206–1214. [PubMed: 22267391]
- Denham J, O'Brien BJ, Charchar FJ. Telomere Length Maintenance and Cardio-Metabolic Disease Prevention Through Exercise Training. *Sports Med*. 2016
- Devlin MJ, Cloutier AM, Thomas NA, Panus DA, Lotinun S, Pinz I, Baron R, Rosen CJ, Bouxsein ML. Caloric restriction leads to high marrow adiposity and low bone mass in growing mice. *J Bone Miner Res*. 2010; 25:2078–2088. [PubMed: 20229598]
- Duncan AI, Koch CG, Xu M, Manlapaz M, Batdorf B, Pitas G, Starr N. Recent metformin ingestion does not increase in-hospital morbidity or mortality after cardiac surgery. *Anesth Analg*. 2007; 104:42–50. [PubMed: 17179241]

- Dutta D, Xu J, Dirain ML, Leeuwenburgh C. Calorie restriction combined with resveratrol induces autophagy and protects 26-month-old rat hearts from doxorubicin-induced toxicity. *Free Radic Biol Med*. 2014; 74:252–262. [PubMed: 24975655]
- Ellingsgaard H, Hauselmann I, Schuler B, Habib AM, Baggio LL, Meier DT, Eppler E, Bouzakri K, Wueest S, Muller YD, Hansen AM, Reinecke M, Konrad D, Gassmann M, Reimann F, Halban PA, Gromada J, Drucker DJ, Gribble FM, Ehses JA, Donath MY. Interleukin-6 enhances insulin secretion by increasing glucagon-like peptide-1 secretion from L cells and alpha cells. *Nat Med*. 2011; 17:1481–1489. [PubMed: 22037645]
- Erickson KI, Voss MW, Prakash RS, Basak C, Szabo A, Chaddock L, Kim JS, Heo S, Alves H, White SM, Wojcicki TR, Mailey E, Vieira VJ, Martin SA, Pence BD, Woods JA, McAuley E, Kramer AF. Exercise training increases size of hippocampus and improves memory. *Proc Natl Acad Sci U S A*. 2011; 108:3017–3022. [PubMed: 21282661]
- Evans WJ. Skeletal muscle loss: cachexia, sarcopenia, and inactivity. *Am J Clin Nutr*. 2010; 91:1123S–1127S. [PubMed: 20164314]
- Fabbri E, An Y, Zoli M, Simonsick EM, Guralnik JM, Bandinelli S, Boyd CM, Ferrucci L. Aging and the burden of multimorbidity: associations with inflammatory and anabolic hormonal biomarkers. *J Gerontol A Biol Sci Med Sci*. 2015; 70:63–70. [PubMed: 25104822]
- Fang Y, Westbrook R, Hill C, Boparai RK, Arum O, Spong A, Wang F, Javors MA, Chen J, Sun LY, Bartke A. Duration of rapamycin treatment has differential effects on metabolism in mice. *Cell Metab*. 2013; 17:456–462. [PubMed: 23473038]
- Ferrucci L, Giallauria F, Schlessinger D. Mapping the road to resilience: novel math for the study of frailty. *Mech Ageing Dev*. 2008; 129:677–679. [PubMed: 18929593]
- Fiatarone MA, O'Neill EF, Ryan ND, Clements KM, Solares GR, Nelson ME, Roberts SB, Kehayias JJ, Lipsitz LA, Evans WJ. Exercise training and nutritional supplementation for physical frailty in very elderly people. *N Engl J Med*. 1994; 330:1769–1775. [PubMed: 8190152]
- Fiori JL, Shin YK, Kim W, Krzysik-Walker SM, Gonzalez-Mariscal I, Carlson OD, Sanghvi M, Moaddel R, Farhang K, Gadkaree SK, Doyle ME, Pearson KJ, Mattison JA, de Cabo R, Egan JM. Resveratrol prevents beta-cell dedifferentiation in nonhuman primates given a high-fat/high-sugar diet. *Diabetes*. 2013; 62:3500–3513. [PubMed: 23884882]
- Fluck M. Functional, structural and molecular plasticity of mammalian skeletal muscle in response to exercise stimuli. *J Exp Biol*. 2006; 209:2239–2248. [PubMed: 16731801]
- Fontana L, Klein S, Holloszy JO. Effects of long-term calorie restriction and endurance exercise on glucose tolerance, insulin action, and adipokine production. *Age (Dordr)*. 2010; 32:97–108. [PubMed: 19904628]
- Fontana L, Meyer TE, Klein S, Holloszy JO. Long-term calorie restriction is highly effective in reducing the risk for atherosclerosis in humans. *Proc Natl Acad Sci U S A*. 2004; 101:6659–6663. [PubMed: 15096581]
- Fontana L, Meyer TE, Klein S, Holloszy JO. Long-term low-calorie low-protein vegan diet and endurance exercise are associated with low cardiometabolic risk. *Rejuvenation Res*. 2007; 10:225–234. [PubMed: 17518696]
- Foretz M, Guigas B, Bertrand L, Pollak M, Viollet B. Metformin: from mechanisms of action to therapies. *Cell Metab*. 2014; 20:953–966. [PubMed: 25456737]
- Forouzanmehr F, Salazar G, Patrushev N, Xiong S, Hilenski L, Fei B, Alexander RW. Metformin beyond diabetes: pleiotropic benefits of metformin in attenuation of atherosclerosis. *J Am Heart Assoc*. 2014; 3:e001202. [PubMed: 25527624]
- Fried LP, Tangen CM, Walston J, Newman AB, Hirsch C, Gottdiener J, Seeman T, Tracy R, Kop WJ, Burke G, McBurnie MA. Frailty in older adults: evidence for a phenotype. *J Gerontol A Biol Sci Med Sci*. 2001; 56:M146–156. [PubMed: 11253156]
- Garcia-Valles R, Gomez-Cabrera MC, Rodriguez-Manas L, Garcia-Garcia FJ, Diaz A, Noguera I, Olaso-Gonzalez G, Vina J. Life-long spontaneous exercise does not prolong lifespan but improves health span in mice. *Longev Healthspan*. 2013; 2:14. [PubMed: 24472376]
- Gardner EM. Caloric restriction decreases survival of aged mice in response to primary influenza infection. *J Gerontol A Biol Sci Med Sci*. 2005; 60:688–694. [PubMed: 15983169]

