Regulation of reproduction and longevity by nutrient-sensing pathways

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Nutrients are necessary for life, as they are a crucial requirement for biological processes including reproduction, somatic growth, and tissue maintenance. Therefore, signaling systems involved in detecting and interpreting nutrient or energy levels—most notably, the insulin/insulin-like growth factor 1 (IGF-1) signaling pathway, mechanistic target of rapamycin (mTOR), and adenosine monophosphate-activated protein kinase (AMPK)—play important roles in regulating physiological decisions to reproduce, grow, and age. In this review, we discuss the connections between reproductive senescence and somatic aging and give an overview of the involvement of nutrient-sensing pathways in controlling both reproductive function and lifespan. Although the molecular mechanisms that affect these processes can be influenced by distinct tissue-, temporal-, and pathway-specific signaling events, the progression of reproductive aging and somatic aging is systemically coordinated by integrated nutrient-sensing signaling pathways regulating somatic tissue maintenance in conjunction with reproductive capacity.

Complex, whole-organism processes such as energy homeostasis, reproduction, and somatic tissue maintenance are coordinated by networks of signaling cascades that direct tissue- and cell-specific physiological changes. Nutrients are crucial requirements for most biological processes; thus, signaling pathways that detect nutrient availability are among those that exert a broad influence within all organisms. Seminal research during the last few decades has revealed that nutrient-sensing systems including the insulin/insulin-like growth factor 1 (IGF-1) signaling (IIS) pathway, mechanistic target of rapamycin (mTOR), and AMP-activated protein kinase (AMPK) influence life history strategies such as those that determine reproductive status and somatic tissue maintenance with age.

Somatic and reproductive aging

Aging can be defined as progressive physiological decline after reproductive maturation, characterized by such features as reduced fecundity, mitochondrial dysfunction, decreased protein homeostasis, genomic instability, epigenetic changes, cellular senescence, and impaired metabolic homeostasis (López-Otín et al., 2013). Targeting mechanisms that control age-dependent changes not only affects specific conditions or aging-related diseases but can also extend lifespan. In fact, the capacity to systemically manipulate somatic aging would not likely exist without the underlying connections between metabolism, reproduction, and longevity.

A decline in female reproductive capacity is one of the earliest hallmarks of age-related deterioration in humans (te Velde and Pearson, 2002; Cohen, 2004). Rates of infertility, birth defects, and unsuccessful pregnancy outcomes increase more than a decade before menopause, well in advance of marked neuroendocrine changes or exhaustion of oocyte supply (Armstrong, 2001; te Velde and Pearson, 2002). The early stages of reproductive decline are likely caused by age-related deterioration in oocyte quality, evident in the rise of chromosomal abnormalities such as aneuploidy (te Velde and Pearson, 2002). Reproductive cessation is followed by a lengthy post-reproductive lifespan in humans, and a tendency for reproductive senescence to precede somatic senescence and/or death has also been documented for the females of numerous mammalian species, including nonhuman primates, toothed whales, lions, African elephants, polar bears, domesticated livestock species, dogs, and laboratory rodents (Cohen, 2004). Interestingly, the reproductive capacity of *Caenorhabditis elegans* hermaphrodites spans only one third to one half of total lifespan under nutrient-replete conditions, and, similar to humans, reproductive decline in this nematode is associated with a deterioration of oocyte quality (Hughes et al., 2007; Luo et al., 2009, 2010). Moreover, there appears to be a degree of evolutionary conservation from *C. elegans* to mice and humans for regulatory mechanisms that determine oocyte quality maintenance and reproductive aging (Hamatani et al., 2004; Steuerwald et al., 2007; Luo et al., 2010). Ongoing investigation into the signaling pathways and molecular mechanisms that control female reproductive senescence will likely continue to shed light on the processes governing reproductive and somatic aging.

Connections between reproductive status, metabolic resources, and longevity

Female reproductive decline is not simply a hallmark of aging; there are many lines of evidence indicating the existence of close

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Abbreviations used: AMPK, AMP-activated protein kinase; IIS, insulin/IGF-1 signaling; ILP, insulin-like peptide; mTOR, mechanistic target of rapamycin; mTORC, mTOR complex; PI3K, phosphatidylinositol 3-kinase; PTEN, phosphatase and tensin homolog; RSK, p90 ribosomal protein S6 kinase; S6K, p70 ribosomal protein S6 kinase.

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ties between reproductive status and longevity. For instance, artificial selection for late-life reproduction was associated with lifespan extension in the fruit fly *Drosophila melanogaster* in addition to reduced early-life fecundity (Rose and Charlesworth, 1980; Luckinbill et al., 1984), whereas selection for extended lifespan correlated with a reduction in overall reproductive activity (Zwaan et al., 1995). In human populations, female fertility late in life and/or increased age at menopause is associated with an increase in life expectancy (Perls et al., 1997; Cooper and Sandler, 1998; Gagnon, 2015; Jaffe et al., 2015). These correlative associations beg the question of whether reproductive function and somatic senescence are causally linked.

Mechanistic connections between the reproductive system and longevity have been explored using *C. elegans* and were later verified in other organisms. Ablation or genetic disruption of germline stem cells in *C. elegans* imparts a significant extension of lifespan (Hsin and Kenyon, 1999; Arantes-Oliveira et al., 2002). This effect on longevity is not caused by infertility per se, as it is abrogated by additional ablation of the somatic gonad (support tissue for the germ cells; Hsin and Kenyon, 1999), and mutations that prevent oocyte or sperm formation cause infertility without changes to lifespan (Arantes-Oliveira et al., 2002). Instead, signaling pathways actively coordinate germline changes with somatic aging and vice versa. To extend lifespan, germline loss in *C. elegans* requires changes in somatic tissue that include nuclear localization of the transcription factor DAF-16, a key IIS target homologous to the mammalian FoxO family (Hsin and Kenyon, 1999; Berman and Kenyon, 2006; Ghazi et al., 2009). Germlineless lifespan extension is mediated through effectors with important roles in fatty acid metabolism and autophagy, downstream of DAF-16/FoxO and other transcription factors (Antebi, 2013). Importantly, germ cell loss also extends lifespan of *D. melanogaster* (Flatt et al., 2008), and transplantation of younger ovaries into female mice (Cargill et al., 2003) or castration in humans (Min et al., 2012) have both been associated with increases in life expectancy. Therefore, manipulating the germline or gonad leads to somatic changes associated with lifespan extension, and this relationship seems to be evolutionarily conserved. Conversely, activities of signaling pathways such as TGF-β Sma/Mab in somatic tissues have non–cell-autonomous effects in the *C. elegans* germline that are associated with regulating oocyte quality maintenance and reproductive aging (Luo et al., 2010). In addition, nutrient cues that convey information such as somatic nutrient stores cause germline responses. For instance, the levels of fatty acids mobilized from somatic tissue in *C. elegans* hermaphrodites are interpreted in the germline and translated into signals that determine commitment to oogenesis versus spermatogenesis (Tang and Han, 2017). Overall, it appears that although the specific cues have not all been uncovered, the germline is an important signaling hub for the coordination of reproductive status with somatic conditions (Antebi, 2013). Furthermore, metabolic pathways and processes are key participants in the bidirectional lines of communication between germline and soma.

