

Chapter 3

Nutrient Sensing, Signaling and Ageing: The Role of IGF-1 and mTOR in Ageing and Age-Related Disease



Simon C. Johnson

Abstract Nutrient signaling through insulin/IGF-1 was the first pathway demonstrated to regulate ageing and age-related disease in model organisms. Pharmacological or dietary interventions targeting nutrient signaling pathways have been shown to robustly attenuate ageing in many organisms. Caloric restriction, the most widely studied longevity promoting intervention, works through multiple nutrient signaling pathways, while inhibition of mTOR through treatment with rapamycin reproducibly delays ageing and disease through specific inhibition of the mTOR complexes. Although the benefits of reduced insulin/IGF-1 in lifespan and health are well documented in model organisms, defining the precise role of the IGF-1 in human ageing and age-related disease has proven more difficult. Association studies provide some insight but also reveal paradoxes. Low serum IGF-1 predicts longevity, but IGF-1 decreases with age and IGF-1 therapy benefits some of age-related pathologies. Circulating IGF-1 has been associated both positively and negatively with risk of age-related diseases in humans, and in some cases both activation and inhibition of IGF-1 signaling have provided benefit in animal models of the same diseases. Interventions designed modulate the nutrient sensing signaling pathways positively or negatively are already available for clinical use, highlighting the need for a clear understanding of the role of nutrient signaling in ageing and age-related disease. This chapter examines data from model organisms and human genetic association studies, with a special emphasis on IGF-1 and mTOR, and discusses potential models for resolving the paradoxes surrounding IGF-1 data.

Keywords mTOR · Nutrient signaling · Ageing · IGF-1 · PI3K

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Introduction

Modern molecular gerontology is in many senses a chaotic and eclectic field of research. Model system approaches to elucidating the mechanisms of ageing range from measuring replicative lifespan studies in budding yeast *Saccharomyces cerevisiae*, consisting of physically counting the number of ‘daughter’ cells individual ‘mother’ yeast cells can produce, to large scale genetic studies in human centenarians, which involve massive long-term clinical follow-up and large-scale next-generation sequencing endeavors. The spectrum of organisms used in modern ageing research includes nematode (*Caenorhabditis elegans* and others) and fly (*Drosophila melanogaster*) models, mice and rats, non-human primates, comparative studies utilizing everything from North Atlantic *Arctica islandica* clams to naked mole rats (*Heterocephalus glaber*), and a whole catalog of exotic ‘emerging’ models aimed at providing fresh perspectives to the ageing field. While this complex mixture of complementary approaches has powered many theories of ageing, the identification of nutrient sensing and signaling pathways as regulators of longevity is arguably the most important discovery in ageing research to date. Nutrient sensing and signaling has been shown to regulate ageing in eukaryotic organisms from yeast to humans through dietary, genetic, and pharmacological manipulation, mutagenesis and RNAi screening, comparative biology, genome-wide association studies (GWAS), and rare genetic variant analysis. Lifespan extending genetic manipulations in nutrient signaling pathways helped legitimize the study of ageing, and more recently have led to the extraordinary – small molecule interventions that modify the underlying process of ageing, improving lifespan and preventing or delaying age-related disease.

The benefits of reduced nutrient signaling on longevity are well-established and broadly conserved across model systems, but a variety of questions remain regarding the impact of these pathways on normal human ageing and age-related disease. What are the downstream effectors of greatest importance? What therapeutic strategies will provide the greatest benefit with the lowest off-target effects? How can we bridge the gap between pre-clinical studies and human treatments? What are the limitations of targeting nutrient sensing in human health? Here, we discuss the role of the major nutrient sensing and signaling pathways in ageing and provide an up to date discussion of these questions, with an emphasis on how NSS impacts human ageing.

Nutrient Sensing Signaling

Insulin/IGF-1 Signaling – the First Pathway of Ageing

The insulin/insulin-like growth factor 1 (IGF-1) signaling pathway was the first defined genetic pathway regulating ageing and age-related disease in model organisms (Kenyon 2011), detailed in landmark studies that provided the first evidence

that genetic manipulation of nutrient sensing signaling (NSS) can modify lifespan (Kenyon et al. 1993, Dorman et al. 1995). Subsequent early studies suggested a linear membrane bound receptor to transcription factor pathway, comprised of the cell surface receptor DAF-2 (homolog of the mammalian IGF-1 Receptor), the PI3 kinase AGE-1, the intracellular kinase AKT/PKB, and the fork head transcription factor DAF-16 (homolog of human Foxo3a) (Paradis and Ruvkun 1998). Numerous additional players have since been identified, with dozens of modifying factors surrounding a central IGF-1/IGF1R/PI3K/AKT/mTOR pathway (see Figs. 3.1 and 3.2). The core intracellular components of NSS (such as TOR, AMPK, and AKT) are widely conserved across the Eukarya domain; for example, the yeast homologs of mTOR, AMPK, and AKT are Tor, Snf1, and Sch9, respectively (see Fig. 3.1).

As the complexity of NSS has been revealed, the linear pathway model for the physical signaling events has become obsolete, making way a more nuanced understanding of NSS. The linear model still provides a reasonable representation of the overall role of NSS in ageing and the benefits of general NSS targeting interventions such as caloric restriction (CR) (see Fig. 3.2), but it is now clear that complex, multi-layered networks of sensors and effectors including feed-back loops, tissue and cell type specific factors, and species specific pathways, modify the core NSS paradigm. Tangled in these networks are multiple points of intracellular and systemic surveillance of nutrient levels and growth favorable conditions, an array of downstream effector pathways and molecules, and a relatively small number of key, highly conserved, intracellular signal hubs which coordinate the many inputs and outputs. Early hopes that a single transcription factor could underlie the majority of the benefits of NSS pathway modulation have proven premature, but intracellular signaling hubs have taken their place as the lead candidates in pharmacological attenuation of ageing. The premier examples are the mechanistic Target of Rapamycin complexes (mTORC1 and mTORC2), central mediators of NSS and established pharmacological targets (see Fig. 3.1; discussed in detail below). Circulating systemic factors, in particular IGF-1 in mammals, are also viewed as potential therapeutic targets in ageing and age-related disease.

Regulation of Nutrient Signaling

Systemic Signaling, Circulating Factors

The canonical PI3K/AKT pathway of ageing can be activated by any of a broad range of hormones, growth factors, and cytokines, acting through either receptor tyrosine kinases (such as IGF-1R/Daf-2 or INSR) or G protein-coupled receptors. In theory, any or all of these may contribute to ageing, but causal evidence is mainly associated with growth hormone (GH) and IGF-1. Growth hormone (GH) is itself the primary driver of circulating IGF-1 levels, driving production through activation of hepatic IGF-1 synthesis. As for GH, it is secreted by the pituitary gland in response to hypothalamic GH-releasing hormone (GHRH), insulin-induced