- Gardner EM, Beli E, Clinthorne JF, Duriancik DM. Energy intake and response to infection with influenza. *Annu Rev Nutr.* 2011; 31:353–367. [PubMed: 21548773]
- Geerling JJ, Boon MR, van der Zon GC, van den Berg SA, van den Hoek AM, Lombes M, Princen HM, Havekes LM, Rensen PC, Guigas B. Metformin lowers plasma triglycerides by promoting VLDL-triglyceride clearance by brown adipose tissue in mice. *Diabetes.* 2014; 63:880–891. [PubMed: 24270984]
- Gillis C, Li C, Lee L, Awasthi R, Augustin B, Gamsa A, Liberman AS, Stein B, Charlebois P, Feldman LS, Carli F. Prehabilitation versus rehabilitation: a randomized control trial in patients undergoing colorectal resection for cancer. *Anesthesiology.* 2014; 121:937–947. [PubMed: 25076007]
- Goldberg EL, Romero-Aleshire MJ, Renkema KR, Ventevogel MS, Chew WM, Uhrlaub JL, Smithey MJ, Limesand KH, Sempowski GD, Brooks HL, Nikolich-Zugich J. Lifespan-extending caloric restriction or mTOR inhibition impair adaptive immunity of old mice by distinct mechanisms. *Aging Cell.* 2015; 14:130–138. [PubMed: 25424641]
- Habold C, Momken I, Ouadi A, Bekaert V, Brasse D. Effect of prior treatment with resveratrol on density and structure of rat long bones under tail-suspension. *J Bone Miner Metab.* 2011; 29:15–22. [PubMed: 20458604]
- Halagappa VK, Guo Z, Pearson M, Matsuoka Y, Cutler RG, F.M. Mattson MP. Intermittent fasting and caloric restriction ameliorate age-related behavioral deficits in the triple-transgenic mouse model of Alzheimer's disease. *Neurobiol Dis.* 2007; 26:212–220. [PubMed: 17306982]
- Halloran J, Hussong SA, Burbank R, Podlutzkaya N, Fischer KE, Sloane LB, Austad SN, Strong R, Richardson A, Hart MJ, Galvan V. Chronic inhibition of mammalian target of rapamycin by rapamycin modulates cognitive and non-cognitive components of behavior throughout lifespan in mice. *Neuroscience.* 2012; 223:102–113. [PubMed: 22750207]
- Harrison DE, Strong R, Allison DB, Ames BN, Astle CM, Atamna H, Fernandez E, Flurkey K, Javors MA, Nadon NL, Nelson JF, Pletcher S, Simpkins JW, Smith D, Wilkinson JE, Miller RA. Acarbose, 17-alpha-estradiol, and nordihydroguaiaretic acid extend mouse lifespan preferentially in males. *Aging Cell.* 2014; 13:273–282. [PubMed: 24245565]
- He C, Bassik MC, Moresi V, Sun K, Wei Y, Zou Z, An Z, Loh J, Fisher J, Sun Q, Korsmeyer S, Packer M, May HI, Hill JA, Virgin HW, Gilpin C, Xiao G, Bassel-Duby R, Scherer PE, Levine B. Exercise-induced BCL2-regulated autophagy is required for muscle glucose homeostasis. *Nature.* 2012a; 481:511–515. [PubMed: 22258505]
- He C, Sumpter R Jr, Levine B. Exercise induces autophagy in peripheral tissues and in the brain. *Autophagy.* 2012b; 8:1548–1551. [PubMed: 22892563]
- He W, Wang Y, Zhang MZ, You L, Davis LS, Fan H, Yang HC, Fogo AB, Zent R, Harris RC, Breyer MD, Hao CM. Sirt1 activation protects the mouse renal medulla from oxidative injury. *J Clin Invest.* 2010; 120:1056–1068. [PubMed: 20335659]
- Heilbronn LK, Smith SR, Martin CK, Anton SD, Ravussin E. Alternate-day fasting in nonobese subjects: effects on body weight, body composition, and energy metabolism. *Am J Clin Nutr.* 2005; 81:69–73. [PubMed: 15640462]
- Heineke J, Molkentin JD. Regulation of cardiac hypertrophy by intracellular signalling pathways. *Nat Rev Mol Cell Biol.* 2006; 7:589–600. [PubMed: 16936699]
- Hepple RT, Baker DJ, Kaczor JJ, Krause DJ. Long-term caloric restriction abrogates the age-related decline in skeletal muscle aerobic function. *FASEB J.* 2005; 19:1320–1322. [PubMed: 15955841]
- Hepple RT, Baker DJ, McConkey M, Muryinka T, Norris R. Caloric restriction protects mitochondrial function with aging in skeletal and cardiac muscles. *Rejuvenation Res.* 2006; 9:219–222. [PubMed: 16706647]
- Hepple RT, Qin M, Nakamoto H, Goto S. Caloric restriction optimizes the proteasome pathway with aging in rat plantaris muscle: implications for sarcopenia. *Am J Physiol Regul Integr Comp Physiol.* 2008; 295:R1231–1237. [PubMed: 18703409]
- Herbig U, Ferreira M, Condel L, Carey D, Sedivy JM. Cellular senescence in aging primates. *Science.* 2006; 311:1257. [PubMed: 16456035]
- Holling CS. Simplifying the Complex - the Paradigms of Ecological Function and Structure. *Futures.* 1994; 26:598–609.

- Holloszy JO, Smith EK, Vining M, Adams S. Effect of voluntary exercise on longevity of rats. *J Appl Physiol* (1985). 1985; 59:826–831. [PubMed: 4055572]
- Holstein JH, Klein M, Garcia P, Histing T, Culemann U, Pizanis A, Laschke MW, Scheuer C, Meier C, Schorr H, Pohlemann T, Menger MD. Rapamycin affects early fracture healing in mice. *Br J Pharmacol*. 2008; 154:1055–1062. [PubMed: 18454167]
- Hoozeboom TJ, Dronkers JJ, Hulzebos EH, van Meeteren NL. Merits of exercise therapy before and after major surgery. *Curr Opin Anaesthesiol*. 2014; 27:161–166. [PubMed: 24500337]
- Hoozeboom TJ, Oosting E, Vrieseckolk JE, Veenhof C, Siemonsma PC, de Bie RA, van den Ende CH, van Meeteren L. Therapeutic validity and effectiveness of preoperative exercise on functional recovery after joint replacement: a systematic review and meta-analysis. *PLoS One*. 2012; 7:e38031. [PubMed: 22675429]
- Huang CC, Chiang WD, Huang WC, Huang CY, Hsu MC, Lin WT. Hepatoprotective Effects of Swimming Exercise against D-Galactose-Induced Senescence Rat Model. *Evid Based Complement Alternat Med*. 2013; 2013:275431. [PubMed: 23843869]
- Hunt ND, Li GD, Zhu M, Miller M, Levette A, Chachich ME, Spangler EL, Allard JS, Hyun DH, Ingram DK, de Cabo R. Effect of calorie restriction and refeeding on skin wound healing in the rat. *Age (Dordr)*. 2012; 34:1453–1458. [PubMed: 22037865]
- Inouye KA, Bisch FC, Elsalanty ME, Zakhary I, Khashaba RM, Borke JL. Effect of metformin on periimplant wound healing in a rat model of type 2 diabetes. *Implant Dent*. 2014; 23:319–327. [PubMed: 24776941]
- Jack S, West M, Grocott MP. Perioperative exercise training in elderly subjects. *Best Pract Res Clin Anaesthesiol*. 2011; 25:461–472. [PubMed: 21925410]
- Jang M, Cai L, Udeani GO, Slowing KV, Thomas CF, Beecher CW, Farnsworth NR, Kinghorn AD, Mehta RG, Moon RC, Pezzuto JM. Cancer chemopreventive activity of resveratrol, a natural product derived from grapes. *Science*. 1997; 275:218–220. [PubMed: 8985016]
- Janssen I, Heymsfield SB, Wang ZM, Ross R. Skeletal muscle mass and distribution in 468 men and women aged 18–88 yr. *J Appl Physiol* (1985). 2000; 89:81–88. [PubMed: 10904038]
- Jeyabalan J, Viollet B, Smitham P, Ellis SA, Zaman G, Bardin C, Goodship A, Roux JP, Pierre M, Chenu C. The anti-diabetic drug metformin does not affect bone mass in vivo or fracture healing. *Osteoporos Int*. 2013; 24:2659–2670. [PubMed: 23644877]
- Jian MY, Alexeyev MF, Wolkowicz PE, Zmijewski JW, Creighton JR. Metformin-stimulated AMPK- α 1 promotes microvascular repair in acute lung injury. *Am J Physiol Lung Cell Mol Physiol*. 2013; 305:L844–855. [PubMed: 24097562]
- Jimenez-Gomez Y, Mattison JA, Pearson KJ, Martin-Montalvo A, Palacios HH, Sossong AM, Ward TM, Younts CM, Lewis K, Allard JS, Longo DL, Belman JP, Malagon MM, Navas P, Sanghvi M, Moaddel R, Tilmont EM, Herbert RL, Morrell CH, Egan JM, Baur JA, Ferrucci L, Bogan JS, Bernier M, de Cabo R. Resveratrol improves adipose insulin signaling and reduces the inflammatory response in adipose tissue of rhesus monkeys on high-fat, high-sugar diet. *Cell Metab*. 2013; 18:533–545. [PubMed: 24093677]
- Joven J, Menendez JA, Fernandez-Sender L, Espinel E, Rull A, Beltran-Debon R, Rodriguez-Gallego E, Riera-Borrull M, Pedro-Botet J, Alonso-Villaverde C, Camps J, Aragones G. Metformin: a cheap and well-tolerated drug that provides benefits for viral infections. *HIV Med*. 2013; 14:233–240. [PubMed: 23171036]
- Kane AE, Hilmer SN, Boyer D, Gavin K, Nines D, Howlett SE, de Cabo R, Mitchell SJ. Impact of Longevity Interventions on a Validated Mouse Clinical Frailty Index. *J Gerontol A Biol Sci Med Sci*. 2015
- Kane AE, Hilmer SN, Boyer D, Gavin K, Nines D, Howlett SE, de Cabo R, Mitchell SJ. Impact of Longevity Interventions on a Validated Mouse Clinical Frailty Index. *J Gerontol A Biol Sci Med Sci*. 2016; 71:333–339. [PubMed: 25711530]
- Keating R, Hertz T, Wehenkel M, Harris TL, Edwards BA, McClaren JL, Brown SA, Surman S, Wilson ZS, Bradley P, Hurwitz J, Chi H, Doherty PC, Thomas PG, McGargill MA. The kinase mTOR modulates the antibody response to provide cross-protective immunity to lethal infection with influenza virus. *Nat Immunol*. 2013; 14:1266–1276. [PubMed: 24141387]