It is well known that nutrient availability is crucial for the energetically expensive processes of reproduction, somatic growth, and tissue maintenance. A connection between food supply and the improved fertility of domestic animals was proposed by Charles Darwin and has likely been observed in some form since the early days of animal husbandry (Wade and Schneider, 1992). Dietary restriction (i.e., reduced nutrient intake without malnutrition) can cause a reduction in progeny number, but importantly, it also significantly delays reproductive senescence in model organisms from *C. elegans* (Hughes et al., 2007; Luo et al., 2009) and *D. melanogaster* (Rauser et al., 2005) to mice and rats (Merry and Holehan, 1979; Nelson et al., 1982; McShane and Wise, 1996; Selesniemi et al., 2008). Moreover, dietary restriction interventions have evolutionarily conserved beneficial effects on age-related health and/or lifespan (McCay et al., 1935; Klass, 1977; Lakowski and Hekimi, 1998; Colman et al., 2009, 2014; Grandison et al., 2009; Mattison et al., 2012; Mercken et al., 2013). Although the mechanisms by which dietary restriction affects health and lifespan are complex and not yet fully elucidated, it appears that nutrient-sensing signaling pathways such as IIS, mTOR, and AMPK play a role (Fontana and Partridge, 2015). Interestingly, rather than depending on a reduction of total calories per se, effects of dietary restriction are observed with intermittent energy restriction or time-restricted feeding regimes that do not reduce cumulative energy intake and can even result from exclusively altering levels of individual macronutrients or amino acids (e.g., methionine; Lee et al., 2008; Maklakov et al., 2008; Grandison et al., 2009; Solon-Biet et al., 2014, 2015; Brandhorst et al., 2015; Fontana and Partridge, 2015). Stimuli such as specific macronutrients trigger different responses among the nutrient-sensing signaling pathways, and the signaling responses to a dietary restriction intervention are likely important for determining its health, reproductive, and lifespan outcomes.

Because nutritional input is required for somatic growth and maintenance as well as reproduction, conceptually, it stands to reason that there would be systems in place to detect nutrient availability and adjust both progeny production and somatic maintenance accordingly. Evolutionarily conserved signaling pathways that detect and interpret levels of specific nutrients fulfill a fundamental aspect of that role. We suggest that the capacity of signaling systems to impact longevity is primarily a byproduct of coupling extended somatic maintenance to an extension of reproductive function, which would optimize chances for reproductive success under stressful conditions. However, although reproductive capacity and longevity may be systemically coordinated by integrated signaling networks, the molecular mechanisms that directly impact these processes are the result of tissue-, temporal-, and/or pathway-specific signaling events. Thus, the signaling pathways directing these life history decisions can be manipulated without the ultimate cost of reducing reproductive output or lifespan (Partridge et al., 2005; Antebi, 2013), likely because of a degree of redundancy between nutrient-sensing systems, specificity in the signaling effects of specific nutrients, and downstream signaling events within individual tissues. Nutrient-sensing signaling pathways thereby determine the progression of both somatic and reproductive aging.

IIS

IIS is a critical coordinator of nutrient availability with energy homeostasis and metabolic processes across diverse invertebrate and vertebrate species. The IIS pathway is activated by insulin-like peptide (ILP) ligands whose levels are responsive to nutrient availability and/or sensory information. Approximately 40 genes in *C. elegans* (Pierce et al., 2001; Li et al., 2003) encode putative ILPs, including both agonists and antagonists of the IIS tyrosine kinase receptor; *C. elegans* ILPs interact within a complex network and exert distinct effects on various physiological processes (Fernandes de Abreu et al., 2014).

D. melanogaster has eight putative ILPs (Brogiolo et al., 2001; Garelli et al., 2012), and the mammalian insulin-like superfamily comprises at least 10 ILPs, although of these, insulin and the insulin-like growth factors IGF-1 and -2 are the only IIS tyrosine kinase receptor ligands. Levels of bioactive IGF-1 and -2 in circulation are determined by growth hormone signaling and IGF binding proteins (Werner et al., 2008). In contrast, insulin levels are acutely altered in response to circulating nutrients, in addition to being basally regulated depending on chronic demand. Immediate fluctuations result from stimulation or repression of insulin secretion from pancreatic β cells; glucose is the primary secretagogue, but other nutrients and circulating factors affect insulin levels, including specific amino acids (e.g., a combination of glutamine and leucine), free fatty acids, and other hormones (Fu et al., 2013). Increased circulating insulin activates the IIS pathway in responsive target tissues, leading to the promotion of nutrient uptake and storage.

Binding of insulin-like agonists to an IIS tyrosine kinase receptor causes receptor activation and the phosphorylation of cellular receptor substrates, which can initiate signal transduction via two major branches of IIS: the phosphatidylinositol 3-kinase (PI3K)/Akt pathway and the Ras/MAPK pathway (Fig. 1). In the PI3K/Akt pathway, activated PI3K generates the second messenger phosphatidylinositol 3,4,5-trisphosphate; controlling $PI(3,4,5)P_3$ levels is one key step for negative regulation of the PI3K/Akt signaling cascade performed by phospholipid phosphatases such as the phosphatase and tensin homolog (PTEN). $PI(3,4,5)P_3$ stimulates recruitment and activation of 3-phosphoinositide–dependent protein kinase-1, which leads to activation of its Akt/protein kinase B substrate (Taniguchi et al., 2006). Akt phosphorylates many targets, including the FoxO transcription factor family (Brunet et al., 1999; Lin et al., 2001; Taniguchi et al., 2006). Phosphorylation by Akt excludes FoxO from the nucleus, leading to reduced transcription of its targets, including genes involved in stress responses, protein homeostasis, cell maintenance, and metabolic pathways (Lin et al., 2001; Murphy et al., 2003; Webb et al., 2016). In mammals, other known substrates of Akt include the Rab-GTPase–activating protein AS160 (Akt substrate of 160 kD), which is involved in controlling glucose uptake; glycogen synthase kinase 3, which represses glycogen synthase activity; and tuberous sclerosis complex (TSC) 1/TSC2, which regulates the activity of mTOR complex (mTORC) 1 (Taniguchi et al., 2006). Consequently, PI3K/Akt signaling is associated with downstream changes that influence stress responses and cell survival in addition to promoting nutrient uptake and storage.

The Ras/MAPK signaling pathway is also largely comprised of a kinase cascade, downstream of receptors that are activated by growth factors and other stimuli. In brief, activation of the small GTPase Ras leads to the stepwise activation of the serine/threonine kinase Raf, MAPK kinase (MEK) 1 and MEK2, and subsequently of ERK1 and ERK2 (Taniguchi et al., 2006; Aksamitiene et al., 2012). Although components of Ras/MAPK signaling appear to be highly conserved between *C. elegans* and mammals, Ras/MAPK signaling is not considered as central for mediating IIS as the PI3K/Akt branch of signaling in invertebrates (Sundaram, 2013; Chi et al., 2016). Nonetheless, the IIS receptor is one of the receptors upstream of the Ras homologue in *C. elegans* (Nanji et al., 2005), and in *D. melanogaster*, the IIS receptor substrate impacts Ras/MAPK signaling (Slack et al., 2015). In mammals, the Ras/MAPK pathway is viewed primarily as a mitogenic pathway; downstream targets of activated ERKs include the p90 ribosomal protein S6 kinase (RSK) and the transcription factor ELK1, which influence cell growth, proliferation, differentiation, and survival (Taniguchi et al., 2006). Importantly, though, multiple levels of cross-talk interactions exist between the PI3K/Akt and Ras/MAPK signaling pathways (Aksamitiene et al., 2012). Collectively, IIS affects energy homeostasis through both metabolic and mitogenic responses.