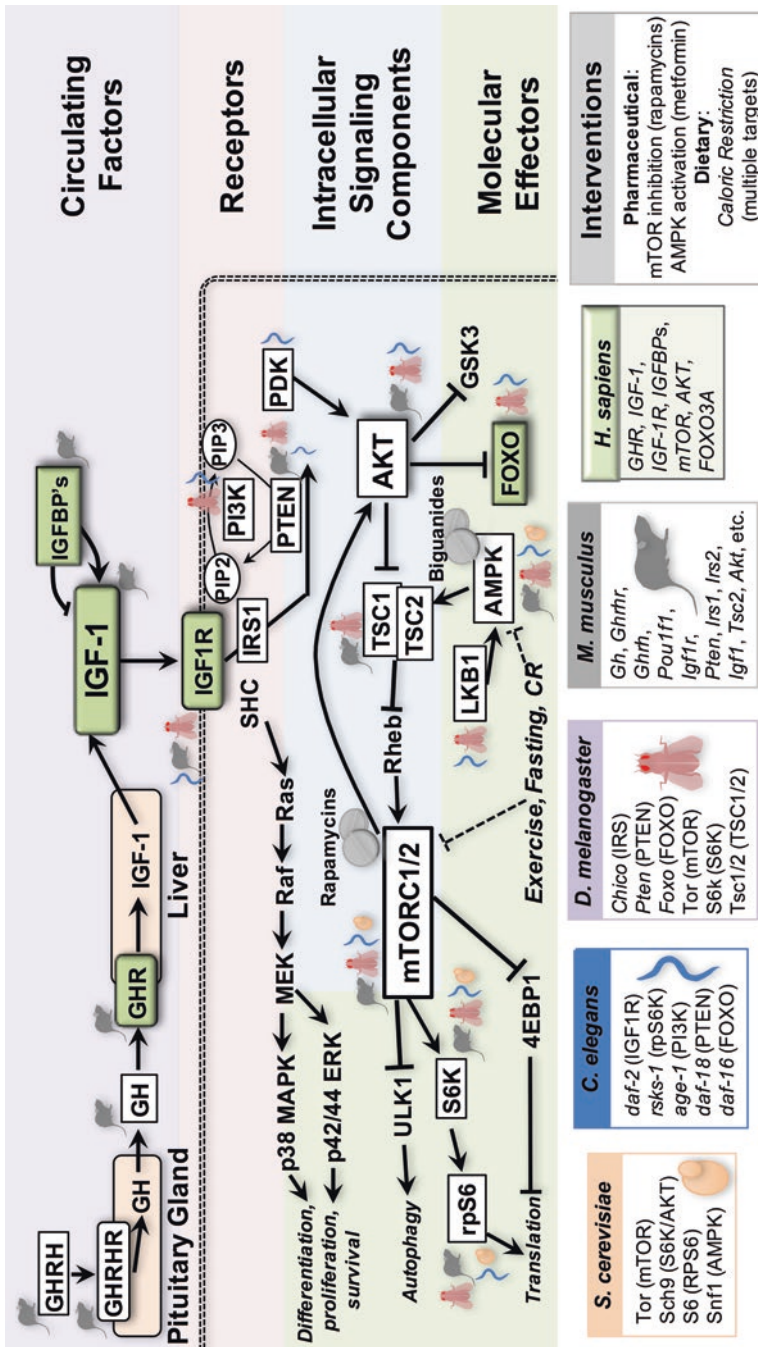


Fig. 3.1 Key Components of Nutrient Sensing Signaling that Regulate Ageing in Eukaryotes. A simplified schematic of core nutrient sensing signaling pathways that regulate ageing, including insulin/IGF-1, mTOR, AMPK, and AKT. Nutrient sensing signaling pathways include circulating factors, cell surface receptors, intracellular signaling components, and molecular effectors. Putative regulators of ageing have been found in each of these categories of macromolecules. Model organisms indicate species in which genetic studies have implicated given factors, with the homolog names of key components listed below. Genes linked to human ageing through genome-wide association or candidate gene genetic association studies are indicated in green. Pharmacological and dietary interventions modulate ageing through their actions on nutrient sensing signaling pathways

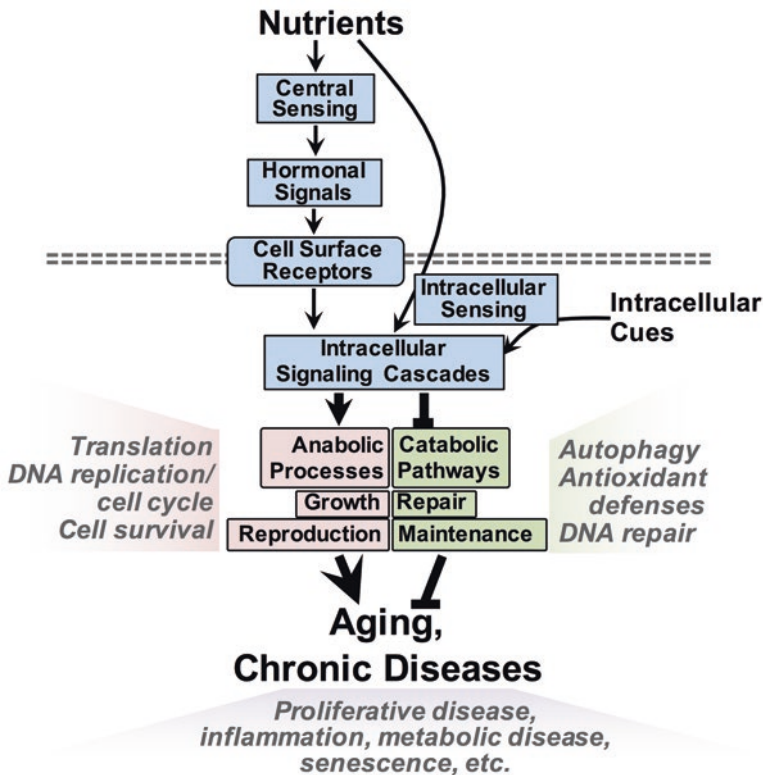


Fig. 3.2 A Linear Model for Nutrient Sensing Signaling in Ageing and Age-related Disease.

A linear model provides a simplified representation of the role of nutrient sensing signaling in ageing and age-related disease. In this model, overall nutritional status in multicellular organisms is sensed through central mechanisms as well as through intracellular nutrient sensing cues. Central sensing regulates the production of circulating hormonal signals, including GH, IGF-1, and insulin, which activate cell surface receptors and stimulate intracellular nutrient signaling pathways. Intracellular cues, such as ATP/ADP, NADH/NAD⁺, amino acid levels, and ribosome assembly, regulate intracellular pathways directly and modifying cellular response to circulating factors. Tissue and cell type specific responses in multicellular organisms are coordinated by differential expression of intracellular factors and cell surface receptors, specificity of systemic factors, and by bioactivity-modifying tissue bound and circulating factors. Together, these signaling cascades promote growth and fecundity at the expense of repair and maintenance. Chronic activation of nutrient sensing signaling drives ageing and many chronic diseases associated with ageing, while targeting nutrient signaling pathways attenuates ageing and age-related disease, as discussed

hypoglycemia, and vigorous exercise; GH production is inhibited by hyperglycemia, glucocorticoids, and negative feedback induced by IGF-1 (Buckler 1971; Barbetti et al. 1990) (see Fig. 3.1). IGF-1 feedback on GH is mediated by inhibition of the cyclic AMP response element binding protein (CREB) binding protein (CBP), a transcriptional co-factor necessary for GH production (Romero et al. 2012).

Low circulating IGF-1 in under-nutrition or fasting results from both decreased GH production and enhanced turnover of serum proteins. IGF-1 bioavailability is modulated by a binding proteins including the IGF-1 binding proteins (IGFBP's) and IGF-1 acid labile subunit (IGFALS) and the ratios of IGFBP's to IGF-1 have been associated with some human diseases (Arafat et al. 2009; Gokulakrishnan et al. 2012). IGF-1 is also produced locally in a tissue-specific manner in response to stimuli such as mechanical stress and injury (Pelosi et al. 2007). IGFBP's, IGFALS, locally produced IGF-1, and factors that modulate signal transduction at or downstream of the IGF-1 receptor (IGF1R) all complicate the interpretation of circulating IGF-1 levels.

IGF-1 has been a major focus of biogerontology, but evidence suggests it may not be the most important circulating factor in mammalian ageing. GH and GHR knockout mice are viable and exceptionally long lived, while knockout of either IGF-1R or IGF-1 are lethal and partial loss only modestly alters lifespan. Intriguingly, liver specific knockout of IGF-1 results in an ~75% reduction in circulating IGF-1, but these mice had normal body growth and produced IGF-1 in several non-hepatic tissues in response to GH (Yakar et al. 1999). This uncoupling of GH and IGF-1/IGF-1R will be discussed further below.

Cellular Interface and Intracellular Regulation

At the cell surface, circulating nutrient sensing signaling factors activate membrane bound receptors and stimulate intracellular signaling cascades. GH acts through the homodimeric receptor tyrosine kinase GHR. IGF-1 activates homodimeric IGF-1R as well as insulin-receptor (INSR) /IGF1R hybrid receptor heterodimers, and, with only weak affinity, homodimer INSR. Insulin similarly activates both INSR and IGF1R. Receptor/ligand binding of IGF-1, Insulin, or GH results in activation of PI3K/AKT and MAPK/ERK signaling through intracellular insulin receptor substrates (IRS1-4) and SHC, respectively (Fig. 3.1). AKT activation leads to inhibition of glycogen synthase kinase 3 (GSK-3) and forkhead box O transcription factors (FOXO's), including FoxO3a, as well as activation of the mechanistic target of rapamycin (mTOR).

mTOR promotes mRNA translation through rpS6K/rpS6 and the eukaryotic initiation factor binding protein 4E-BP1 and decreases autophagy through inhibition of ULK1. The ERK/MAPK pathway activates mitogenic factors such as the proto-oncogene c-MYC, and promotes translation through activation of rpS6 via phosphorylation at rpS6K independent sites (Pende et al. 2004). Together, these processes enact intracellular growth signaling, mRNA translation, catabolic pathways, and metabolism, which together modulate eukaryotic healthspan and longevity (Fig. 3.1).