- Kim HN, Han L, Iyer S, de Cabo R, Zhao H, O'Brien CA, Manolagas SC, Almeida M. Sirtuin1 Suppresses Osteoclastogenesis by Deacetylating FoxOs. *Mol Endocrinol*. 2015; 29:1498–1509. [PubMed: 26287518]
- Kim J, Kwak HJ, Cha JY, Jeong YS, Rhee SD, Kim KR, Cheon HG. Metformin suppresses lipopolysaccharide (LPS)-induced inflammatory response in murine macrophages via activating transcription factor-3 (ATF-3) induction. *J Biol Chem*. 2014; 289:23246–23255. [PubMed: 24973221]
- Kirwan JP, Solomon TP, Wojta DM, Staten MA, Holloszy JO. Effects of 7 days of exercise training on insulin sensitivity and responsiveness in type 2 diabetes mellitus. *Am J Physiol Endocrinol Metab*. 2009; 297:E151–156. [PubMed: 19383872]
- Kitada M, Kume S, Takeda-Watanabe A, Tsuda S, Kanasaki K, Koya D. Calorie restriction in overweight males ameliorates obesity-related metabolic alterations and cellular adaptations through anti-aging effects, possibly including AMPK and SIRT1 activation. *Biochim Biophys Acta*. 2013; 1830:4820–4827. [PubMed: 23800577]
- Knight RJ, Villa M, Laskey R, Benavides C, Schoenberg L, Welsh M, Kerman RH, Podder H, Van Buren CT, Katz SM, Kahan BD. Risk factors for impaired wound healing in sirolimus-treated renal transplant recipients. *Clin Transplant*. 2007; 21:460–465. [PubMed: 17645704]
- Kodali M, Parihar VK, Hattiangady B, Mishra V, Shuai B, Shetty. Resveratrol prevents age-related memory and mood dysfunction with increased hippocampal neurogenesis and microvasculature, and reduced glial activation. *Sci Rep*. 2015; 5:8075. [PubMed: 25627672]
- Koopman R, Manders RJ, Zorenc AH, Hul GB, Kuipers H, Keizer HA, van Loon LJ. A single session of resistance exercise enhances insulin sensitivity for at least 24 h in healthy men. *Eur J Appl Physiol*. 2005; 94:180–187. [PubMed: 15761746]
- Kraemer WJ, Ratamess NA. Hormonal responses and adaptations to resistance exercise and training. *Sports Med*. 2005; 35:339–361. [PubMed: 15831061]
- Krishnamurthy J, Torrice C, Ramsey MR, Kovalev GI, Al-Regaiey K, Su L, Sharpless NE. Ink4a/Arf expression is a biomarker of aging. *J Clin Invest*. 2004; 114:1299–1307. [PubMed: 15520862]
- Kristan DM. Chronic calorie restriction increases susceptibility of laboratory mice (*Mus musculus*) to a primary intestinal parasite infection. *Aging Cell*. 2007; 6:817–825. [PubMed: 17973970]
- Kristan DM. Calorie restriction and susceptibility to intact pathogens. *Age (Dordr)*. 2008; 30:147–156. [PubMed: 19424864]
- Kronenberg G, Bick-Sander A, Bunk E, Wolf C, Ehninger D, Kempermann G. Physical exercise prevents age-related decline in precursor cell activity in the mouse dentate gyrus. *Neurobiol Aging*. 2006; 27:1505–1513. [PubMed: 16271278]
- Lamming DW, Ye L, Katajisto P, Goncalves MD, Saitoh M, Stevens DM, Davis JG, Salmon AB, Richardson A, Ahima RS, Guertin DA, Sabatini DM, Baur JA. Rapamycin-induced insulin resistance is mediated by mTORC2 loss and uncoupled from longevity. *Science*. 2012; 335:1638–1643. [PubMed: 22461615]
- Lamming DW, Ye L, Sabatini DM, Baur JA. Rapalogs and mTOR inhibitors as anti-aging therapeutics. *J Clin Invest*. 2013; 123:980–989. [PubMed: 23454761]
- Larson-Meyer DE, Heilbronn LK, Redman LM, Newcomer BR, Frisard MI, Anton S, Smith SR, Alfonso A, Ravussin E. Effect of calorie restriction with or without exercise on insulin sensitivity, beta-cell function, fat cell size, and ectopic lipid in overweight subjects. *Diabetes Care*. 2006; 29:1337–1344. [PubMed: 16732018]
- LeBrasseur NK, Tchkonja T, Kirkland JL. Cellular Senescence and the Biology of Aging, Disease, and Frailty. *Nestle Nutr Inst Workshop Ser*. 2015; 83:11–18. [PubMed: 26485647]
- Lee-Chang C, Bodogai M, Martin-Montalvo A, Wejksza K, Sanghvi M, Moaddel R, de Cabo R, Biragyn A. Inhibition of breast cancer metastasis by resveratrol-mediated inactivation of tumor-evoked regulatory B cells. *J Immunol*. 2013; 191:4141–4151. [PubMed: 24043896]
- Lee C, Longo VD. Fasting vs dietary restriction in cellular protection and cancer treatment: from model organisms to patients. *Oncogene*. 2011; 30:3305–3316. [PubMed: 21516129]
- Lee C, Raffaghello L, Brandhorst S, Safdie FM, Bianchi G, Martin-Montalvo A, Pistoia V, Wei M, Hwang S, Merlino A, Emionite L, de Cabo R, Longo VD. Fasting cycles retard growth of tumors and sensitize a range of cancer cell types to chemotherapy. *Sci Transl Med*. 2012a; 4:124ra127.