Although core IIS components are highly conserved from invertebrates to humans, there are additional layers of complexity in these signaling networks. For instance, in *C. elegans*, the IIS tyrosine kinase receptor (DAF-2) and the FoxO transcription factor homologue (DAF-16) both have splice isoforms with distinct roles in biological processes including lifespan control, taste avoidance learning, and regulation of target genes (Lin et al., 2001; Ohno et al., 2014; Chen et al., 2015a). In mammals, the IIS tyrosine kinase receptors include an IGF-1 receptor and two functionally distinct splice isoforms of the insulin receptor, in addition to hybrids between receptor subunits; insulin, IGF-1, and IGF-2 vary in their binding affinities to these receptors (Taniguchi et al., 2006). Different signaling effects of these ligands are therefore based in part on the receptors being differentially distributed temporally and spatially as well as exhibiting preferential association with distinct cellular receptor substrates (Taniguchi et al., 2006). Many downstream signaling components of the mammalian IIS network are also known to have multiple forms and isoforms, with differences in tissue distribution, cellular localization, activation kinetics, and binding partner interactions (Taniguchi et al., 2006). This allows IIS to mediate diverse and intricate downstream effects in different tissues in response to sensory input and/or nutrient availability. IIS is therefore ideal for coordinating fundamental whole-organism processes—such as energy homeostasis, reproductive status, and somatic growth or maintenance—with environmental conditions.

IIS and reproduction. IIS governs metabolism, growth, tissue maintenance, and reproduction in response to nutrient abundance. Therefore, altering IIS changes the rates of these processes and by extension affects longevity (Fig. 1). For example, its role in jointly controlling reproductive status and survival is evident in larval *C. elegans*. DAF-2/DAF-16 signaling is one of the primary pathways, along with the TGF-β Dauer pathway, regulating the formation of dauer larvae; the dauer larval stage is an alternative prereproductive stage that allows prolonged survival under stressful conditions, with the capacity to later develop into adults with full reproductive competence (Riddle et al., 1981; Thomas et al., 1993; Gottlieb and Ruvkun, 1994). Notably, the IIS pathway and the Sma/Mab branch of TGF-β signaling (Luo et al., 2009) are both important regulators of age-related reproductive decline in *C. elegans* adults. For instance, deletion of *daf-28*, *ins-6*, *ins-13*, or *ins-31* (genes encoding ILPs) extends the reproductively competent period of adulthood (i.e., reproductive span; Fernandes de Abreu et al., 2014). Moreover, although reduction-of-function IIS receptor mutants (i.e., *daf-2(−)* mutants) can show a slight reduction in total progeny production (Kenyon et al., 1993), they also exhibit a dramatic reproductive span extension that is dependent on activity of the DAF-16/FoxO transcription factor in somatic tissue (Hughes et al., 2007; Luo et al., 2009, 2010). This is associated with improvements in germline and oocyte maintenance with age, which leads to increased viability of the oocytes and embryos produced by aging *daf-2(−)* worms (Luo et al., 2010). IIS regulates several stages of germ cell and oocyte development in

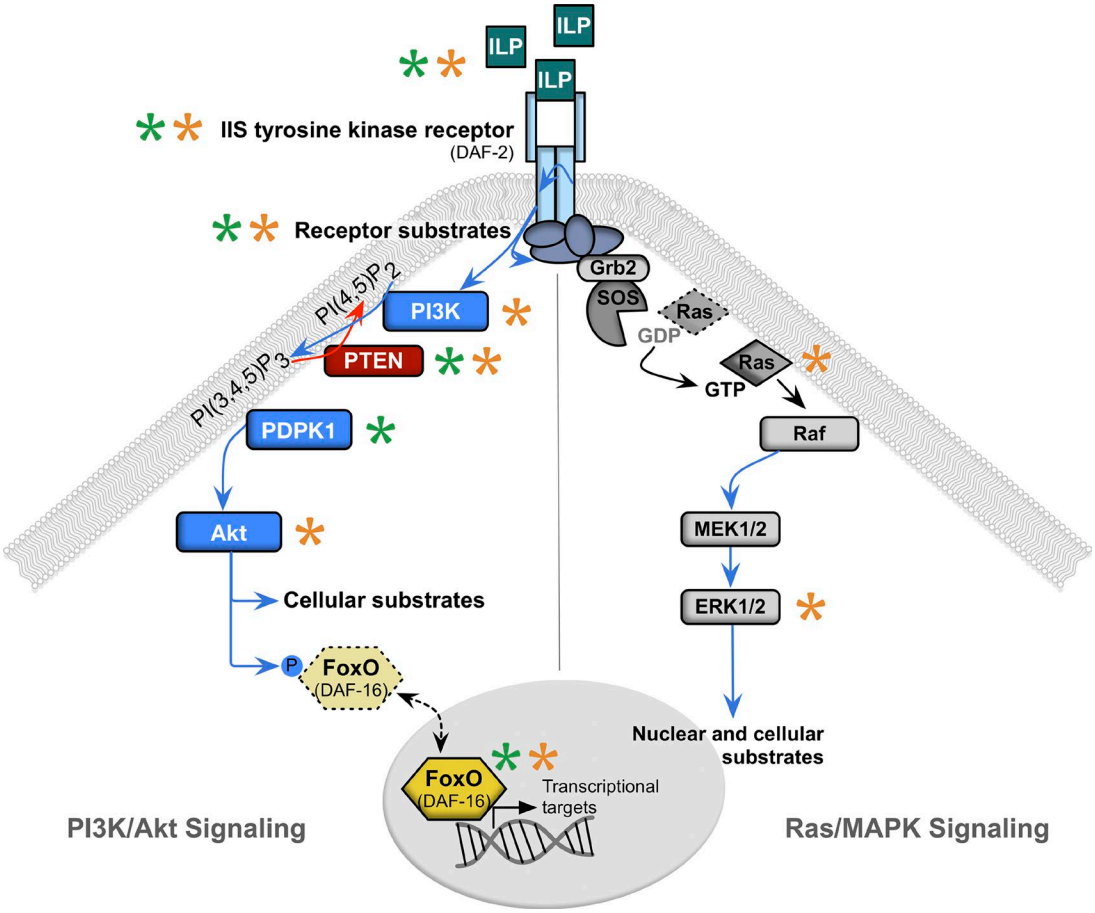

Figure 1. **IIS and its effects on reproduction and longevity.** Many IIS components have been shown to affect reproductive function (green asterisks) and/or lifespan (orange asterisks) in *C. elegans*, *D. melanogaster*, and/or mice; these signaling components are indicated by asterisks in this simplified IIS schematic. ILP ligands bind to a transmembrane IIS tyrosine kinase receptor (DAF-2 in *C. elegans*), which autophosphorylates and then recruits and activates key substrates, either directly or through receptor substrate intermediates. In the PI3K/Akt branch of IIS (left), activated PI3K converts $PI(4,5)P_2$ into second messenger $PI(3,4,5)P_3$; $PI(3,4,5)P_3$ levels are negatively regulated by phospholipid phosphatases such as the PI3-phosphatase PTEN. $PI(3,4,5)P_3$ stimulates recruitment and activation of 3-phosphoinositide–dependent protein kinase-1 (PDPK1) and its substrate, Akt/protein kinase B. Once activated through phosphorylation, Akt phosphorylates many cellular substrates not depicted in this image, including the Rab-GTPase–activating protein AS160, glycogen synthase kinase-3, and TSC1/TSC2. One key target of Akt is the FoxO transcription factor (DAF-16 in *C. elegans*); phosphorylation by Akt results in its exclusion from the nucleus and prevention of its transcriptional activity. In the Ras/MAPK branch of IIS (right), binding of the adapter protein Grb2 and the guanine nucleotide exchange protein Son of sevenless (SOS) to the activated IIS receptor, either directly or via a docking protein, allows SOS to catalyze a transformation of inactive GDP-bound Ras to active GTP-bound Ras. The activated small GTPase Ras stimulates activation of the serine/threonine kinase Raf, which leads to stepwise phosphorylation and activation of MEK1/MEK2 and then ERK1/ERK2. Activated ERK1/2 phosphorylates many cellular and nuclear substrates not depicted in this image, including RSK and the transcription factor ELK1. Blue arrows indicate phosphorylation (kinase activity); red arrows indicate dephosphorylation (phosphatase activity).