Intracellular Sensing

Nutrient sensing occurs intracellularly through a number of distinct nutrient, energy, and growth permissive condition monitoring systems. These include ATP level surveillance by the AMP activated protein kinase AMPK; NADH/NAD⁺ monitoring by NAD⁺ dependent protein post-translational modification regulators Sirtuins (not discussed in this chapter); oxygen sensing by REDD1/REDD2, the Hif-1 pathway; small molecule sensing at the lysosome; and various ligand nutrient/hormone ligand dependent transcription factors such as Peroxisome proliferator-activated receptor gamma (PPAR- γ). While many of these individual sensors has been tied to ageing and disease in one or more model systems, one intracellular sensing hub has stood out as a major, and modifiable, target in ageing: mTOR.

mTOR is a key intracellular mediator of nutrient sensing signaling and, as a result, of ageing and disease (Johnson et al. 2013). The mTOR complexes, mTORC1 and mTORC2, are uniquely important for two reasons: first, these complexes synthesize input nutrient and growth information from a broad array of unique molecular signals and coordinate extensive cellular responses by tuning anabolic and catabolic pathways (Fig. 3.3). Second, key mTORC components show sufficient structural conservation from yeast to man that antifungal macrolides targeting Tor in yeast also robustly and specifically inhibit mTOR in mammals (discussed below).

In addition to activation downstream of cell surface receptors, mTOR is involved in cellular response to many of the nutrient sensing factors detailed above. Well-established points of regulation include activation by amino acid sensing at the lysosome mediated by the Ragulator complex (Kim and Kim 2016); inhibition resulting from a low cellular ATP/ADP ratio mediated by AMPK; inhibition by low oxygen levels mediated by the intracellular sensors REDD1 and REDD2 (Vadysirisack and Ellisen 2012); and ribosome capacity sensing by mTORC2, which directly couples nutrient sensing signaling at mTOR to cellular ability to enact mRNA translation (Zinzalla et al. 2011). A variety of additional signals have been shown to attenuate mTOR activity, such as glucose concentration and the NADH/NAD⁺ ratio (through the action of Sirtuins and other factors), but the precise mechanisms mediating these points of control remain to be fully defined. In sum, ATP status, oxygen level, ribosome capacity, amino acid concentration, systemic growth signaling, and other yet to be defined sensors all converge at mTORC1 and/or mTORC2, which together coordinate cellular proliferative and maintenance programs in response to these inputs.

Downstream of mTOR

mTORC1 drives proliferation and growth through inhibition of autophagy, activation of mRNA translation/protein synthesis, and regulation of metabolism. mTORC1 promotes protein synthesis by activating ribosomal protein subunit S6, downstream of S6 kinase, and by releasing the eukaryotic translation initiation binding factor eIF4E-BP1 (or 4E-BP1) and allowing for cap-dependent mRNA translation.

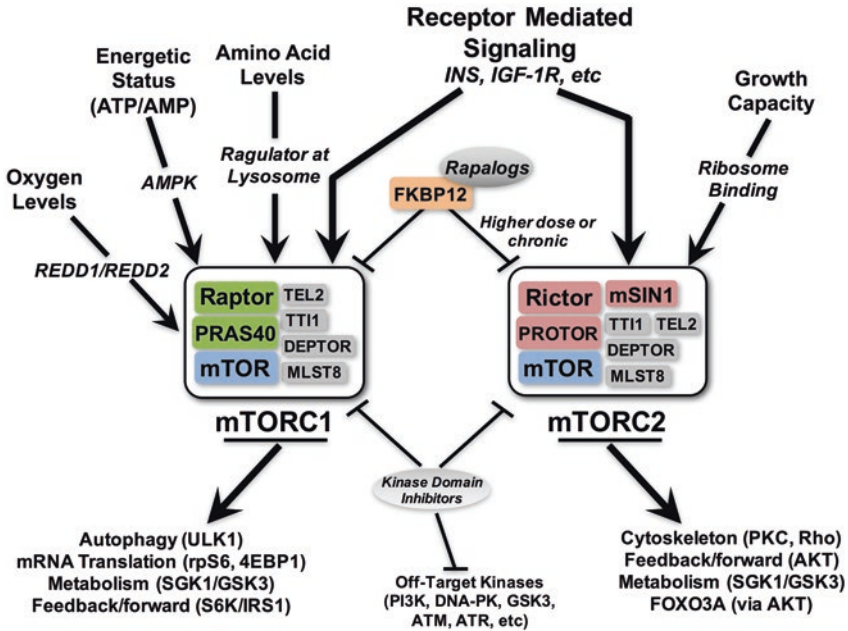


Fig. 3.3 Intracellular Integration of Nutrient Sensing Signals through mTOR Signaling. A simplified representation of mTOR complexes 1 and 2 as intracellular hubs for nutrient sensing signaling. mTORC1 and 2 are activated or inhibited by a variety of intracellular cues, including amino acid sensing, energetic status, and oxygen levels, as well as downstream of cell-surface receptors for extracellular signals (directionality of individual pathways not shown). mTORC1 and 2 integrate these inputs and enact various downstream cellular processes through their protein kinase activities. Key outputs of mTORC1 include regulation of mRNA translation through rpS6 and 4EBP1, autophagy through ULK1, metabolism through SGK1 and GSK3, and feedback regulation of receptor mediated signaling through modulation of IRS1 phosphorylation. mTORC2 regulates cytoskeletal organization through PKC and Rho Kinase, metabolism through SGK1 and GSK3, and Foxo3a activity and positive and negative feedback loops through actions on AKT. mTOR inhibitors target both complexes with differential action on the two dependent on dose, duration, cell type, and precise pharmacological target. Rapamycins or rapalogs inhibit mTORC1 and 2 in complex with the protein FKBP12. Kinase domain targeting inhibitors provide more complete inhibition, but with off-target effects on other kinases

Autophagy, the intracellular catabolic process of recycling through lysosome-mediated degradation, is inhibited by active mTOR. Thus, active mTOR promotes synthesis over recycling, while mTOR inhibition permits increased catabolism while dampening the biosynthetic process of protein synthesis. This shift exemplifies the role of mTOR in cellular adaptations to conditions permissive of or unsuitable for proliferation.

Both mRNA translation and autophagy appear to be key players in ageing and age-related pathologies. Decreasing mRNA translation increases longevity in multiple models; knockdown or deletion of ribosomal proteins increases lifespan in yeast, flies and nematodes, and S6K deletion extends lifespan and decreases body

size in mice. Pharmacological inhibition of translation has also been shown to increase lifespan in yeast. Some studies suggest that differential translation of certain mRNA's that rely on cap-dependent translation, rather than simply overall decreased translation, may play a role in the benefits of mTOR inhibition. Such a model has been established in budding yeast – translation of the low-nutrient response transcription factor Gcn4 is preferentially increased when global translation is reduced, and Gcn4 is necessary for the benefits of caloric restriction in this model. How differential mRNA translation impacts nutrient responses in mammals remains to be clarified.

Induction of autophagy is necessary for the benefits of reduced nutrient sensing signaling, but unlike translation has not been shown to be sufficient for lifespan extension. Damaged macromolecules, including aggregated proteins, oxidized lipids, and dysfunctional organelles, are known to accumulate during ageing and thought to contribute to cellular and tissue dysfunction.

Finally, mTORC2 contributes to nutrient responses by regulating the cytoskeleton, modifying metabolism, and providing a feed-forward activation of AKT through phosphorylation at serine 473. The feed-forward to AKT provides a clear role for mTORC2 in linking ribosome capacity to growth signaling through mTORC1.

Pharmacological Targeting of mTOR

The importance of mTOR in ageing has been demonstrated through genetic studies, as described, as well as through the NIH intervention testing program (ITP) experiments which utilized large-scale, multi-center, blinded mouse trials to test the efficacy of mTOR inhibition in mouse ageing using the compound rapamycin (Warner 2015). These trials demonstrated that mTOR inhibition reproducibly and significantly increases mouse lifespan in mammals, even when treatment begins late in life, and that lifespan increases are both dose-dependent and occur in both males and females with similar efficacy when equivalent blood levels are achieved (Harrison et al. 2009; Wilkinson et al. 2012). These findings have proven highly reproducible, and recent work has shown that even transient treatment at higher doses can dramatically increase survival (Bitto et al. 2016).