- Lee C, Safdie FM, Raffaghello L, Wei M, Madia F, Parrella E, Hwang D, Cohen P, Bianchi G, Longo VD. Reduced levels of IGF-I mediate differential protection of normal and cancer cells in response to fasting and improve chemotherapeutic index. *Cancer Res.* 2010; 70:1564–1572. [PubMed: 20145127]
- Lee YE, Kim JW, Lee EM, Ahn YB, Song KH, Yoon KH, Kim HW, Park CW, Li G, Liu Z, Ko SH. Chronic resveratrol treatment protects pancreatic islets against oxidative stress in db/db mice. *PLoS One.* 2012b; 7:e50412. [PubMed: 23226280]
- Levine ME, Suarez JA, Brandhorst S, Balasubramanian P, Cheng CW, Madia F, Fontana L, Mirisola MG, Guevara-Aguirre J, Wan J, Passarino G, Kennedy BK, Wei M, Cohen P, Crimmins EM, Longo VD. Low protein intake is associated with a major reduction in IGF-1, cancer, and overall mortality in the 65 and younger but not older population. *Cell Metab.* 2014; 19:407–417. [PubMed: 24606898]
- Lexell J, Taylor CC, Sjostrom M. What is the cause of the ageing atrophy? Total number, size and proportion of different fiber types studied in whole vastus lateralis muscle from 15- to 83-year-old men. *J Neurol Sci.* 1988; 84:275–294. [PubMed: 3379447]
- Liao CY, Rikke BA, Johnson TE, Diaz V, Nelson JF. Genetic variation in the murine lifespan response to dietary restriction: from life extension to life shortening. *Aging Cell.* 2010; 9:92–95. [PubMed: 19878144]
- Liu MH, Lin XL, Guo DM, Zhang Y, Yuan C, Tan TP, Chen YD, Wu SJ, Ye ZF, He J. Resveratrol protects cardiomyocytes from doxorubicin-induced apoptosis through the AMPK/P53 pathway. *Mol Med Rep.* 2016; 13:1281–1286. [PubMed: 26675978]
- Liu X, Niu Y, Yuan H, Huang J, Fu L. AMPK binds to Sestrins and mediates the effect of exercise to increase insulin-sensitivity through autophagy. *Metabolism.* 2015; 64:658–665. [PubMed: 25672217]
- Liu X, Yuan H, Niu Y, Niu W, Fu L. The role of AMPK/mTOR/S6K1 signaling axis in mediating the physiological process of exercise-induced insulin sensitization in skeletal muscle of C57BL/6 mice. *Biochim Biophys Acta.* 2012; 1822:1716–1726. [PubMed: 22846606]
- Longo VD, Fabrizio P. Regulation of longevity and stress resistance: a molecular strategy conserved from yeast to humans? *Cell Mol Life Sci.* 2002; 59:903–908. [PubMed: 12169020]
- Longo VD, Fontana L. Calorie restriction and cancer prevention: metabolic and molecular mechanisms. *Trends Pharmacol Sci.* 2010; 31:89–98. [PubMed: 20097433]
- Lopez-Otin C, Blasco MA, Partridge L, Serrano M, Kroemer G. The hallmarks of aging. *Cell.* 2013; 153:1194–1217. [PubMed: 23746838]
- Lou Y, Wang Z, Xu Y, Zhou P, Cao J, Li Y, Chen Y, Sun J, Fu L. Resveratrol prevents doxorubicin-induced cardiotoxicity in H9c2 cells through the inhibition of endoplasmic reticulum stress and the activation of the Sirt1 pathway. *Int J Mol Med.* 2015; 36:873–880. [PubMed: 26202177]
- Mannick JB, Del Giudice, Lattanzi G, Valiante M, Praestgaard NM, Huang J, Lonetto B, Maecker MA, Kovarik HT, Carson J, Glass S, Klickstein DJ. L.B. mTOR inhibition improves immune function in the elderly. *Sci Transl Med.* 2014; 6:268ra179.
- Mao-Ying QL, Kavelaars A, Krukowski K, Huo XJ, Zhou W, Price TJ, Cleeland C, Heijnen CJ. The anti-diabetic drug metformin protects against chemotherapy-induced peripheral neuropathy in a mouse model. *PLoS One.* 2014; 9:e100701. [PubMed: 24955774]
- Markofski MM, Dickinson JM, Drummond MJ, Fry CS, Fujita S, Gundermann DM, Glynn EL, Jennings K, Paddon-Jones D, Reidy PT, Sheffield-Moore M, Timmerman KL, Rasmussen BB, Volpi E. Effect of age on basal muscle protein synthesis and mTORC1 signaling in a large cohort of young and older men and women. *Exp Gerontol.* 2015; 65:1–7. [PubMed: 25735236]
- Martin-Montalvo A, Mercken EM, Mitchell SJ, Palacios HH, Mote PL, Scheibye-Knudsen M, Gomes AP, Ward TM, Minor RK, Blouin MJ, Schwab M, Pollak M, Zhang Y, Yu Y, Becker KG, Bohr VA, Ingram DK, Sinclair DA, Wolf NS, Spindler SR, Bernier M, de Cabo R. Metformin improves healthspan and lifespan in mice. *Nat Commun.* 2013; 4:2192. [PubMed: 23900241]
- Masoro EJ. Hormesis and the antiaging action of dietary restriction. *Exp Gerontol.* 1998; 33:61–66. [PubMed: 9467717]
- Mattison JA, Wang M, Bernier M, Zhang J, Park SS, Maudsley S, An SS, Santhanam L, Martin B, Faulkner S, Morrell C, Baur JA, Peshkin L, Sosnowska D, Csiszar A, Herbert RL, Tilmont EM,

- Ungvari Z, Pearson KJ, Lakatta EG, de Cabo R. Resveratrol prevents high fat/sucrose diet-induced central arterial wall inflammation and stiffening in nonhuman primates. *Cell Metab*. 2014; 20:183–190. [PubMed: 24882067]
- McCaskey SJ, Rondini EA, Langohr IM, Fenton JI. Differential effects of energy balance on experimentally-induced colitis. *World J Gastroenterol*. 2012; 18:627–636. [PubMed: 22363133]
- McKiernan SH, Colman RJ, Aiken E, Evans TD, Beasley TM, Aiken JM, Weindruch R, Anderson RM. Cellular adaptation contributes to calorie restriction-induced preservation of skeletal muscle in aged rhesus monkeys. *Exp Gerontol*. 2012; 47:229–236. [PubMed: 22226624]
- Meyer TE, Kovacs SJ, Ehsani AA, Klein S, Holloszy JO, Fontana L. Long-term caloric restriction ameliorates the decline in diastolic function in humans. *J Am Coll Cardiol*. 2006; 47:398–402. [PubMed: 16412867]
- Miller RA, Buehner G, Chang Y, Harper JM, Sigler R, Smith-Wheelock M. Methionine-deficient diet extends mouse lifespan, slows immune and lens aging, alters glucose, T4, IGF-I and insulin levels, and increases hepatocyte MIF levels and stress resistance. *Aging Cell*. 2005; 4:119–125. [PubMed: 15924568]
- Mitchell JR, Verweij M, Brand K, van de Ven M, Goemaere N, van den Engel S, Chu T, Forrer F, Muller C, de Jong M, van IW, JN II, Hoeijmakers JH, de Bruin RW. Short-term dietary restriction and fasting preconditioning against ischemia reperfusion injury in mice. *Aging Cell*. 2010; 9:40–53. [PubMed: 19878145]
- Moore SC, Patel AV, Matthews CE, Berrington de Gonzalez A, Park Y, Katki HA, Linet MS, Weiderpass E, Visvanathan K, Helzlsouer KJ, Thun M, Gapstur SM, Hartge P, Lee IM. Leisure time physical activity of moderate to vigorous intensity and mortality: a large pooled cohort analysis. *PLoS Med*. 2012; 9:e1001335. [PubMed: 23139642]
- Morales DR, Morris AD. Metformin in cancer treatment and prevention. *Annu Rev Med*. 2015; 66:17–29. [PubMed: 25386929]
- Munoz-Espin D, Serrano M. Cellular senescence: from physiology to pathology. *Nat Rev Mol Cell Biol*. 2014; 15:482–496. [PubMed: 24954210]
- Murphy EA, Davis JM, Carmichael MD, Gangemi JD, Ghaffar A, Mayer EP. Exercise stress increases susceptibility to influenza infection. *Brain Behav Immun*. 2008; 22:1152–1155. [PubMed: 18616997]
- Naji P, Griffin BP, Barr T, Asfahan F, Gillinov AM, Grimm RA, Rodriguez LL, Mihaljevic T, Stewart WJ, Desai MY. Importance of exercise capacity in predicting outcomes and determining optimal timing of surgery in significant primary mitral regurgitation. *J Am Heart Assoc*. 2014; 3:e001010. [PubMed: 25213567]
- Nakamoto H, Kaneko T, Tahara S, Hayashi E, Naito H, Radak Z, Goto S. Regular exercise reduces 8-oxodG in the nuclear and mitochondrial DNA and modulates the DNA repair activity in the liver of old rats. *Exp Gerontol*. 2007; 42:287–295. [PubMed: 17204389]
- Nashan B, Citterio F. Wound healing complications and the use of mammalian target of rapamycin inhibitors in kidney transplantation: a critical review of the literature. *Transplantation*. 2012; 94:547–561. [PubMed: 22941182]
- Navarro A, Gomez C, Lopez-Cepero JM, Boveris A. Beneficial effects of moderate exercise on mice aging: survival, behavior, oxidative stress, and mitochondrial electron transfer. *Am J Physiol Regul Integr Comp Physiol*. 2004; 286:R505–511. [PubMed: 14615275]
- Neff F, Flores-Dominguez D, Ryan DP, Horsch M, Schroder S, Adler T, Afonso LC, Aguilar-Pimentel JA, Becker L, Garrett L, Hans W, Hettich MM, Holtmeier R, Holter SM, Moreth K, Pehn C, Puk O, Racz I, Rathkolb B, Rozman J, Naton B, Ordemann R, Adamski J, Beckers J, Bekeredjian R, Busch DH, Ehninger G, Graw J, Hofler H, Klingenspor M, Klopstock T, Ollert M, Stypmann J, Wolf E, Wurst W, Zimmer A, Fuchs H, Gailus-Durner V, Hrabe de Angelis M, Ehninger D. Rapamycin extends murine lifespan but has limited effects on aging. *J Clin Invest*. 2013; 123:3272–3291. [PubMed: 23863708]
- O'Gorman DJ, Karlsson HK, McQuaid S, Yousif O, Rahman Y, Gasparro D, Glund S, Chibalin AV, Zierath JR, Nolan JJ. Exercise training increases insulin-stimulated glucose disposal and GLUT4 (SLC2A4) protein content in patients with type 2 diabetes. *Diabetologia*. 2006; 49:2983–2992. [PubMed: 17019595]