C. elegans, including germline stem cell proliferation and maintenance (Luo et al., 2010; Michaelson et al., 2010; Qin and Hubbard, 2015) and oocyte meiotic progression (Lopez et al., 2013). Consistent with the demonstrated importance of IIS for *C. elegans* reproduction, reducing expression of specific *D. melanogaster* ILPs (Grönke et al., 2010) or overexpressing the *D. melanogaster* FoxO homologue (Giannakou et al., 2004) can lead to reduced total progeny production, and female *D. melanogaster* with reduction-of-function mutations of the IIS receptor are sterile (Tatar et al., 2001). Loss-of-function mutations of the IIS receptor have cell-autonomous effects in female *D. melanogaster* germlines, causing reduced germline stem cell proliferation and vitellogenesis (LaFever and Drummond-Barbosa, 2005), and IIS receptor loss-of-function in somatic tissue impairs germline stem cell maintenance (Hsu and Drummond-Barbosa, 2009). Therefore, IIS is clearly involved in regulating reproductive function in invertebrates.

IIS also has important effects on mammalian reproduction. Whole-body insulin receptor substrate (IRS)-2 deletion (Burks et al., 2000) or neuronal-specific disruption of the insulin receptor (Brüning et al., 2000) significantly reduces fertility in mice, associated with dysregulation of the hypothalamic–pituitary–gonadal axis as well as fewer follicles or impaired follicle maturation. Although some degree of oocyte-specific 3-phosphoinositide–dependent protein kinase-1 signaling is required to maintain survival of primordial follicles (Reddy et al., 2009), whole-body disruption of the FoxO3A isoform (Castrillon et al., 2003; Hosaka et al., 2004) or oocyte-specific loss of IIS negative regulator PTEN (Reddy et al., 2008) leads to activation of the entire follicular pool and the subsequent premature depletion of functional ovarian follicles in female mice, thereby causing infertility early in adulthood. Conversely, overexpression of constitutively active FoxO3 increases ovarian reproductive capacity and fertility of female mice (Pelosi et al.,

2013). Screening the coding region of *FOXO3* in populations of women with premature ovarian failure identified rare single-nucleotide polymorphisms in that locus (Watkins et al., 2006; Gallardo et al., 2008; Wang et al., 2010), although this form of ovarian dysfunction may not be representative of the normal progression of reproductive aging. Nonetheless, numerous lines of evidence have demonstrated that central and peripheral IIS is involved in regulating oocyte development, ovarian function, and reproductive status (Sliwowska et al., 2014; Das and Arur, 2017). Given the apparent evolutionary conservation of mechanisms that determine oocyte quality maintenance (Hamatani et al., 2004; Steuerwald et al., 2007; Luo et al., 2010), we suggest that IIS may also influence reproductive aging in humans.

IIS and somatic aging. Systemic IIS likely has coordinated effects on reproductive function and somatic maintenance because down-regulation of IIS is also associated with increased longevity from invertebrates to humans. For instance, centenarians of a human population had lower fasting insulin levels than the ∼78-yr-old comparison group (Paolisso et al., 1996), and decreased composite IIS scores were associated with reduced mortality in women (Van Heemst et al., 2005). Reduction of *ins-7* (which encodes a putative ILP agonist of the DAF-2 receptor) extends *C. elegans* lifespan, whereas conversely, intestinal overexpression of INS-7 or reduction of *ins-18* (which encodes a putative DAF-2 antagonist), shortens lifespan (Murphy et al., 2003, 2007). Similarly, knockdown of the *D. melanogaster* ILP *dilp2* gene extends *D. melanogaster* lifespan (Grönke et al., 2010). In mice, directly or indirectly reducing bioactive and/or circulating IGF-1 levels is associated with lifespan extension (Conover and Bale, 2007; Svensson et al., 2011; Lorenzini et al., 2014), and specifically reducing insulin without changing levels of *Igf1* or circulating IGF-1 also extends lifespan (Templeman et al., 2017). Maintaining some degree of IIS is clearly necessary, so extreme down-regulation or deletion of IIS is detrimental for invertebrates and mammals. However, although the degree of lifespan extension varies (depending on such factors as diet, background strain, sex, and the targeted signaling component), reduction-of-function mutations of IIS pathway components can result in as much as a ∼1,000% increase in *C. elegans* lifespan (Ayyadevara et al., 2008), ∼40–85% increase in *D. melanogaster* lifespan (Clancy et al., 2001; Tatar et al., 2001), and ∼6–33% lifespan extension in mice (Holzenberger et al., 2003; Taguchi et al., 2007; Selman et al., 2008; Foukas et al., 2013).

Genetic down-regulation of many core IIS signaling components has an evolutionarily conserved effect on longevity (Fig. 1). In *C. elegans* and *D. melanogaster*, reduction-of-function mutations of the gene encoding the IIS tyrosine receptor cause lifespan extension (Kenyon et al., 1993; Tatar et al., 2001). In mice, partial whole-body inactivation of IGF-1 receptors can extend lifespan (Holzenberger et al., 2003), and brain-specific reduction of IGF-1 receptors is associated with metabolic alterations and lifespan extension (Kappeler et al., 2008). Insulin receptor knockout under the adipocyte protein 2 promoter (which might not effectively target all white adipocytes and affects other cell types such as endothelial cells; Jeffery et al., 2014) significantly extends lifespan in mice (Blüher et al., 2003); however, adipose tissue knockout of insulin receptors under the more specific and more effective adiponectin promoter (Jeffery et al., 2014) is severe enough to cause serious disruption of metabolic homeostasis, resulting in impaired insulin-stimulated glucose uptake, lipodystrophy, nonalcoholic fatty liver disease, and a shortened lifespan (Friesen et al., 2016; Qiang et al., 2016). Adult-only partial inactivation of the insulin receptor in nonneuronal tissues is not sufficient to alter lifespan (Merry et al., 2017); collectively, it seems that effects of insulin receptor knockdown on murine lifespan depend on temporal considerations, tissue-specific effects, and the degree to which IIS is down-regulated. Interestingly, increased human longevity has been associated with variation in the insulin receptor gene (Kojima et al., 2004) or reduction-of-function mutations of the IGF-1 receptor (Suh et al., 2008), and genetic variation in the IGF-1 receptor gene linked to lower circulating IGF-1 levels can also be detected with increased frequency in long-lived humans (Bonafè et al., 2003). Downstream of IIS tyrosine kinase receptors, reduction-of-function mutation of an IIS receptor substrate extends lifespan in *D. melanogaster* (Clancy et al., 2001); similarly, decreasing whole-body expression of IRS-1 (Selman et al., 2008) or reducing IRS-2 levels through whole-body haploinsufficiency or brain-specific deletion (Taguchi et al., 2007) extends lifespan in mice. Reducing levels of the PI3K catalytic subunit extends lifespan in both *C. elegans* and mice (Friedman and Johnson, 1988; Foukas et al., 2013), and haploinsufficiency of the Akt1 isoform increases lifespan in mice (Nojima et al., 2013). Concurrent reduction-of-function mutation of the phospholipid phosphatase negative regulator of the PI3K/Akt pathway counteracts IIS-mediated lifespan expansion in *C. elegans* (Dorman et al., 1995; Larsen et al., 1995) and transgenic overexpression of the homologous phospholipid phosphatase extends lifespan in both *D. melanogaster* and mice (Hwangbo et al., 2004; Ortega-Molina et al., 2012). Most of these investigations have focused on the PI3K/Akt pathway; inhibiting Ras/MAPK signaling only extends lifespan by ∼4–8% in *D. melanogaster* (Slack et al., 2015), and in mice with deficient Ras/MAPK signaling in pancreatic β cells and brain regions, lowered circulating insulin and IGF-1 may contribute to lifespan extension by altering systemic PI3K/Akt signaling (Borrás et al., 2011). The PI3K/Akt branch of IIS clearly has an important, evolutionarily conserved influence on somatic aging and longevity.