Rapamycin, or sirolimus, was the first identified pharmacological inhibitor of mTOR, for which yeast target of rapamycin, aka Tor, was named. Various modified forms with improved solubility or stability are now available, including temsirolimus, everolimus, and deforolimus (Nasr et al. 2015). These agents, collectively 'rapamycins', are special among small molecule inhibitors in that they do not bind directly to mTOR but, rather, bind the adapter protein FKBP12 (RBP1 in yeast) and only the FKBP12-rapamycin complex inhibits mTOR (Koltin et al. 1991). This two-tier mechanism provides incredible target specificity which has not yet been demonstrated with any of the newer mTOR active-site inhibitors, and the maximum biological effect of rapamycins is limited by cellular levels of FKBP12. Active site inhibitors, including Torin 1 and 2, can provide greater levels of mTOR inhibition

by binding directly to mTOR, but these compounds also show substantial off-target inhibition of other, structurally related, protein kinases such as DNA-PK, GSK3, ATM, and ATR (see Fig. 3.3), particularly at high concentrations (Liu et al. 2013). Rapamycins, conversely, remain specific to mTOR even at high doses.

Specific targeting of mTORC1 versus mTORC2 has been a major focus of recent work in mTOR. The rationale for this goal is that mTORC1 directed processes have been robustly associated with disease and ageing, while mTORC2 is considered by many to be involved only in off-target effects of mTOR inhibition such as altered glucose handling. Rapamycins are often described as mTORC1 specific inhibitors, but this oft-repeated statement has been proven a historic fallacy. mTORC1 and mTORC2 are both inhibited by rapamycin when treatment is chronic or in ‘high dose’ paradigms (Sarbasov et al. 2006). Various factors influence the relative sensitivity of mTORC1 and mTORC2 to rapamycin, as well the differential sensitivities of individual downstream targets (Mukhopadhyay et al. 2016). While very acute treatment with low concentration rapamycin may be mTORC1 specific, these conditions represent the exception rather than the rule.

mTORC1 and mTORC2 specific inhibitors are beginning to become available, and the next few years should shed new insight into the relative importance of these two complexes. The focus in ageing have been mTORC1, but the rationale for this focus has largely been a result of the convenience of following up on a better characterized complex coupled with regular misinterpretations of the primary literature. As discussed above, rapamycin is often called mTORC1 specific, but the statement in this form is not supported by evidence. In addition, the glucose-handling effects have been largely attributed to mTORC2, while a very modest and gender specific lifespan extension in mice appears to be possible with specific inhibition of mTORC1 (Lamming et al. 2012). Though intriguing, this partial genetic uncoupling neither precludes a benefit from mTORC2 inhibition, nor definitively demonstrates that mTORC1 inhibition alone can recapitulate the benefits of rapamycin. And, critically, the ‘off-target’ effects on glucose handling have not truly been demonstrated to be off-target at all – rather, the full benefits of mTOR inhibition may rely on mechanisms that modify glucose tolerance in vivo. Common non-physiologically relevant methods for measuring glucose handling likely misrepresent biology in vivo, and differences in glucose handling following bolus delivery may be misleading. This is exemplified by so-called ‘hunger diabetes’ in caloric restriction, and the fact that both caloric restriction and rapamycin treatment extend lifespan and prevent diabetes related diseases while also resulting in ‘abnormal’ glucose handling and insulin sensitivity in common bolus response paradigms (Blagosklonny 2011; Pigué et al. 2012).

There is also direct evidence suggesting mTORC2 specific pathways are important to at least some age-related diseases. For example, the mTORC2 driven regulation of lipid synthesis and cytoskeletal functions appear to be key factors in cancer (Benavides-Serrato et al. 2017; Bian et al. 2017; Guri et al. 2017) and mTORC2 has been shown to mediate inflammation related dermal ageing (Choi et al. 2016), while a number of the cytoskeletal and metabolic pathways directly regulated by mTORC2 have been linked to ageing and age-related diseases. In

particular, cytoskeletal regulation by Rho kinase has now been shown to delay cellular senescence and has been linked to disease progression in multiple age-related neurodegenerative diseases (Feng et al. 2016; Henderson et al. 2016; Kumper et al. 2016). Determining the relative importance of mTORC1 and 2 in ageing and age-related disease is a major focus of current research in ageing.

Nutrient Signaling in Ageing

Several components of NSS regulate lifespan and healthspan, the period of an organism's life spent free from significant morbidities, in model organisms or have been associated with healthy ageing in humans (Fig. 3.1). Dwarf mice defective in GH are long-lived and, as in humans, disease resistant, as are GHRH deficient and *Irs1* null mice (Selman et al. 2008; Sun et al. 2013). Interventions reducing IGF-1 signaling are associated with improved outcome in some murine models of AD and proteotoxicity models in invertebrates (Cohen et al. 2009; Cohen 2011; Parrella et al. 2013). Long-lived *Gh*, *S6K*, and *Igf1r* mutant mice have a markedly attenuated onset and severity of age-related pathologies including age-associated cardiac dysfunction, cancers, and age-related proteotoxicities (Cohen et al. 2009; Selman et al. 2009). PTEN, an antagonist of PI3K/IGF-1 signaling through de-phosphorylation of PIP3, promotes longevity in worms, flies, and mice, and is necessary for lifespan extension in IGF1R mutants (Ortega-Molina et al. 2012). PDK mediates signaling to AKT, limiting lifespan in worms (Paradis et al. 1999). Depletion of rpS6 or S6K increases lifespan in yeast, worms, and mice (Selman et al. 2009). FoxO3a, a transcription factor which is inhibited by IGF-1 signaling, is required for lifespan extension by reduced NSS in worms and flies and variants in the *FOXO3A* locus have been reproducibly associated with human longevity (Flachsbarth et al. 2009). Both common and rare variants in *AKT* and *IGF1R* have also been associated with human lifespan (Pawlikowska et al. 2009).

Multiple evolutionarily conserved nutrient/growth signaling pathways involved in nutrient sensing influence healthspan and lifespan (Laplante and Sabatini 2012; Johnson et al. 2013). AMP activated protein kinase (AMPK) is activated by low energy levels, inhibited by insulin/IGF-1 signaling, and is a positive regulator of lifespan in eukaryotes from yeast to mice (Martin-Montalvo et al. 2013). Metformin, an AMPK activator, has been shown to increase lifespan in *C. elegans* (Chen et al. 2017) and extend healthspan in mouse studies (although lifespan was not increased) and is the first compound headed to human trials tracking multiple age-related diseases (ARD's) (Check Hayden 2015; Barzilai et al. 2016). As discussed, mTOR is a key mediator of NSS and a well-established regulator of lifespan in eukaryotes (discussed above) (Johnson et al. 2013). Inhibition of mTOR by rapamycin, genetic disruption of the mTOR complexes, and hypomorphic mTOR alleles all extend murine lifespan and slow mouse ageing (Lamming et al. 2012; Wu et al. 2013). Finally, caloric restriction (CR), the oldest and most widely reported longevity-enhancing and ARD delaying intervention, acts through attenuation of all these pathways. CR is

the only longevity intervention reported in primates; two recent studies reported healthspan benefits, one also reporting increase lifespan (Mattison et al. 2012; Colman et al. 2014). Moreover, clinical trials examining the safety of CR in healthy individuals have very recently been published, with some early signs of benefits (Fontana et al. 2016; Martin et al. 2016; Romashkan et al. 2016). Interestingly, these studies report that in humans circulating inhibitory IGFBP-1 is significantly increased by CR but circulating IGF-1 is unaltered, a deviation from CR results in rodents.

In addition to these reported benefits of reduced NSS, elevated IGF-1 is associated with some age-related human diseases. High circulating IGF-1 is associated with the progression of prostate, breast, pancreatic, bladder, and small-cell lung cancer (Schernhammer et al. 2005; Fidler et al. 2012; Price et al. 2012; Belardi et al. 2013; Kubasiak et al. 2015). These observations led to the development of IGF-1R neutralizing antibodies as a therapeutic for cancer, although they have not consistently proven effective as monotherapies (You et al. 2013). High circulating IGF-1 has also been associated with chronic heart failure and increased all-cause mortality and is positively associated with risk of metabolic syndrome in longitudinal studies (Andreassen et al. 2009; Chisalita et al. 2011; Friedrich et al. 2013). Taken together, this evidence establishes IGF-1 and the growth and nutrient/growth signaling network surrounding it as central regulators of eukaryotic healthspan and lifespan and suggests that interventions designed to decrease IGF-1 signaling might promote health and longevity in humans.