- Ochoa-Gonzalez F, Cervantes-Villagrana AR, Fernandez-Ruiz JC, Nava-Ramirez HS, Hernandez-Correa AC, Enciso-Moreno JA, Castaneda-Delgado JE. Metformin Induces Cell Cycle Arrest, Reduced Proliferation, Wound Healing Impairment In Vivo and Is Associated to Clinical Outcomes in Diabetic Foot Ulcer Patients. *PLoS One*. 2016; 11:e0150900. [PubMed: 26963096]
- Onken B, Driscoll M. Metformin induces a dietary restriction-like state and the oxidative stress response to extend *C. elegans* Healthspan via AMPK, LKB1, and SKN-1. *PLoS One*. 2010; 5:e8758. [PubMed: 20090912]
- Orchard TJ, Temprosa M, Goldberg R, Haffner S, Ratner R, Marcovina S, Fowler S. The effect of metformin and intensive lifestyle intervention on the metabolic syndrome: the Diabetes Prevention Program randomized trial. *Ann Intern Med*. 2005; 142:611–619. [PubMed: 15838067]
- Palmer AK, Tchkonja T, LeBrasseur NK, Chini EN, Xu M, Kirkland JL. Cellular Senescence in Type 2 Diabetes: A Therapeutic Opportunity. *Diabetes*. 2015; 64:2289–2298. [PubMed: 26106186]
- Panici JA, Harper JM, Miller RA, Bartke A, Spong A, Masternak MM. Early life growth hormone treatment shortens longevity and decreases cellular stress resistance in long-lived mutant mice. *FASEB J*. 2010; 24:5073–5079. [PubMed: 20720157]
- Pedersen BK, Febbraio MA. Muscles, exercise and obesity: skeletal muscle as a secretory organ. *Nat Rev Endocrinol*. 2012; 8:457–465. [PubMed: 22473333]
- Pedersen BK, Saltin B. Evidence for prescribing exercise as therapy in chronic disease. *Scand J Med Sci Sports*. 2006; 16(Suppl 1):3–63. [PubMed: 16451303]
- Pence BD, DiPietro LA, Woods JA. Exercise speeds cutaneous wound healing in high-fat diet-induced obese mice. *Med Sci Sports Exerc*. 2012; 44:1846–1854. [PubMed: 22543735]
- Petersen AM, Pedersen BK. The anti-inflammatory effect of exercise. *J Appl Physiol* (1985). 2005; 98:1154–1162. [PubMed: 15772055]
- Petrovski G, Gurusamy N, Das DK. Resveratrol in cardiovascular health and disease. *Ann N Y Acad Sci*. 2011; 1215:22–33. [PubMed: 21261638]
- Piggott DA, Varadhan R, Mehta SH, Brown TT, Li H, Walston JD, Leng SX, Kirk GD. Frailty, Inflammation, and Mortality Among Persons Aging With HIV Infection and Injection Drug Use. *J Gerontol A Biol Sci Med Sci*. 2015; 70:1542–1547. [PubMed: 26386010]
- Pilegaard H, Ordway GA, Saltin B, Neufer PD. Transcriptional regulation of gene expression in human skeletal muscle during recovery from exercise. *Am J Physiol Endocrinol Metab*. 2000; 279:E806–814. [PubMed: 11001762]
- Pollack RM, Crandall JP. Resveratrol: therapeutic potential for improving cardiometabolic health. *Am J Hypertens*. 2013; 26:1260–1268. [PubMed: 24025725]
- Rabassa M, Zamora-Ros R, Urpi-Sarda M, Bandinelli S, Ferrucci L, Andres-Lacueva C, Cherubini A. Association of habitual dietary resveratrol exposure with the development of frailty in older age: the Invecchiare in Chianti study. *Am J Clin Nutr*. 2015; 102:1534–1542. [PubMed: 26490492]
- Radak Z, Chung HY, Koltai E, Taylor AW, Goto S. Exercise, oxidative stress and hormesis. *Ageing Res Rev*. 2008; 7:34–42. [PubMed: 17869589]
- Radak Z, Kumagai S, Nakamoto H, Goto S. 8-Oxoguanosine and uracil repair of nuclear and mitochondrial DNA in red and white skeletal muscle of exercise-trained old rats. *J Appl Physiol* (1985). 2007; 102:1696–1701. [PubMed: 17204574]
- Radak Z, Naito H, Kaneko T, Tahara S, Nakamoto H, Takahashi R, Cardozo-Pelaez F, Goto S. Exercise training decreases DNA damage and increases DNA repair and resistance against oxidative stress of proteins in aged rat skeletal muscle. *Pflugers Arch*. 2002; 445:273–278. [PubMed: 12457248]
- Rashidi M, Esmaily S, Fiane AE, Gude E, K AT, Ueland T, Gustafsson F, Eiskjaer H, Radegran G, Dellgren G. Wound complications and surgical events in de novo heart transplant patients treated with everolimus: Post-hoc analysis of the SCHEDULE trial. *Int J Cardiol*. 2016; 210:80–84. [PubMed: 26938682]
- Ravussin E, Redman LM, Rochon J, Das SK, Fontana L, Kraus WE, Romashkan S, Williamson DA, Meydani SN, Villareal DT, Smith SR, Stein RI, Scott TM, Stewart TM, Saltzman E, Klein S, Bhapkar M, Martin CK, Gilhooly CH, Holloszy JO, Hadley EC, Roberts SB. A 2-Year Randomized Controlled Trial of Human Caloric Restriction: Feasibility and Effects on Predictors

of Health Span and Longevity. *J Gerontol A Biol Sci Med Sci*. 2015; 70:1097–1104. [PubMed: 26187233]