IIS affects longevity by regulating processes such as metabolism, protein homeostasis, and stress responses. Reduction-of-function mutations of PI3K/Akt signaling components affect lifespan in *C. elegans* by commandeering at least some of the same downstream mechanisms that extend survival in dauer larvae (Murphy et al., 2003; Wang and Kim, 2003; Ewald et al., 2015). Interestingly, the branch of TGF-β signaling that is involved with dauer formation also influences adult *C. elegans* lifespan through its interactions with IIS (Shaw et al., 2007). Importantly, however, lifespan extension can be experienced by reproductively competent adults that never entered the dauer stage (Friedman and Johnson, 1988; Kenyon et al., 1993; Dillin et al., 2002). In both *C. elegans* and *D. melanogaster*, the FoxO transcription factor homologue plays a fundamental, required role in mediating the lifespan extension that results from down-regulating IIS components (Dorman et al., 1995; Larsen et al., 1995; Lin et al., 1997; Ogg et al., 1997; Slack et al., 2011), and overexpression of this transcription factor in the fly fat body is sufficient to extend lifespan in *D. melanogaster* (Giannakou et al., 2004; Hwangbo et al., 2004). Notably, genetic variation in *FOXO1* (Lunetta et al., 2007; Li et al., 2009) and *FOXO3A* (Willcox et al., 2008; Flachsbart et al., 2009; Li et al., 2009; Pawlikowska et al., 2009; Broer et al., 2015) has been linked with long human lifespan. DAF-16/FoxO transcriptional targets that contribute to *C. elegans* IIS-mediated lifespan extension

include genes involved in stress responses, pathogen resistance, protein homeostasis, and metabolic pathways (Murphy et al., 2003; Tepper et al., 2013), and many of the targeted processes are conserved in *D. melanogaster*, mice, and humans (Webb et al., 2016). Other key IIS-responsive transcription factors that contribute to regulation by IIS of lifespan in *C. elegans* (likely in part through functional relationships with DAF-16/FoxO, in addition to independent transcriptional targets) include heat shock transcription factor HSF-1 (Hsu et al., 2003), Nrf family transcription factor SKN-1 (Tullet et al., 2008; Ewald et al., 2015), and the zinc finger transcription factor PQM-1 (Tepper et al., 2013). IIS therefore governs somatic aging and longevity through some of the same transcription factors and processes that mediate IIS-dependent effects on reproduction and reproductive aging.

Although it is likely that signaling systems only affect longevity in order to optimize somatic integrity for reproductive success, the arms of the pathways that affect reproduction and longevity can be dissected using genetic tools. Initiating down-regulation of IIS only during adulthood (via *daf-2* RNA interference) is sufficient to achieve full extension of lifespan in *C. elegans*, but down-regulation of IIS is required during late development/early adulthood to regulate reproduction, which indicates that there are different temporal requirements for IIS to control somatic and reproductive aging (Dillin et al., 2002; Luo et al., 2010). In addition, although DAF-16/FoxO activity in the intestine and hypodermis—but not in muscle—contributes to extending the lifespan of *daf-2(−) C. elegans* (Libina et al., 2003; Zhang et al., 2013), this transcription factor acts in the intestine and muscle to mediate the reproductive span extension of *daf-2(−)* mutants (Luo et al., 2010) and in the somatic gonad to influence germline progenitor cell maintenance (Qin and Hubbard, 2015). Therefore, although somatic maintenance and reproductive function are systemically coordinated by the same signaling pathway, age-specific and tissue-specific IIS events are important for determining the progression of each.

mTOR signaling

Other evolutionarily conserved nutrient-sensing systems have also been demonstrated to regulate both reproductive processes and longevity. The serine/threonine kinase mTOR plays an integral role in regulating growth and metabolism in response to several upstream cues, including signals from IIS and other growth factors, the cellular energy sensor AMPK, proinflammatory cytokines, nutrients such as amino acids (particularly leucine and arginine), and oxygen levels (Johnson et al., 2013; Saxton and Sabatini, 2017). mTOR is the catalytic subunit of two distinct complexes—mTORC1 and mTORC2—that differ with respect to some of the proteins forming the complexes, downstream signaling effects, and sensitivity to the drug rapamycin (which acutely inhibits the activity of mTORC1, the better characterized of the two complexes; Johnson et al., 2013; Saxton and Sabatini, 2017). The kinase activity of mTORC1 can be regulated through direct phosphorylation, or, in *D. melanogaster* and mammals, through regulation of its TSC1/2 repressor (Fig. 2; Johnson et al., 2013; Saxton and Sabatini, 2017). For instance, the Akt kinase of IIS directly phosphorylates an mTORC1 component and also increases mTORC1 activity by inactivating the TSC1/2 complex (Inoki et al., 2002; Manning et al., 2002; Potter et al., 2002; Sancak et al., 2007; Vander Haar et al., 2007). mTORC1 promotes mRNA translation and protein synthesis by phosphorylating p70 ribosomal protein S6 kinase (S6K) and eukaryotic translation initiation factor 4E–binding protein 1 (Brunn et al., 1997; Burnett et al., 1998; Gingras et al., 1999), and it also represses autophagy through multiple substrates (Kim et al., 2011; Saxton and Sabatini, 2017). In addition, mTORC1 regulates lipid synthesis, glucose metabolism, and mitochondrial function (Johnson et al., 2013; Saxton and Sabatini, 2017). mTOR therefore integrates information from multiple upstream nutrient and energy sensors to regulate metabolic processes essential for coordinating energy homeostasis, reproductive status, and somatic maintenance.