IGF-1 in Human Health

In humans, strong defects in IGF-1 signaling cause dwarfism but protect against some age-related diseases, while some evidence suggests that subtler deficiencies confer resistance to diseases of ageing without marked effects on growth. Although the benefits of reduced insulin/IGF-1 in lifespan and health are well documented, defining the precise role of the IGF-1 in age-related disease, particularly human age-related diseases, has remained a complex problem, with many apparent paradoxes involving IGF-1. Low serum IGF-1 predicts longevity, but IGF-1 decreases with age and IGF-1 therapy benefits some of age-related pathologies. Circulating IGF-1 has been associated both positively and negatively with risk of age-related diseases in humans, and in some cases both activation and inhibition of IGF-1 signaling have provided benefit in animal models of the same diseases. Interventions designed to modulate the insulin/IGF-1 pathway positively or negatively are already available for clinical use, highlighting the need for a clear understanding of the role of IGF-1 in ageing and age-related disease.

Insulin-like growth factor 1, IGF-1, is a small hormone protein with endocrine, paracrine, and autocrine functions. IGF-1 was first described as the serum factor responsible for stimulating protein synthesis following growth hormone (GH) treatment, having insulin-like properties not repressible by insulin neutralizing antibodies (Froesch et al. 1963). IGF-1 stimulates growth in most mammalian cell types

and is critical for normal development. GH receptor (GHR) defects or production of GHR neutralizing antibodies leads to impaired IGF-1 production and Laron syndrome dwarfism. Both primary IGF-1 deficiency and Laron syndrome are treated using recombinant IGF-1.

While the clinical significance of IGF-1 in dwarfism is well established, the role of IGF-1 in chronic and age-related diseases remains controversial. Genetic manipulation in model organisms and comparative genetics using human centenarians have demonstrated that insulin/IGF-1 signaling drives age-related pathologies but, conversely, IGF-1 therapy has been shown to benefit certain models of age-related disease and low serum IGF-1 is a predictor of disease risk in many human association studies. These paradoxical results have led to both pro- and anti- NSS strategies for overlapping pathologies, most notably in neurodegenerative diseases. Given the availability of both activating and inhibitory interventions targeting the IGF-1 pathway there is an urgency to clarify the seemingly paradoxical roles of IGF-1 in human disease (further discussed below in *Resolving the Paradoxes – Competing Models*).

Nutrient Signaling in Age-related Disease – a Focus on IGF-1

Neurodegenerative Disease

Clinical studies and rodent models give a mixed view of NSS in AD, Huntington's disease (HD), and dementia. IGF-1 resistance has been reported in mouse models of neurodegenerative disease and in human AD and HD patients, and intranasal insulin and IGF-1 are under consideration as a therapeutic strategy in AD, HD, and stroke (Hanson and Frey 2008; Lopes et al. 2014; Lioutas et al. 2015). A number of animal studies have reported beneficial effects of intranasal insulin or IGF-1 in models of stroke, AD, and HD, and injury-induced neurological damage, and preliminary human data suggests intranasal administration of the long-acting insulin analogue Detemir improves cognition in adults with mild cognitive impairment or early stage AD dementia (Cai et al. 2011; Chen et al. 2014; Lopes et al. 2014; Claxton et al. 2015; Lioutas et al. 2015; Mao et al. 2016).

On the other hand, decreased NSS is associated with reduced risk of age-related neurological decline in model organisms. In humans high serum IGF-1 has been associated with increased risk of AD, independent of ApoE status (van Exel et al. 2014), and two recent longitudinal reports describe a human IGF-1 allele enriched in AD patients and associated with increased circulating IGF-1 (Vargas et al. 2011; Wang et al. 2012a, b). Additionally, serum IGF-1 is significantly increased in the offspring of Alzheimer's patients compared to individuals with no family history of Alzheimer's, independently of ApoE status, suggesting a heritable mechanistic link (van Exel et al. 2014), and IGF-1 receptor activating activity of serum, a bioactivity measure that is thought to reflect IGF-1 function better than serum levels alone, was also recently shown to associate with a higher prevalence and incidence of dementia and Alzheimer's (de Bruijn et al. 2014).

Ischemic Stroke and Cardiovascular Disease

Single nucleotide polymorphisms, SNPs, in the *IGF1* gene associate with ischemic stroke and cardiovascular disease (CVD) risk in candidate-based studies, suggesting some role for IGF-1 in these diseases (Aoi et al. 2012). In mice, treatment with IGF-1 following ischemic injury is beneficial, but increasing IGF-1 *prior* to an ischemic event results in a greater infarct size and worsened pathology; in agreement, decreasing IGF-1 prior to the ischemic injury through preconditioning attenuates disease (see Fig. 3.4) (Endres et al. 2007; Zhu et al. 2008). In humans, a recent study identified an *IGF1* SNP associated with increased serum IGF-1 levels and improved post-stroke outcome but found no *IGF1* variant associated with the risk of having a stroke (Aberg et al. 2013). The uncoupling of stroke risk and post-stroke outcome suggests that IGF-1 may have unique roles in each setting.

The relationship between ischemic CVD risk and serum IGF-1 is similarly complex. Some studies have suggest a u-shaped relationship between serum IGF-1 and CVD, both high and low IGF-1 predicting CVD mortality, but these reports are limited by their use of prospective design using already aged participants (van Bunderen et al. 2013). A recent study examining nearly 4,000 elderly men followed over a 4–6 year period found no association between serum IGF-1 and CVD-related mortality or overall mortality but did observe levels of both IGFBP1 and IGFBP3 to be predictive, IGFBP1 positively and IGFBP3 negatively, of survival (Yeap et al.

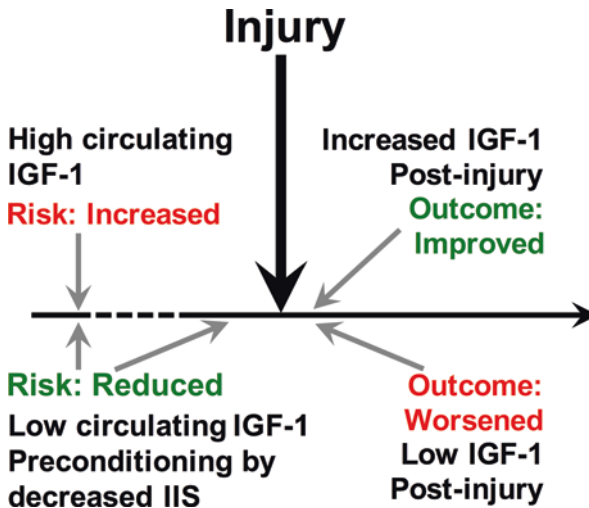


Fig. 3.4 Temporal Specificity of IGF-1 in Ischemic Injury. Temporal complexities of IGF-1 in response to injury. Available evidence indicates that IGF-1 is necessary for repair responses to ischemic injury events, while high-IGF-1/IIS signaling prior to an ischemic event is associated with poor outcome. This setting highlights the complexities of modeling and analyzing age-related pathologies. To clarify the role of IGF-1 in acute disease events pre- and post- injury levels are needed, and event risk versus response must be carefully distinguished

2011). Long-term longitudinal studies starting with healthy cohorts and measuring IGF-1, IGFBPs, and IGF-1 signaling in affected tissues will be necessary to uncover the true relationship between serum IGF-1 and ischemic stroke or CVD. Identifying gene variants that impact IGF-1 levels or signaling throughout life will also allow for better assessment of the role of IGF-1 in human ischemic disease in humans.

Sarcopenia

Much of the data supporting IGF-1 treatment as an intervention in age-related muscle disease are based on rodent models using acute injury. Among these are skeletal muscle injury models of sarcopenia using denervation, hind-limb unloading, and cardiotoxin injection. The beneficial effects of IGF-1 in these settings have been well reported, but their ability to accurately model age-related disease, versus acute injury, is not clear so they will not be discussed here.

A recent study examining the role of IGF-1 in normative human and rodent ageing found that although serum IGF-1 levels decrease during ageing, skeletal muscle NSS did not decrease in human or mouse; in fact, mTOR/S6 kinase activity actually increased with age (Sandri et al. 2013). Genetically increasing AKT activity in old mice resulted in exacerbated muscle decline and reduced lifespan, supporting a pro-ageing role for NSS in skeletal muscle. An independent study found that while chronic exercise prevents age-related sarcopenia in mouse quadriceps muscles, overexpression of IGF-1 in skeletal muscle had no benefit (McMahon et al. 2014).