- Reiser K, McGee C, Rucker R, McDonald R. Effects of aging and caloric restriction on extracellular matrix biosynthesis in a model of injury repair in rats. *J Gerontol A Biol Sci Med Sci*. 1995; 50A:B40–47. [PubMed: 7814778]
- Robertson LT, Mitchell JR. Benefits of short-term dietary restriction in mammals. *Exp Gerontol*. 2013; 48:1043–1048. [PubMed: 23376627]
- Robertson LT, Trevino-Villarreal JH, Mejia P, Grondin Y, E. Hine C, Vargas D, Zheng H, Ozaki CK, Kristal BS, Simpson SJ, Mitchell JR. Protein and Calorie Restriction Contribute Additively to Protection from Renal Ischemia Reperfusion Injury Partly via Leptin Reduction in Male Mice. *J Nutr*. 2015; 145:1717–1727. [PubMed: 26041674]
- Robida-Stubbs S, Glover-Cutter K, Lamming DW, Mizunuma M, Narasimhan SD, Neumann-Haefelin E, Sabatini DM, Blackwell TK. TOR signaling and rapamycin influence longevity by regulating SKN-1/Nrf and DAF-16/FoxO. *Cell Metab*. 2012; 15:713–724. [PubMed: 22560223]
- Rolland Y, Czerwinski S, Abellan Van Kan G, Morley JE, Cesari M, Onder G, Woo J, Baumgartner R, Pillard F, Boirie Y, Chumlea WM, Vellas B. Sarcopenia: its assessment, etiology, pathogenesis, consequences and future perspectives. *J Nutr Health Aging*. 2008; 12:433–450. [PubMed: 18615225]
- Rueff-Barroso CR, Milagres D, do Valle J, Casimiro-Lopes G, Nogueira-Neto JF, Zanier JF, Porto LC. Bone healing in rats submitted to weight-bearing and non-weight-bearing exercises. *Med Sci Monit*. 2008; 14:BR231–236. [PubMed: 18971865]
- Safdie F, Brandhorst S, Wei M, Wang W, Lee C, Hwang S, Conti PS, Chen TC, Longo VD. Fasting enhances the response of glioma to chemo- and radiotherapy. *PLoS One*. 2012; 7:e44603. [PubMed: 22984531]
- Safdie FM, Dorff T, Quinn D, Fontana L, Wei M, Lee C, Cohen P, Longo VD. Fasting and cancer treatment in humans: A case series report. *Aging (Albany NY)*. 2009; 1:988–1007. [PubMed: 20157582]
- Salmon AB, Murakami S, Bartke A, Kopchick J, Yasumura K, Miller RA. Fibroblast cell lines from young adult mice of long-lived mutant strains are resistant to multiple forms of stress. *Am J Physiol Endocrinol Metab*. 2005; 289:E23–29. [PubMed: 15701676]
- Samitz G, Egger M, Zwahlen M. Domains of physical activity and all-cause mortality: systematic review and dose-response meta-analysis of cohort studies. *Int J Epidemiol*. 2011; 40:1382–1400. [PubMed: 22039197]
- Sataranatarajan K, Ikeno Y, Bokov A, Feliars D, Yalamanchili H, Lee HJ, Mariappan MM, Tabatabai-Mir H, Diaz V, Prasad S, Javors MA, Ghosh Choudhury G, Hubbard GB, Barnes JL, Richardson A, Kasinath BS. Rapamycin Increases Mortality in db/db Mice, a Mouse Model of Type 2 Diabetes. *J Gerontol A Biol Sci Med Sci*. 2015
- Schumacher B, van der Pluijm I, Moorhouse MJ, Kostea T, Robinson AR, Suh Y, Breit TM, van Steeg H, Niedernhofer LJ, van Ijcken W, Bartke A, Spindler SR, Hoeijmakers JH, van der Horst GT, Garinis GA. Delayed and accelerated aging share common longevity assurance mechanisms. *PLoS Genet*. 2008; 4:e1000161. [PubMed: 18704162]
- Sehdev A, Shih YC, Vekhter B, Bissonnette MB, Olopade OI, Polite BN. Metformin for primary colorectal cancer prevention in patients with diabetes: a case-control study in a US population. *Cancer*. 2015; 121:1071–1078. [PubMed: 25424411]
- Shi Y, Li Y, Huang C, Ying L, Xue J, Wu H, Chen Z, Yang Z. Resveratrol enhances HBV replication through activating Sirt1-PGC-1 α -PPAR α pathway. *Sci Rep*. 2016; 6:24744. [PubMed: 27098390]
- Simon-Szabo L, Kokas M, Mandl J, Keri G, Csala M. Metformin attenuates palmitate-induced endoplasmic reticulum stress, serine phosphorylation of IRS-1 and apoptosis in rat insulinoma cells. *PLoS One*. 2014; 9:e97868. [PubMed: 24896641]
- Simpson RJ, Lowder TW, Spielmann G, Bigley AB, LaVoy EC, Kunz H. Exercise and the aging immune system. *Ageing Res Rev*. 2012; 11:404–420. [PubMed: 22465452]
- Singh F, Newton RU, Galvao DA, Spry N, Baker MK. A systematic review of pre-surgical exercise intervention studies with cancer patients. *Surg Oncol*. 2013; 22:92–104. [PubMed: 23434347]