mTOR signaling and reproduction. mTOR signaling influences both reproduction and longevity (Fig. 2). Although effects of mTOR on age-dependent reproductive decline have not been extensively studied, loss-of-function of mTOR or the downstream mTORC1 effector S6K leads to reduced progeny production and/or a shifted reproductive period in *C. elegans* (Vellai et al., 2003; Pan et al., 2007), associated with delayed cell cycle progression of larval germ cells and reduced germline stem cell proliferation (Korta et al., 2012). In addition, loss of function of mTOR cell-autonomously impairs germline stem cell proliferation and maintenance in female *D. melanogaster* (LaFever et al., 2010), and the mTORC1 inhibitor rapamycin reduces fecundity in *D. melanogaster* in a dose-dependent manner (Bjedov et al., 2010). In female mice, mTORC1 signaling in granulosa cells regulates primordial follicular activation and triggers the PI3K/Akt pathway in oocytes (Zhang et al., 2014), and mice with granulosa cell-specific overactivation of mTORC1 exhibit increased ovulation and reproductive activity (Huang et al., 2013). Oocyte-specific overactivation of mTORC1 through deletion of TSC1 or TSC2 in oocytes of primordial and developing follicles leads to global follicular activation and thus follicle depletion and premature infertility in female mice (Adhikari et al., 2009, 2010), resembling the phenotype of female mice with disrupted FoxO3A or PTEN (Castrillon et al., 2003; Hosaka et al., 2004; Reddy et al., 2008); the PI3K/Akt and mTORC1 signaling pathways and/or their downstream targets might intersect or overlap within oocytes (Adhikari et al., 2010, 2013). mTORC2 also influences follicle function and supply, as oocyte-specific ablation of the essential mTORC2 component Rictor leads to extensive follicular death, depletion of functional ovarian follicles, abnormal sex hormone levels, and premature infertility in female mice (Chen et al., 2015b). In addition to these peripheral actions, mTOR appears to centrally regulate reproductive status (Roa and Tena-Sempere, 2014). Collectively, these studies support a role for mTOR signaling in the control of reproductive processes.

mTOR signaling and somatic aging. mTOR is also involved in lifespan regulation (Fig. 2). Loss of function of the mTOR serine/threonine kinase extends lifespan in *C. elegans* (Vellai et al., 2003; Jia et al., 2004), *D. melanogaster* (Kapahi et al., 2004), and, if combined with knockdown of mTORC subunit LST8, mice (Lamming et al., 2012). Inhibiting mTORC1 activity by mutating the gene encoding the mTORC1 complex subunit Raptor in *C. elegans* or by overexpressing the genes encoding TSC1 or TSC2 in *D. melanogaster* also extends lifespan (Jia et al., 2004; Kapahi et al., 2004). Furthermore, treatment with the mTORC1 inhibitor rapamycin extends lifespan of *C. elegans* (Robida-Stubbs et al., 2012), *D. melanogaster* (Bjedov et al., 2010), and mice, even when treatment is not initiated until late adulthood (Harrison et al., 2009). With respect to downstream mTORC1 substrates, reducing levels of the effector S6K can also extend lifespan in all of these model

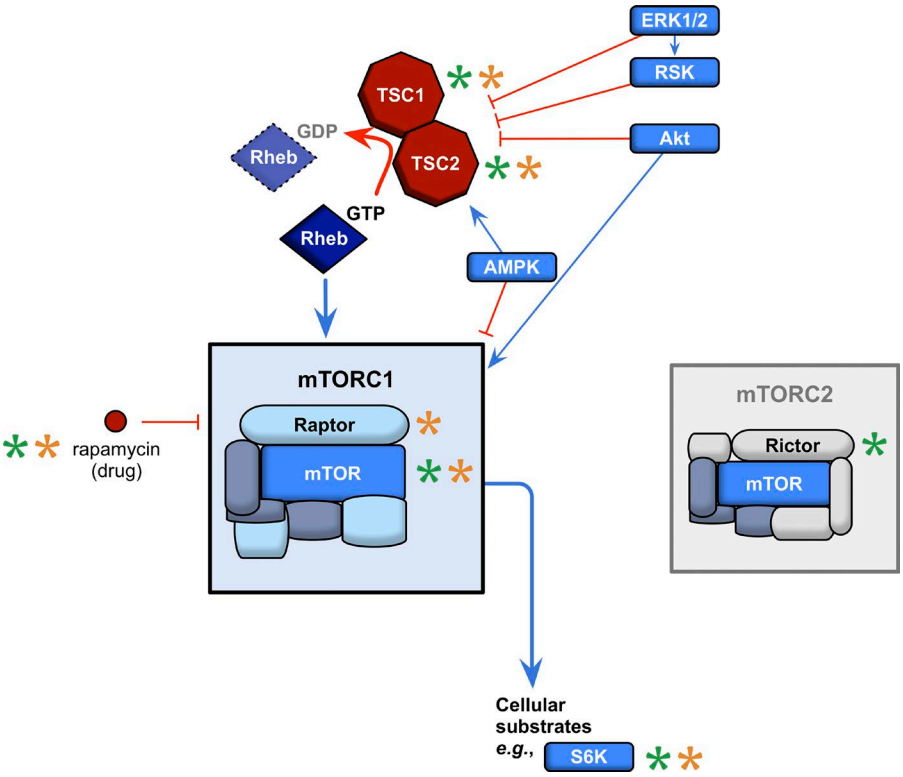

Figure 2. **mTORC1 signaling and its effects on reproduction and longevity.** Many mTOR signaling components have been shown to affect reproductive function (green asterisks) and/or lifespan (orange asterisks) in *C. elegans*, *D. melanogaster*, and/or mice; these signaling components are indicated by asterisks in this simplified mTOR schematic. The serine/threonine kinase mTOR is the catalytic subunit of two distinct complexes, mTORC1 (which includes the constituent protein Raptor, among others) and mTORC2 (which includes the constituent protein Rictor, among others). The kinase activity of mTORC1 is strongly stimulated by the GTP-bound form of Rheb (Ras homologue enriched in brain); mTORC1 is thereby negatively regulated by TSC1/TSC2 complex, which converts Rheb to its inactive GDP-bound state. mTORC1 activity can be directly regulated (i.e., by AMPK or Akt phosphorylating constituent proteins of the complex or by rapamycin acutely inhibiting mTORC1 activity), but upstream signals also indirectly control mTORC1 activity through the TSC1/2 repressor. For instance, effector kinases of the PI3K/Akt and Ras/MAPK branches of IIS (Akt or ERK1/2 and RSK, respectively) inactivate the TSC1/2 complex. In contrast, phosphorylation by AMPK increases GTPase-activating protein activity of TSC2 toward Rheb, leading to inhibition of mTORC1 activity. Other upstream regulators (not depicted) also control mTORC1 activity. mTORC1 phosphorylates many substrates, including S6K.

organisms (Kapahi et al., 2004; Hansen et al., 2007; Pan et al., 2007; Selman et al., 2009). Collectively, mTORC1 signaling contributes to the regulation of reproductive function, and, consistent with the concept that key nutrient-sensing pathways link environmental conditions to both reproductive status and somatic maintenance, mTORC1 also has an evolutionarily conserved role in influencing longevity.

AMPK signaling

AMPK is a highly conserved, critical sensor of energy status that is activated in response to cellular energy depletion, causing downstream effects generally associated with the induction of catabolic pathways and repression of anabolic pathways (Hardie et al., 2012, 2016). AMPK is a complex comprised of a catalytic subunit and two regulatory subunits; its kinase activity is activated or increased by direct AMP binding and by upstream regulatory kinases responding to elevated cellular levels of AMP, ADP, and/or calcium (Hardie et al., 2016). Numerous metabolic processes are influenced by AMPK through its phosphorylation of enzymes, regulatory proteins, and other involved cellular components (Hardie et al., 2012). For instance, AMPK suppresses protein synthesis and promotes autophagy in part through its inhibition of mTORC1 (Hardie et al., 2012; Laplante and Sabatini, 2012). In addition, AMPK is indirectly involved in altering expression levels of proteins involved in metabolic pathways through regulating coactivators and transcription factors such as the *C. elegans* DAF-16 and the human homologue FoxO3 (Greer et al., 2007a,b). Collectively, in response to low cellular energy levels (i.e., an indirect indication of nutrient availability), AMPK activity (a) stimulates energy production through the promotion of such processes as glucose and fatty acid cellular uptake, glycolysis and β-oxidation, mitochondrial biogenesis, and autophagy, and it also (b) down-regulates pathways involved in the biosynthesis of lipids, carbohydrates, proteins, or ribosomal RNA, to reduce cellular energy consumption (Hardie et al., 2012).