Age-related Bone Loss

The relationship between the GH/NSS axis and bone health is complex. Circulating IGF-1 positively associates with bone mineral density (BMD) in post-menopausal women, is reduced in osteoporosis patients, and GH therapy in adults with GH deficiency improves BMD (Appelman-Dijkstra et al. 2014; Mo et al. 2015). In contrast, while GHR deficiency in Laron dwarfism is associated with dramatic reduction in circulating IGF-1 and overall body size, it does not appear to result in decreased BMD (Benbassat et al. 2003). GH drives circulating IGF-1, and consequently serum IGF-1 levels reflect GH status, so reported associations between IGF-1 and BMD may simply reflect the GH/BMD relationship. Further complicating the subject, it has been argued that GH impacts BMD predominately through changes in skeletal muscle mass, rather than direct effects on bone, and that there is a limited direct role for either serum GH or IGF-1 on bone (Klefter and Feldt-Rasmussen 2009).

Recent studies have begun to address some of these questions using tissue specific modulation of IGF-1. Osteocyte specific *Igf1* deletion suggest that local, but not circulating, IGF-1 is important for bone mineral metabolism (Sheng et al. 2014). Hepatic IGF-1 null mice with increased GH and GH overexpressing mice both show impaired bone architecture, while loss of hepatic IGF-1 in the context of normal GH has no impact on bone (Nordstrom et al. 2011; Lim et al. 2015). In agreement, it was

recently demonstrated that deletion of IGF-1 during early post-natal development results in a 67% increase in bone volume and increased density and trabecular number (Ashpole et al. 2015); consequently, BMD appears to be acutely sensitive to GH levels, with circulating IGF-1 impacting bone primarily via its role in feedback inhibition of GH, while locally produced IGF-1 plays a direct role in bone maintenance. The extent to which skeletal muscle mass plays a role in each of these settings remains to be defined.

Metabolic Syndrome and Obesity

Metabolic syndrome (MS) and obesity have repeatedly been associated with circulating IGF-1 levels in humans but a clear role for the factor has been elusive. Recent data suggests that study design may account for some of the discrepancies. A recent report comparing cross-sectional and longitudinal data from the same cohort found that while a cross-sectional analysis suggests a relationship between low serum IGF-1 and the prevalence of MS, a longitudinal assessment of the same population revealed that high serum IGF-1 is a predictive risk factor for the development of MS and serum IGF-1 levels decrease as MS progresses (Friedrich et al. 2013). Similarly, while cross sectional data suggests that low serum IGF-1 is associated with obesity, early life IGF-1 levels positively associate with risk of later life obesity (Madsen et al. 2011).

Evidence from Genome-wide Association Studies

A number of genes encoding factors involved in the insulin and IGF-1 signaling have been linked to human disease through genome-wide association studies (GWAS) (Table 3.1 and Fig. 3.1). These studies provide strong evidence that genetic variation in NSS influences a wide range of human diseases from cancer to autism and include many classic age-related pathologies such as Alzheimer's disease, age-related hearing loss, and cardiovascular disease. Meta-analyses of the NHGRI GWAS catalog, which acts as a repository for all reported significant GWAS findings, indicate that genes in NSS are enriched among age-related diseases, consistent with the notion that this pathway is a key regulator of ageing and age-related disease in humans (Cluett and Melzer 2009, Johnson et al. 2015). While GWAS provide robust evidence that identified genetic loci influence traits, they lack information regarding the directional impact of identified genetic variation or the mechanistic role of trait associated factors. Candidate gene studies in humans and model organisms have been critical in providing functional evidence linking NSS to disease and ageing, though these studies, particularly human clinical association studies, have provided a mixed view of NSS in disease.

Table 3.1 Genes in Insulin/IGF-1 signaling linked to human disease through genome wide association studies

Gene	Disease	References
AKT3	Schizophrenia, diabetic retinopathy	Grassi et al. (2011), Ripke et al. (2013) and Schizophrenia Working Group of the Psychiatric Genomics (2014)
EIF4E2	Non-small cell lung cancer (survival)	Sato et al. (2011)
EIF4ENIF1	Age-related hearing impairment	Fransen et al. (2015)
GHR	Systemic lupus erythematosus	Hom et al. (2008)
MRAS	Coronary heart and artery disease, amyotrophic lateral sclerosis (sporadic)	Erdmann et al. (2009), Schunkert et al. (2011), Dichgans et al. (2014) and Xie et al. (2014)
RRAS	Schizophrenia	Schizophrenia Working Group of the Psychiatric Genomics (2014)
RRAS2	Alzheimer's disease	Sherva et al. (2014)
NRAS	Autism	Xia et al. (2014)
IGFBP7	Age-related macular degeneration	Arakawa et al. (2011)
IGF1R	Arthritis (juvenile idiopathic)	Thompson et al. (2012)
IGF2, INS	Prostate cancer, type 1 diabetes autoantibodies	Eeles et al. (2009) and Plagnol et al. (2011)
IGF2BP2	Type 2 diabetes, gestational diabetes	Diabetes Genetics Initiative of Broad Institute of Harvard and MIT, Lund University, and Novartis Institutes of BioMedical Research et al. (2007), Scott et al. (2007), Zeggini et al. (2007), Unoki et al. (2008), Zeggini et al. (2008), Takeuchi et al. (2009), Voight et al. (2010), Parra et al. (2011), Saxena et al. (2013), Hara et al. (2014), Replication et al. (2014) and Anderson et al. (2015)
IGF2R	Brain lesion load, periodontitis	Baranzini et al. (2009) and Teumer et al. (2013)
IGFB2	Esophageal cancer	Wu et al. (2012)
IGFBP1	Rheumatoid arthritis	Padyukov et al. (2011)
IGFBP1, IGFBP3	Major depressive disorder	Investigators et al. (2013)
IGFBP5, IGFBP2	Mitral valve prolapse	Dina et al. (2015)
IRS1	Type 2 diabetes	Rung et al. (2009), Voight et al. (2010) and Replication et al. (2014)
STK11	Psychosis in Alzheimer's disease	Hollingsworth et al. (2012)

(continued)

Table 3.1 (continued)

Gene	Disease	References
MAP2K5	Obesity	Speliotes et al. (2010), Wen et al. (2012), Berndt et al. (2013), Wen et al. (2014) and Locke et al. (2015)
MAP3K1	Breast cancer, type 2 diabetes	Easton et al. (2007), Thomas et al. (2009), Turnbull et al. (2010), Michailidou et al. (2013), Tabassum et al. (2013) and Ahsan et al. (2014)
MAP3K11	Gout	Matsuo et al. (2016)
MAP3K13	Airflow obstruction	Wilk et al. (2012)
MAP3K14	Multiple sclerosis	International Multiple Sclerosis Genetics et al. (2011)
MAP3K4	Ageing	Edwards et al. (2013)
MAP3K7	Amyotrophic lateral sclerosis, Graves' disease, celiac disease	Dubois et al. (2010), Chu et al. (2011) and Xie et al. (2014)
MAP3K7IP1	Primary biliary cirrhosis, Crohn's disease	Franke et al. (2010) and Mells et al. (2011)
MAP3K7IP2	Crohn's disease, inflammatory bowel disease, diabetic retinopathy	Grassi et al. (2011) and Liu et al. (2015)
MAP3K8	Inflammatory bowel disease	Jostins et al. (2012)
MAP4K4	Psychiatric disorders (combined)	Cross-Disorder Group of the Psychiatric Genomics (2013)
MAP4K5	Lupus nephritis in systemic lupus erythematosus	Chung et al. (2014)
MAPK1	Multiple sclerosis	International Multiple Sclerosis Genetics et al. (2011)
MAPK10	Peripheral artery disease	Kullo et al. (2014)
PDK1	Erectile dysfunction in type 1 diabetes	Hotaling et al. (2012)
PIK3C2A	Schizophrenia or bipolar disorder	Ruderfer et al. (2014)
PIK3C3	Periodontitis	Teumer et al. (2013)
PIK3R1	Alzheimer's disease	Ramanan et al. (2014)
PTEN	Type 2 diabetes, periodontitis	Teumer et al. (2013) and Replication et al. (2014)
PRKAA1	Gastric cancer	Shi et al. (2011) and Hu et al. (2016)
PRKAB1	Ulcerative colitis, inflammatory bowel disease	Liu et al. (2015)
PRKACB	Breast cancer (male)	Orr et al. (2012)

(continued)

Table 3.1 (continued)