- Singhal A, Jie L, Kumar P, Hong GS, Leow MK, Paleja B, Tsenova L, Kurepina N, Chen J, Zolezzi F, Kreiswirth B, Poidinger M, Chee C, Kaplan G, Wang YT, De Libero G. Metformin as adjunct antituberculosis therapy. *Sci Transl Med*. 2014; 6:263ra159.
- Smith DL Jr, Elam CF Jr, Mattison JA, Lane MA, Roth GS, Ingram DK, Allison DB. Metformin supplementation and life span in Fischer-344 rats. *J Gerontol A Biol Sci Med Sci*. 2010; 65:468–474. [PubMed: 20304770]
- Snow-Harter C, Whalen R, Myburgh K, Arnaud S, Marcus R. Bone mineral density, muscle strength, and recreational exercise in men. *J Bone Miner Res*. 1992; 7:1291–1296. [PubMed: 1466254]
- Soares JP, Silva AM, Oliveira MM, Peixoto F, Gaivao I, Mota MP. Effects of combined physical exercise training on DNA damage and repair capacity: role of oxidative stress changes. *Age (Dordr)*. 2015; 37:9799. [PubMed: 26044257]
- Solon-Biet SM, McMahon AC, Ballard JW, Ruohonen K, Wu LE, Cogger VC, Warren A, Huang X, Pichaud N, Melvin RG, Gokarn R, Khalil M, Turner N, Cooney GJ, Sinclair DA, Raubenheimer D, Le Couteur DG, Simpson SJ. The ratio of macronutrients, not caloric intake, dictates cardiometabolic health, aging, and longevity in ad libitum-fed mice. *Cell Metab*. 2014; 19:418–430. [PubMed: 24606899]
- Sorrell JM. Resilience in aging. *J Psychosoc Nurs Ment Health Serv*. 2008; 46:8–9.
- Speakman JR, Hambly C. Starving for life: what animal studies can and cannot tell us about the use of caloric restriction to prolong human lifespan. *J Nutr*. 2007; 137:1078–1086. [PubMed: 17374682]
- Sridharan A, Willette AA, Bendlin BB, Alexander AL, Coe CL, Voytko ML, Colman RJ, Kemnitz JW, Weindruch RH, Johnson SC. Brain volumetric and microstructural correlates of executive and motor performance in aged rhesus monkeys. *Front Aging Neurosci*. 2012; 4:31. [PubMed: 23162464]
- St Sauver JL, Boyd CM, Grossardt BR, Bobo WV, Finney Rutten LJ, Roger VL, Ebbert JO, Therneau TM, Yawn BP, Rocca WA. Risk of developing multimorbidity across all ages in an historical cohort study: differences by sex and ethnicity. *BMJ Open*. 2015; 5:e006413.
- Strong R, Miller RA, Astle CM, Baur JA, de Cabo R, Fernandez E, Guo W, Javors M, Kirkland JL, Nelson JF, Sinclair DA, Teter B, Williams D, Zaveri N, Nadon NL, Harrison DE. Evaluation of resveratrol, green tea extract, curcumin, oxaloacetic acid, and medium-chain triglyceride oil on life span of genetically heterogeneous mice. *J Gerontol A Biol Sci Med Sci*. 2013; 68:6–16. [PubMed: 22451473]
- Sumantri S, Setiati S, Purnamasari D, Dewiasty E. Relationship between metformin and frailty syndrome in elderly people with type 2 diabetes. *Acta Med Indones*. 2014; 46:183–188. [PubMed: 25348180]
- Sun L, Sadighi Akha AA, Miller RA, Harper JM. Life-span extension in mice by preweaning food restriction and by methionine restriction in middle age. *J Gerontol A Biol Sci Med Sci*. 2009; 64:711–722. [PubMed: 19414512]
- Tchkonia T, Zhu Y, van Deursen J, Campisi J, Kirkland JL. Cellular senescence and the senescent secretory phenotype: therapeutic opportunities. *J Clin Invest*. 2013; 123:966–972. [PubMed: 23454759]
- Tissenbaum HA. Genetics, life span, health span, and the aging process in *Caenorhabditis elegans*. *J Gerontol A Biol Sci Med Sci*. 2012; 67:503–510. [PubMed: 22499764]
- Toth P, Tarantini S, Springo Z, Tucsek Z, Gautam T, Giles CB, Wren JD, Koller A, Sonntag WE, Csiszar A, Ungvari Z. Aging exacerbates hypertension-induced cerebral microhemorrhages in mice: role of resveratrol treatment in vasoprotection. *Aging Cell*. 2015; 14:400–408. [PubMed: 25677910]
- Ungvari Z, Orosz Z, Rivera A, Labinskyy N, Xiangmin Z, Olson S, Podlitsky A, Csiszar A. Resveratrol increases vascular oxidative stress resistance. *Am J Physiol Heart Circ Physiol*. 2007; 292:H2417–2424. [PubMed: 17220179]
- van Deursen JM. The role of senescent cells in ageing. *Nature*. 2014; 509:439–446. [PubMed: 24848057]
- Varadhan R, Seplaki CL, Xue QL, Bandeen-Roche K, Fried LP. Stimulus-response paradigm for characterizing the loss of resilience in homeostatic regulation associated with frailty. *Mech Ageing Dev*. 2008; 129:666–670. [PubMed: 18938195]

- Vaynman S, Ying Z, Gomez-Pinilla F. Hippocampal BDNF mediates the efficacy of exercise on synaptic plasticity and cognition. *Eur J Neurosci.* 2004; 20:2580–2590. [PubMed: 15548201]
- Villareal DT, Fontana L, Das SK, Redman L, Smith SR, Saltzman E, Bales C, Rochon J, Pieper C, Huang M, Lewis M, Schwartz AV. Effect of Two-Year Caloric Restriction on Bone Metabolism and Bone Mineral Density in Non-obese Younger Adults: a Randomized Clinical Trial. *J Bone Miner Res.* 2015
- Villareal DT, Fontana L, Das SK, Redman L, Smith SR, Saltzman E, Bales C, Rochon J, Pieper C, Huang M, Lewis M, Schwartz AV. Effect of Two-Year Caloric Restriction on Bone Metabolism and Bone Mineral Density in Non-Obese Younger Adults: A Randomized Clinical Trial. *J Bone Miner Res.* 2016; 31:40–51. [PubMed: 26332798]
- Vinciguerra M, Musaro A, Rosenthal N. Regulation of muscle atrophy in aging and disease. *Adv Exp Med Biol.* 2010; 694:211–233. [PubMed: 20886766]
- Waaijer ME, Parish WE, Strongitharm BH, van Heemst D, Slagboom PE, de Craen AJ, Sedivy JM, Westendorp RG, Gunn DA, Maier AB. The number of p16INK4a positive cells in human skin reflects biological age. *Aging Cell.* 2012; 11:722–725. [PubMed: 22612594]
- Wang CP, Lorenzo C, Espinoza SE. Frailty Attenuates the Impact of Metformin on Reducing Mortality in Older Adults with Type 2 Diabetes. *J Endocrinol Diabetes Obes.* 2014; 2
- Weeks KL, McMullen JR. The athlete's heart vs. the failing heart: can signaling explain the two distinct outcomes? *Physiology (Bethesda).* 2011; 26:97–105. [PubMed: 21487028]
- Weindruch R. Effect of caloric restriction on age-associated cancers. *Exp Gerontol.* 1992; 27:575–581. [PubMed: 1426090]
- Weindruch R. The retardation of aging by caloric restriction: studies in rodents and primates. *Toxicol Pathol.* 1996; 24:742–745. [PubMed: 8994305]
- Werner C, Furster T, Widmann T, Poss J, Roggia C, Hanhoun M, Scharhag J, Buchner N, Meyer T, Kindermann W, Haendeler J, Bohm M, Laufs U. Physical exercise prevents cellular senescence in circulating leukocytes and in the vessel wall. *Circulation.* 2009; 120:2438–2447. [PubMed: 19948976]
- Whitson HE, Pieper CF, Cohen HJ. New light on an age-old issue. *Mech Ageing Dev.* 2008; 129:673–674. [PubMed: 18926846]
- Wilmot EG, Edwardson CL, Achana FA, Davies MJ, Gorely T, Gray LJ, Khunti K, Yates T, Biddle SJ. Sedentary time in adults and the association with diabetes, cardiovascular disease and death: systematic review and meta-analysis. *Diabetologia.* 2012; 55:2895–2905. [PubMed: 22890825]
- Wook Yoo S, Han CE, Shin JS, Won Seo S, Na DL, Kaiser M, Jeong Y, Seong JK. A Network Flow-based Analysis of Cognitive Reserve in Normal Ageing and Alzheimer's Disease. *Sci Rep.* 2015; 5:10057. [PubMed: 25992968]
- Xu M, Tchkonja T, Ding H, Ogronnik M, Lubbers ER, Pirtskhalava T, White TA, Johnson KO, Stout MB, Mezera V, Giorgadze N, Jensen MD, LeBrasseur NK, Kirkland JL. JAK inhibition alleviates the cellular senescence-associated secretory phenotype and frailty in old age. *Proc Natl Acad Sci U S A.* 2015a; 112:E6301–6310. [PubMed: 26578790]
- Xu M, Tchkonja T, Ding H, Ogronnik M, Lubbers ER, Pirtskhalava T, White TA, Johnson KO, Stout MB, Mezera V, Giorgadze N, Jensen MD, LeBrasseur NK, Kirkland JL. JAK inhibition alleviates the cellular senescence-associated secretory phenotype and frailty in old age. *Proc Natl Acad Sci U S A.* 2015b; 112:E6301–6310. [PubMed: 26578790]
- Yaman I, Derici H, Kara C, Kamer E, Diniz G, Ortac R, Sayin O. Effects of resveratrol on incisional wound healing in rats. *Surg Today.* 2013; 43:1433–1438. [PubMed: 23242670]
- Yang H, Youm YH, Dixit VD. Inhibition of thymic adipogenesis by caloric restriction is coupled with reduction in age-related thymic involution. *J Immunol.* 2009; 183:3040–3052. [PubMed: 19648267]
- Ye L, Widlund AL, Sims CA, Lamming DW, Guan Y, Davis JG, Sabatini DM, Harrison DE, Vang O, Baur JA. Rapamycin doses sufficient to extend lifespan do not compromise muscle mitochondrial content or endurance. *Aging (Albany NY).* 2013; 5:539–550. [PubMed: 23929887]
- Yoshino J, Conte C, Fontana L, Mittendorfer B, Imai S, Schechtman KB, Gu C, Kunz I, Rossi Fanelli F, Patterson BW, Klein S. Resveratrol supplementation does not improve metabolic function in

nonobese women with normal glucose tolerance. *Cell Metab.* 2012; 16:658–664. [PubMed: 23102619]