AMPK signaling and reproduction. AMPK contributes to the regulation of reproduction and survival through its involvement with energy homeostasis and metabolic pathways. In *C. elegans* larvae, AMPK regulates whole-body energy stores and the cell cycle of germline stem cells under nutrient-poor conditions. Several different stages of *C. elegans* larvae survive stressful or nutrient-deficient conditions by entering specialized alternative larval stages associated with germline stem cell quiescence while development is suspended; AMPK is required for cessation of germline stem cell proliferation in L1-arrested larvae (Fukuyama et al., 2012) and dauer larvae (Narbonne and Roy, 2006), potentially through AMPK-mediated inhibition of mTORC1. Loss-of-function double mutation of *aak-1* and *aak-2*, genes encoding AMPK catalytic subunits, causes sterility in adult *C. elegans* that have survived this L1 arrest (Fukuyama et al., 2012), demonstrating that AMPK signaling in nutrient-deficient conditions is crucial for the future reproductive function of *C. elegans* larvae. Transgenic expression of constitutively active *aak-2* appears to cause a shift in the reproductive period of adult *C. elegans* under nutrient-replete conditions, with fewer eggs produced early but more eggs produced later in the reproductive period, compared with WT animals (Burkewitz et al., 2015). In addition, AMPK regulates mammalian reproduction. For instance, in vitro treatment of rat granulosa cells with an AMPK-activating adenosine analogue alters expression levels of cell cycle–regulatory proteins (Kayampilly and Menon, 2009) and reduces progesterone secretion (Tosca et al., 2005), indicating that AMPK is involved in suppressing ovarian granulosa cell proliferation and regulating sex hormone production. As seen with IIS and mTOR signaling,

AMPK also acts in the brain to centrally affect reproductive processes by mediating responses to hormones, modulating the hypothalamic–pituitary–gonadal axis, and influencing such processes as estrous cycling and puberty onset (Roa and Tena-Sempere, 2014).

AMPK signaling and somatic aging. In addition to its effects on reproductive function, AMPK also influences survival and longevity. Loss-of-function mutation of both *C. elegans* AMPK catalytic subunits decreases the viability of L1-
arrested larvae (Fukuyama et al., 2012), and *aak-2(-)* dauers have reduced survival as a result of rapid consumption of their stored fat reserves (Narbonne and Roy, 2009). Loss of function of *aak-2* also reduces the lifespan of *C. elegans* adults under normal, nutrient-replete conditions (Apfeld et al., 2004), whereas transgenic overexpression of either *aak-2* (Apfeld et al., 2004) or a modified, constitutively active *aak-2* (Mair et al., 2011) increases lifespan. One AMPK target that mediates these longevity effects in *C. elegans* adults is the cAMP-responsive element binding protein-regulated transcription coactivator CRTC-1; phosphorylation by AMPK causes the nuclear exclusion and inactivation of this transcription cofactor, and overexpression of active *aak-2* does not extend the lifespan of *C. elegans* mutants expressing a modified CRTC-1 that is refractory to AMPK phosphorylation (Mair et al., 2011). This is also the case when the modified, refractory CRTC-1 is only expressed neuronally, where it appears to counteract the pro-longevity effects of *aak-2* through whole-body transcriptional changes associated with mitochondrial metabolic processes (Burkewitz et al., 2015). Importantly, CRTC-1 does not impact the effects of AMPK on reproduction, indicating that this is a signaling node where reproductive function and longevity are uncoupled (Burkewitz et al., 2015). Consistent with the beneficial effects that AMPK has on *C. elegans* survival, *D. melanogaster* with increased AMP/ATP and ADP/ATP ratios caused by heterozygous mutations of AMP biosynthetic enzymes are long lived; lifespan is also increased by transgenic overexpression of AMPK in the fly's fat body or muscle, and decreased by RNAi-mediated AMPK knockdown in these tissues (Stenesen et al., 2013). Neuronal-specific or intestinal transgenic up-regulation of the AMPK catalytic subunit also increases lifespan in *D. melanogaster* (Ulgherait et al., 2014). Effects of AMPK on lifespan have not yet been directly tested in mammals, although interestingly, AMPK activation declines with age in several different tissues of rats and mice (Salminen and Kaarniranta, 2012). Therefore, AMPK is a critical energy-sensing kinase that regulates processes and pathways associated with reproduction, somatic maintenance, and survival.

Integration of nutrient-sensing systems

Despite a tendency to conceptualize and investigate IIS, mTOR, and AMPK as separate signaling pathways, it is important to consider that there is cross-talk between them, and some amount of overlap in their downstream targets. For instance, AMPK phosphorylates regulatory sites of both the *C. elegans* DAF-16 and its human homologue, FoxO3, leading to up-regulated transcriptional activity of this key IIS-responsive transcription factor (Greer et al., 2007a,b). Interestingly, loss of function of an AMPK catalytic subunit significantly suppresses the lifespan extension of *C. elegans* dauers or adults with reduction-of-function mutations of the IIS receptor (Narbonne and Roy, 2006). In mammalian cells, AMPK and mTORC1 have counteracting effects on autophagy in part through their opposing regulation of a shared substrate, the autophagy-initiating kinase Ulk1 (Kim et al., 2011). In addition, AMPK inhibits mTORC1 itself through direct phosphorylation of the mTORC1 subunit Raptor (Gwinn et al., 2008), and by increasing suppression of mTORC1 activity by TSC2 (Inoki et al., 2003). IIS leads to up-regulated mTORC1 activity; Akt increases mTORC1 activity by directly phosphorylating mTORC1 constituent protein PRAS40 (Sancak et al., 2007; Vander Haar et al., 2007), and the TSC1/2 repressor is inactivated by effector kinases of the PI3K/Akt or Ras/MAPK branches of IIS (Akt, or ERK1/2 and RSK, respectively; Inoki et al., 2002; Manning et al., 2002; Potter et al., 2002; Roux et al., 2004; Ma et al., 2005). IIS FoxO transcription factors also transcriptionally regulate several mTOR signaling components in invertebrates and mammals, including TSC1, specific mTORC1 subunit proteins, and some mTORC1 substrates (Johnson et al., 2013). Based on these examples and other points of interaction or feedback between IIS, mTOR, and AMPK signaling, it is evident that these nutrient-sensing pathways do not act in isolation within a system. Signaling pathway overlap is therefore an important consideration when dissecting the processes involved in regulating somatic and reproductive aging.