Gene	Disease	References
PRKAG2	Chronic kidney disease, bipolar disorder	Kottgen et al. (2010) and Belmonte Mahon et al. (2011)
RAF1	Cardiac hypertrophy	Parsa et al. (2011)
RPS6KA1	Amyotrophic lateral sclerosis (sporadic)	Xie et al. (2014)
RPS6KA2	Inflammatory bowel disease, dental caries	Jostins et al. (2012), Wang et al. (2012a, b) and Zeng et al. (2014)
RPS6KA4	Primary biliary cirrhosis, leprosy	Mells et al. (2011) and Zhang et al. (2011)
RPS6KB1	Multiple sclerosis, inflammatory bowel disease	International Multiple Sclerosis Genetics et al. (2011), Jostins et al. (2012)
SHC1	Prostate cancer	Eeles et al. (2013)
NR	Schizophrenia	Goes et al. (2015)
SHC4	Major depressive disorder, eating disorders	Aragam et al. (2011)
TSC1	Psoriasis, migraine without aura	Nair et al. (2009), Anttila et al. (2013)

A summary of gene-disease associations identified through genome-wide association studies involving key human genes in NSS, as shown in Fig. 3.1. Associations here achieved a genome-wide significance association threshold of $p < 10^{-5}$. Endophenotype associations, including associations with disease markers, not shown. GWAS data publicly available through the National Human Genome Research Institute GWAS Catalog

Paradoxes of IGF-1

The longevity and healthspan promoting benefits of reduced NSS are generally undisputed, but the impact of individual factors tends to be much more controversial, as in the case of IGF-1. IGF-1 has been a major focus of biogerontology, likely owing both to its historic context (the discovery of the nematode insulin/IGF-1 like receptor Daf-2) and the relative ease of measuring circulating IGF-1 in human cohorts for correlative studies. Although widely studied, the precise role of IGF-1 has remained stubbornly obscure. Mixed reports of IGF-1 in age-related diseases have led to various non-mutually exclusive models describing IGF-1 in human health. Both pro- and anti- IGF-1 therapies are in various stages of clinical trials, giving urgency to the paradoxes of IGF-1. Given the potential impact of these

therapeutic approaches to human health and the substantial attention given to this molecule in biogerontology, a detailed inspection of the data surrounding IGF-1 itself in ageing and age-related disease is warranted.

Evidence for Benefits of Reducing IGF-1 Signaling in Ageing

As discussed, the insulin/IGF-1-like signaling pathway was the first identified and is arguably the best characterized genetic pathway regulating lifespan in evolutionarily diverse organisms including nematodes, flies, and mice, with intracellular components also regulating lifespan in single cell eukaryotes (Fig. 3.1). Low serum IGF-1 is a positive predictor of lifespan in genetically heterogeneous mice, and humans with low IGF-1 resulting from GHR defects have a reduced incidence of age-associated cancers and metabolic disease (Harper et al. 2004; Guevara-Aguirre et al. 2011). Mx-cre driven deletion of IGF-1 in the liver dramatically reduces circulating IGF-1 and increases lifespan in mice (Svensson et al. 2011). A recent human genome-wide association study found that variants associated with low serum IGF-1 are also associated with increased likelihood of survival beyond 90 years (Teumer et al. 2016). Likewise, low IGF-1 is positively predictive of survival in already long-lived humans, and the offspring of centenarians tend to have low serum levels and bioactivity of IGF-1 (Guevara-Aguirre et al. 2011; Vitale et al. 2012; Milman et al. 2014). Human centenarians are enriched for rare variants in the *IGF1R* that reduce receptor function and impair IGF-1 stimulation of signaling in cultured cells (Tazearslan et al. 2011). Notably, *IGF1R* reduction of function allele carriers have increased serum IGF-1, presumably due to altered feedback inhibition of IGF-1 production. Together, this data strongly suggests that IGF-1 driven signaling promotes ageing and age-related disease.

Evidence for a Beneficial Role of IGF-1 in Disease

The evidence that IGF-1 signaling promotes ageing and age-related pathologies is substantial, but the precise role of IGF-1 in human age-related diseases in many instances remains controversial (excluding cancer, which will not be discussed here, as the disease-promoting role of NSS is well established). Serum IGF-1 was found in a 1985 study to decline during human ageing and it was suggested that this partly explains age-related bone and muscle loss. Supporting this view, low serum IGF-1 has been associated with metabolic syndrome (MS), cardiovascular disease (CVD) mortality, and hepatic steatosis (Oh et al. 2012), and low IGF-1 has been positively associated with mortality risk in some clinical studies (Tang et al. 2014). At least one recent study suggests there is a healthspan tradeoff of reduced NSS in invertebrates (Bansal et al. 2015), but the majority of paradoxical NSS data has arisen from studies of disease in rodents and humans.

Resolving the Paradoxes of IGF-1 – Competing Models

Central Versus Peripheral IGF-1

Given that IGF-1 has regulatory functions in the central nervous system, including regulation of GH at the pituitary gland, distinct from those of circulating IGF-1 it has been proposed that benefits and detriments of IGF-1 can be separated by uncoupling central (brain) and peripheral levels (Fig. 3.5) (Huffman et al. 2016; Milman et al. 2016). In this model systemic (hepatic) IGF-1 drives diseases such as cancer while central IGF-1 is necessary for proper regulatory function. Consistent with this model it has recently been demonstrated that intracerebroventricular infusion of IGF-1 in old rats rescues age-related declines in whole-body insulin sensitivity and glucose metabolism (Huffman et al. 2016). A related idea linked to the mixed neurodegenerative disease data is that neuronal health itself depends on central IGF-1 and neurodegenerative disease simply has a different relationship with IGF-1 than other age-related pathologies. While it remains to be seen if specific perturbations of brain versus peripheral IGF-1 will result in greater benefits than reducing NSS systemically in normal ageing or disease, and the mechanistic relationship further probed, it is an intriguing model which, given the existing intranasal delivery route, could lead to novel approaches to treating human age-related disease.

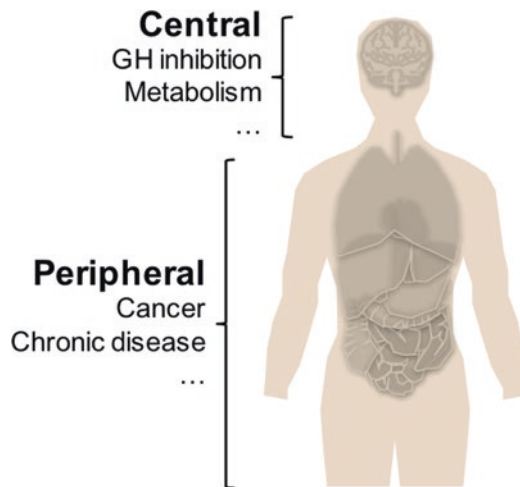


Fig. 3.5 Central Versus Peripheral IGF-1. The central versus peripheral model for the complex role of IGF-1 in ageing and age-related disease. In this model, circulating IGF-1, predominately produced in the liver, drives tissue ageing and age-related diseases, particularly cancer, in peripheral tissues, while brain-localized IGF-1 drives centrally regulated processes and neuron survival that combat age-related neurodegenerative diseases. While highly controversial, this model highlights the tissue-specificity of IGF-1 actions and may provide a partial explanation for complexity of IGF-1 in ageing

Temporal Specificity

One explanation for the discordant data in ischemic disease and injury models is that the role of IGF-1 in acute injury is highly dependent on timing. Lifespan studies generally show protective effects of reduced IGF-1 on chronic, including ischemic vascular, diseases, whereas injury models often show that IGF-1 treatment improves outcome. These observations support a model where chronic IGF-1 signaling drives risk of ischemic injury whereas NSS is necessary for a proper response to injury. In agreement, IGF-1 expression is induced during injury, and IGF-1 has been shown to play pleotropic roles in ischemic stroke, cardiovascular disease, and sarcopenia models (including acute injury models), as discussed (see Fig. 3.4) (Wagner et al. 2003). A precedent for this model has been established by recent studies of the senescence associated secretory phenotype (SASP). SASP is a well-documented driver of chronic and ARD's and reduced SASP signaling delays ARD's, while activation of SASP is beneficial in promoting wound repair (Demaria et al. 2014; Baker et al. 2016).

IGF-1 Resistance

The mixed role of IGF-1 in Alzheimer's disease may also be partly explained by observations that Alzheimer's brains show IGF-1 resistance and IGF-1 therapy provides a benefit in this setting, whereas genetic models suggest that chronic IGF-1 stimulation promotes the pathogenesis of IGF-1 resistance itself (de la Monte 2012; Zemva and Schubert 2014). Neuronal insulin/IGF-1 resistance precipitates a variety of defects, including altered glucose metabolism and neuronal viability, which are attenuated by IGF-1 treatment (Chen and Zhong 2013; Zemva and Schubert 2014). This model suggests IGF-1 benefits in AD are mechanistic similar to insulin injection in type 2 diabetes (T2D) – insulin prevents morbidities by normalizing blood glucose but does not improve the underlying defect of insulin insensitivity. Early routine use of insulin is associated with a variety of side-effects; behavioral modification and insulin-sensitizing agents, such as metformin, are preferred therapies (Lebovitz 2011). It seems prudent that caution be exercised in considering IGF-1 as a therapy in neurodegenerative disorders, but the lack of available treatment options and late-onset of the diseases should be weighed against potential side-effects.