- Yu AF, Jones LW. Modulation of cardiovascular toxicity in Hodgkin lymphoma: potential role and mechanisms of aerobic training. *Future Cardiol.* 2015; 11:441–452. [PubMed: 26234325]
- Yuan J, Lu L, Zhang Z, Zhang S. Dietary intake of resveratrol enhances the adaptive immunity of aged rats. *Rejuvenation Res.* 2012; 15:507–515. [PubMed: 22950432]
- Yuede CM, Zimmerman SD, Dong H, Kling MJ, Bero AW, Holtzman DM, Timson BF, Csernansky JG. Effects of voluntary and forced exercise on plaque deposition, hippocampal volume, and behavior in the Tg2576 mouse model of Alzheimer's disease. *Neurobiol Dis.* 2009; 35:426–432. [PubMed: 19524672]
- Zhang Y, Bokov A, Gelfond J, Soto V, Ikeno Y, Hubbard G, Diaz V, Sloane L, Maslin K, Treaster S, Rendon S, van Remmen H, Ward W, Javors M, Richardson A, Austad SN, Fischer K. Rapamycin extends life and health in C57BL/6 mice. *J Gerontol A Biol Sci Med Sci.* 2014; 69:119–130. [PubMed: 23682161]
- Zhou G, Myers R, Li Y, Chen Y, Shen X, Fenyk-Melody J, Wu M, Ventre J, Doebber T, Fujii N, Musi N, Hirshman MF, Goodyear LJ, Moller DE. Role of AMP-activated protein kinase in mechanism of metformin action. *J Clin Invest.* 2001; 108:1167–1174. [PubMed: 11602624]
- Zhou W, Kavelaars A, Heijnen CJ. Metformin Prevents Cisplatin-Induced Cognitive Impairment and Brain Damage in Mice. *PLoS One.* 2016; 11:e0151890. [PubMed: 27018597]
- Zhu Y, Tchkonja T, Fuhrmann-Stroissnigg H, Dai HM, Ling YY, Stout MB, Pirtskhalava T, Giorgadze N, Johnson KO, Giles CB, Wren JD, Niedernhofer LJ, Robbins PD, Kirkland JL. Identification of a Novel Senolytic Agent, Navitoclax, Targeting the Bcl-2 Family of Anti-Apoptotic Factors. *Aging Cell.* 2015a
- Zhu Y, Tchkonja T, Pirtskhalava T, Gower AC, Ding H, Giorgadze N, Palmer AK, Ikeno Y, Hubbard GB, Lenburg M, O'Hara SP, LaRusso NF, Miller JD, Roos CM, Verzosa GC, LeBrasseur NK, Wren JD, Farr JN, Khosla S, Stout MB, McGowan SJ, Fuhrmann-Stroissnigg H, Gurkar AU, Zhao J, Colangelo D, Dorronsoro A, Ling YY, Barghouthy AS, Navarro DC, Sano T, Robbins PD, Niedernhofer LJ, Kirkland JL. The Achilles' heel of senescent cells: from transcriptome to senolytic drugs. *Aging Cell.* 2015b; 14:644–658. [PubMed: 25754370]

Figure 1. Energetic Interventions to increase resilience and extend healthspan

There is compelling evidence that caloric restriction (CR) and exercise prevent and defend against multiple forms of aging-associated molecular and cellular damage, which mediate the intrinsic and progressive functional decline with aging. In contrast, nutrient excess and physical inactivity raise disease risk and accelerate aging. Through somatic maintenance, CR and exercise improve an organism's resilience to challenges and maintain physiological function (solid blue line). In the absence of resilience, chronic disease, multimorbidity, disability, and frailty manifest and compromise healthspan and lifespan (solid red line). Paradoxically, beneficial effects of CR on resiliency do not appear to be universal, as energy restriction may impair response to infections, as well as wound and fracture healing, which could lead to an inability to completely rebound from a challenge (dashed blue line). However, short-term re-feeding may be able to negate these effects of CR, while alternative approaches, such as fasting, can be uniquely leveraged to improve resilience to chemotherapy.

Table 1

Effect of energetic interventions on aspects of resiliency and stress resistance

Subdomains of Resiliency	Exercise	Caloric Restriction	Rapamycin and derivatives	Resveratrol	Metformin	Senolytics
Immune function and response to infection	↑(Davis and others 2004; de Araujo and others 2012; Simpson and others 2012) *	↔(Goldberg and others 2015; Yang and others 2009)	↑(Goldberg and others 2015; Mannick and others 2014)	↔(Shi and others 2016; Yuan and others 2012)	↑(Joven and others 2013; Kim and others 2014; Singhal and others 2014)	↑(Zhu and others 2015b)
Surgical stress response	↔(Hoogboom and others 2014; Hoogetboom and others 2012; Naji and others 2014)	↑(Masoro 1998; Robertson and others 2015)	ND	ND	↑↔(Duncan and others 2007)	ND
Tissue and cellular stress resistance	↔(Calvert and others 2011; Radak and others 2007)	↔(Campbell and Richardson 1988; Mitchell and others 2010; Robertson and others 2015) **	↑(Robida-Stubbs and others 2012)	↑(He and others 2010; Lee and others 2012b)	↑(Onken and Driscoll 2010; Simon-Szabo and others 2014)	ND
Wound healing response	↑(Pence and others 2012)	↓(Reiser and others 1995)	↓↔(Knight and others 2007; Rashidi and others 2016)	↔(Brakenhielm and others 2001; Cakmak and others 2009; Yaman and others 2013)	↑↔(Inouye and others 2014; Jian and others 2013; Ochoa-Gonzalez and others 2016)	↓(Zhu and others 2015b)
Counteract Immobility and bed rest	↔(Brooks and others 2008)	↓(Biolo and others 2007)	ND	↑(Habold and others 2011)	ND	ND
Chemotherapy stress response	↑(Yu and Jones 2015)	↔ with fasting (Lee and Longo 2011; Lee and others 2012a)	ND	↑(Danz and others 2009; Dutta and others 2014; Liu and others 2016)	↑(Mao-Ying and others 2014; Zhou and others 2016)	ND
Bone density, Resistance to fracture and healing capacity	↔(Rueff-Barroso and others 2008; Snow-Harter and others 1992)	↓(Villareal and others 2016)	↓(Holstein and others 2008)	↑(Casarin and others 2014)	↔↔(Jeyabalan and others 2013)	↑(Zhu and others 2015b)
Protection from Frailty Syndrome	↔(Fiatarone and others 1994)	↑(Kane and others 2016)	ND	↑(Bennett and others 2013; Kane and others 2016)	↑(Wang and others 2014)	↑(Zhu and others 2015b)
Protection from metabolic duress (obesity, metabolic syndrome, nutrition overload)	↔(Fontana and others 2010; Kirwan and others 2009)	↔(Fontana and others 2010; Fontana and others 2007)	↔(Fang and others 2013; Sataranatarajan and others 2015)	↑↔(Baur and others 2006; Yoshino and others 2012)	↑(Orchard and others 2005)	↑(Zhu and others 2015b)

ND=To the best of our knowledge, these aspects of resilience have not been directly determined to date

* While moderate exercise is linked to beneficial effects on immune response, strenuous exercise has been linked to increased susceptibility to infection (Murphy and others 2008)

** Most robust response appears to occur with short-term CR