In addition to the intracellular interactions between nutrient-sensing systems, intercellular or intertissue interactions increase the complexity of these signaling networks. Although signaling pathways can have cell-autonomous effects, there are also situations where nutrient levels sensed in specific tissue types lead to downstream effects in other tissues. For instance, neuronal-specific IIS, mTOR, and AMPK signaling can have nonautonomous effects on somatic maintenance and/or reproductive processes through such mechanisms as altering hormone responses or modulating the hypothalamic–pituitary–gonadal axis (Brüning et al., 2000; Taguchi et al., 2007; Roa et al., 2009; Roa and Tena-Sempere, 2014; Sliwowska et al., 2014; Ulgherait et al., 2014; Das and Arur, 2017). This points to a central component of these signaling pathways' regulation of systemic physiological processes, in addition to signaling cascades within other key tissues. Interactions between signaling pathways can also occur intercellularly, such as PI3K/Akt pathway activation in mouse oocytes resulting from mTORC1 signaling in the nearby granulosa cells (Zhang et al., 2014). Further investigations into intercellular and intertissue lines of communication will be invaluable for uncovering the mechanisms coordinating major systemic processes such as reproduction and somatic maintenance.

Stress or altered food availability is also likely to exert coordinated effects on multiple signaling pathways. These nutrient-sensing signaling pathways vary in their responsiveness to assorted nutrient signals, which contributes to the wide range of physiological effects that can occur under different conditions. However, food depletion or abundance often represents a changed availability of numerous nutrient cues, thus causing signaling effects downstream of multiple pathways. In nutrient-rich conditions, reduced AMPK activity in combination with elevated IIS and mTORC1 signaling would be expected in certain tissues, collectively leading to the up-regulation of processes geared toward increasing growth and reproduction (i.e., promotion of nutrient uptake and storage, mitogenic and anabolic pathways, mRNA translation and protein synthesis,

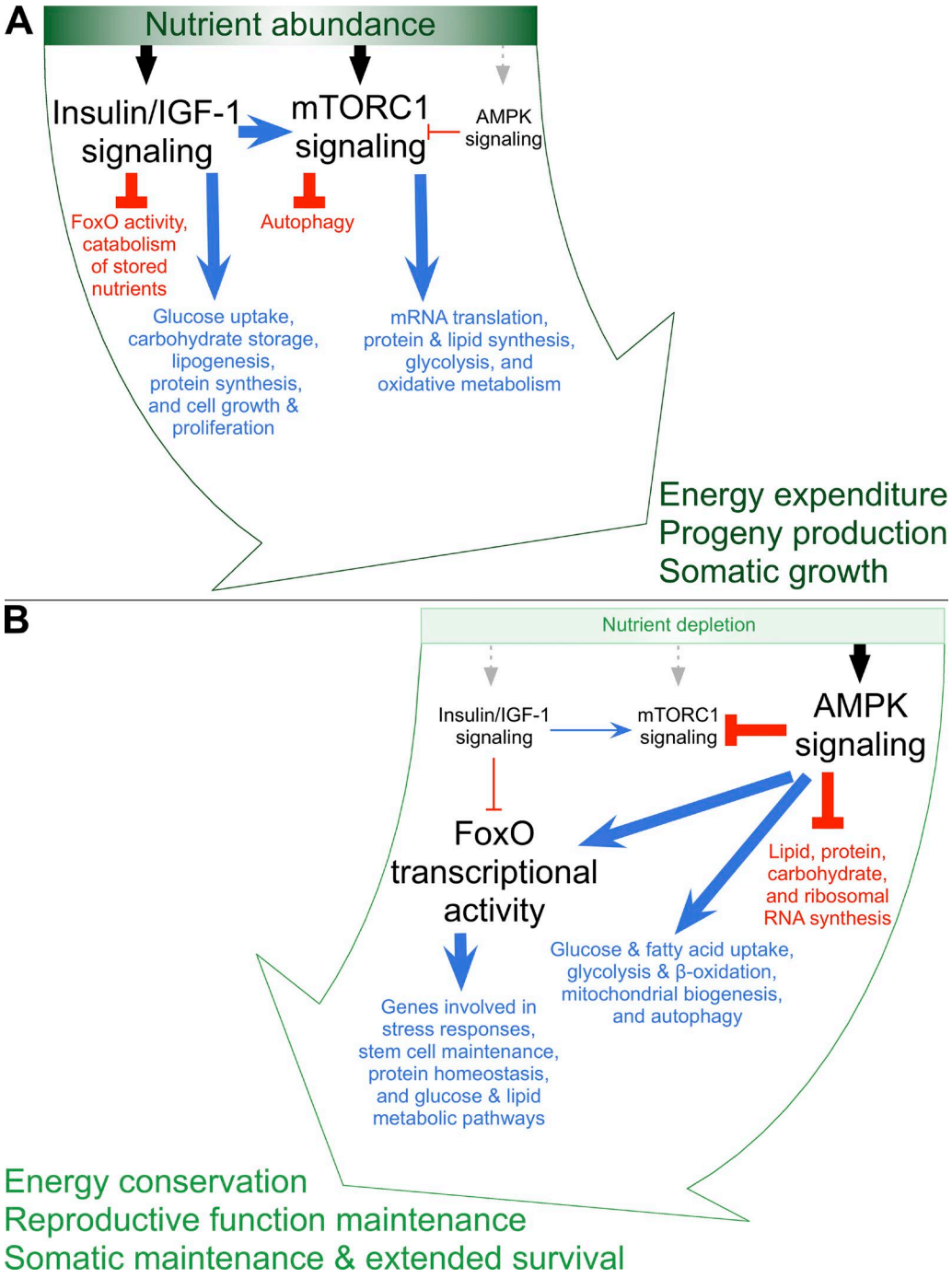

Figure 3. **Regulation of energy homeostasis, reproductive processes, and somatic growth or maintenance by signaling pathways that perceive and respond to nutrient availability.** (A) Nutrient abundance leads to increased insulin/IGF-1 and mTORC1 signaling, which collectively promote cellular processes that support energy storage or expenditure, increased reproduction, and growth. (B) Nutrient depletion leads to increased AMPK signaling and transcriptional activity of FoxO transcription factors, which promote protective cellular processes that support energy production or conservation, maintenance of reproductive function rather than progeny production, and lifespan extension. This simplified model does not account for macronutrient-specific responses or tissue-specific nutrient detection, and it does not distinguish between different tissues when summarizing downstream signaling effects. Black arrows indicate increased stimulation of a signaling pathway in response to the environmental conditions, and gray dotted arrows indicate little or no stimulation of a signaling pathway under the environmental conditions. Large text or arrows indicate relatively high levels of signaling compared with small text or arrows; blue indicates up-regulation or promotion, and red indicates down-regulation or suppression.

etc.; Fig. 3 A). Conversely, with detection of nutrient depletion, the rates of these functions would be generally slowed in favor of processes important for energy production, tissue maintenance, stress resistance, and extended survival because of the combination of increased AMPK activity, down-regulated mTORC1 signaling, and the increased transcriptional activity of FoxO transcription factors downstream of reduced IIS (Fig. 3 B). Systemic outputs such as reproductive function or somatic maintenance are likely broadly controlled by these integrated signaling pathways.

Concluding remarks

Both reproduction and somatic maintenance are governed by a requirement for nutrients. Key signaling networks such as IIS, mTOR, and AMPK signaling are involved in perceiving and interpreting nutrient levels and subsequently regulating the physiological decisions to reproduce, grow, or age. Other signaling pathways that respond to such cues as nutrient availability are therefore good candidates for coordinating energy homeostasis, reproductive status, and somatic maintenance with age. Moreover, we suggest that disentangling intertissue communicating signals and downstream molecular mechanisms acting within distinct tissue and cell types will reveal processes directly affecting the progression of reproductive and somatic aging.

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