While perhaps best-supported by experiments in AD models, age-related IGF-1 resistance may explain other observed benefits of IGF-1 therapy in aged animals and warrants further direct study.

Optimal Dose, Context Specificity

Perhaps the simplest model for IGF-1 in ARD and ageing is the notion that there is an ideal dosage which balances the beneficial and detrimental effects of IGF-1 and maximizes lifespan (Fig. 3.6). This model, supported by human clinical data (Burgers

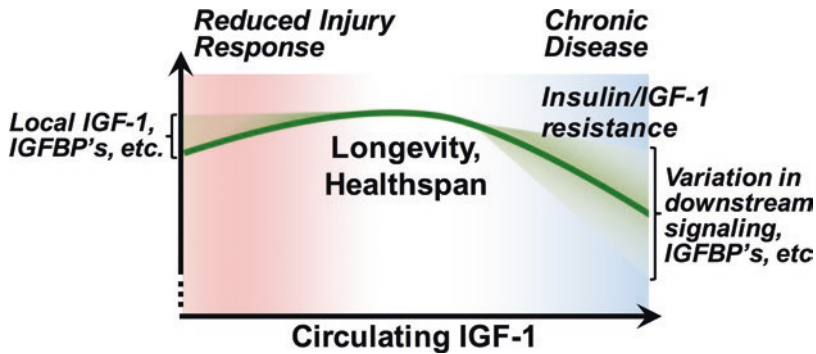


Fig. 3.6 Optimal Dose and IGF-1 Resistance. A dose-dependent model for the overall role of IGF-1 follows a u-shaped curve. IGF-1 levels may include IGF-1 produced in the liver and tissue localized production, depending on the context. At sub-optimal IGF-1 concentrations responses to acute injury are negatively affected. At high concentrations diseases are promoted by chronic IGF-1 stimulation. Chronic stimulation is associated with insulin/IGF-1 resistance, explaining the apparent benefits of local IGF-1 treatment in some neurodegenerative disease models. Circulating and intracellular factors modify signaling at both ends of the u-curve. Sufficient local IGF-1 production may be sufficient to negate the detrimental effects of reduced circulating IGF-1 in the context of acute injury

et al. 2011), likely accounts for the overall pleiotropy of IGF-1 but alone provides limited framework to consider interventions targeting this factor. Some intermediate level of circulating IGF-1 may in fact limit the development of chronic diseases without leading to detrimental effects, such as reduced wound healing, but tissue targeted and context specific interventions would undoubtedly provide greater benefit.

As stated, these models are non-mutually exclusive, and it is likely that each are at least partially true, or true in specific context. Which, if any, provide efficacious new approaches to age-related disease is the question at hand.

Circulating Factors – More Than Just IGF-1

IGF-1, acting through the IGF-1 receptor, is largely treated as the only, or at least the primary, mediator of systemic NSS in mammals. This has largely been historically driven; IGF-1 and IGF-1R represented attractive targets after the 1997 report that the longevity regulating DAF-2 receptor in *C. elegans* is a homolog of the human insulin/IGF-1 receptor (Kimura et al. 1997). While available data does support the notion that IGF-1 and IGF-1R do act as regulators of longevity in mammals, it is important to note the distinctions between nematode and mammalian insulin/IGF-1 signaling and, critically, the data suggesting that alternative systemic nutrient signals play equal or greater role in ageing. GH and GHRH are not only upstream of IGF-1 but activate intracellular NSS pathways themselves. GH, through GHR, stimulates PI3K/AKT/mTOR and MAPK/ERK pathways independent of

IGF-1. In addition, insulin and IGF-2 both have overlapping roles with IGF-1. Even in *C. elegans*, where the IGF-1R homolog DAF-2 has strongly influences lifespan, there are over 30 insulin/IGF-1 like signaling molecules and the relative contribution of each is unclear (Gahoi and Gautam 2016). Thus, hindsight would suggest that IGF-1 may not be as important in isolate as initially assumed.

The relatively overemphasized role of IGF-1/IGF-1R *per se* is highlighted by genetic models of longevity in mice: pituitary loss of function Ames and Snell dwarf mice, and GH, GHR, or GHRH knockout animals all show substantially increased lifespan compared to normal animals, with median survival improved by 50–70% (Sun et al. 2013). IGF-1R heterozygous mice are reportedly long-lived, but this phenotype is milder and appears to be gender and strain specific. Conditional knockout of IGF-1 in liver, which produces ~80% of circulating levels, has been found to extend median lifespan of mice but only by ~10% (Svensson et al. 2011). This extends beyond the upstream regulators of IGF-1; overexpression of FGF21, a fasting hormone secreted by the liver, was shown to increase median lifespan in mice by 36%, reportedly through modulation of mTOR, AKT, and the GH-IGF-1 axis in liver (Zhang et al. 2012). Direct relative effect comparisons between these studies are impossible given the complexity of the experiments and the complications associated with deleting IGF-1 and IGF-1R which, when homozygous deleted, are neonatal lethal (Epaud et al. 2012; Pais et al. 2013). Nevertheless, the general trend would suggest that circulating factors other than IGF-1 may prove better candidates for intervention in ageing and warrant further attention.

Experimental Considerations and Future Directions

While association studies are valuable for linking phenotypes to genetic variation or biomarkers, results should be interpreted with extreme caution. In particular, cross-sectional association data involving a dynamic parameter like IGF-1, which is strongly influenced by health status, should be approached with great caution. Chronic renal failure, hepatic dysfunction, and malnutrition all cause a reduction in levels or serum bioactivity of IGF-1, among broader changes to circulating factors (Moller and Becker 1990; Moller and Becker 1992; Tonshoff et al. 2005; Sirbu et al. 2013). Since IGF-1 is itself altered by the presence of underlying pathology causality should not be inferred from cross sectional data alone even when robust associations are observed.

Similarly, genetic modeling provides an immense amount of information regarding the role of individual factors in ageing and disease, but results from genetic models must always be interpreted with care. The more complex the genetic modulation, the greater the room for unintended consequences. Complex heterozygotes or conditional mutants may provide useful complimentary data, but off-target effects,

temporal or spacial gene functions (including developmental functions), leaky promoters, and gene dosing effects are all complicating factors that are too often ignored when model data is published. Pharmacological approaches have also been limited by over-interpretation or lack of proper controls. The ageing literature is littered with unrepeated studies identifying intervention strategies of unclear validity. Greater effort should be focused on multi-center collaborations, as typified by the intervention testing program, where published findings are least likely to be influenced by bias. The sum of available data on nutrient sensing signaling paints a clear landscape where reduced signaling delays pathologies of ageing, but individual studies must be taken in context.

Study design is critical for interpreting association data, but pleiotropic effects can dramatically complicate interpretation even in the most rigorously designed study. As discussed, experimental evidence suggests that nutrient signaling plays different roles in altering the risk of an ischemic events versus promoting recovery following such events. For this reason, abstract or overly simplified models for age-related disease may not accurately reflect the intended pathology. The most notable examples are acute injury in muscle models using toxins or physical injury (as discussed), but examples of age-related disease models with no clear link to actual ageing are abundant. There are also important considerations that must be accounted for in clinical studies; retrospective studies will likely be enriched for patients harboring factors that promote survival and may be misleading if they are used to predict the effects of genetic variability on risk, while prospective studies that track only incidence but lack survival data may obscure important associations.

Remaining unanswered questions regarding the role of nutrient sensing signaling in disease will require tissue and context specific animal models and cautious interpretation of experimental findings. In human studies, functional genetics defining the impact of disease or longevity associated genetic variation on the expression of IGF-1 or related factors will provide further insight into the relationship between IGF-1 and disease. Creative synthesis of modern high-throughput datasets to identify and describe genetic variants with IGF-1 eQTL's, including those with tissue specific impact, will add new depth to our current understanding of the regulation and role of IGF-1 in human disease. Circulating NSS factors, including IGF-1 modifiers such as the IGFBP's, deserve greater attention in studies focused on systemic signaling; they are both major confounding factors in NSS studies and promising targets for future therapies. Addressing these issues and identifying the downstream targets of importance will lead to novel therapeutic strategies and pharmacological targets.

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