2009). A number of animal models support a causative impact of chaperone decline on longevity. In particular, transgenic worms and flies overexpressing chaperones are long-lived (Morrow et al., 2004; Walker and Lithgow, 2003). Also, mutant mice deficient in a cochaperone of the heat-shock family exhibit accelerated aging phenotypes, whereas long-lived mouse strains show a marked upregulation of some heat-shock proteins (Min et al., 2008; Swindell et al., 2009). Moreover, activation of the master regulator of the heat-shock response, the transcription factor HSF-1, increases longevity and thermotolerance in nematodes (Chiang et al., 2012; Hsu et al., 2003), while amyloid-binding components can maintain proteostasis during aging and extend lifespan (Alavez et al., 2011). In mammalian cells, deacetylation of HSF-1 by SIRT1 potentiates the transactivation of heat-shock genes such as Hsp70, whereas downregulation of SIRT1 attenuates the heat-shock response (Westerheide et al., 2009).

Several approaches for maintaining or enhancing proteostasis aim at activating protein folding and stability mediated by chaperones. Pharmacological induction of the heat-shock protein Hsp72 preserves muscle function and delays progression of dystrophic pathology in mouse models of muscular dystrophy (Gehrig et al., 2012). Small molecules may be also employed as pharmacological chaperones to assure the refolding of damaged proteins and to improve age-related phenotypes in model organisms (Calamini et al., 2012).

### *Proteolytic Systems*

The activities of the two principal proteolytic systems implicated in protein quality control—namely, the autophagy-lysosomal system and the ubiquitin-proteasome system—decline with aging (Rubinsztein et al., 2011; Tomaru et al., 2012), supporting the idea that collapsing proteostasis constitutes a common feature of old age.

Regarding autophagy, transgenic mice with an extra copy of the chaperone-mediated autophagy receptor LAMP2a do not experience aging-associated decline in autophagic activity and preserve improved hepatic function with aging (Zhang and Cuervo, 2008). Interventions using chemical inducers of macroautophagy (another type of autophagy different than chaperone-mediated autophagy) have spurred extraordinary interest after the discovery that constant or intermittent administration of the mTOR inhibitor rapamycin can increase the lifespan of middle-aged mice (Blagosklonny, 2011; Harrison et al., 2009). Notably, rapamycin delays multiple aspects of aging in mice (Wilkinson et al., 2012). The lifespan-extending effect of rapamycin is strictly dependent on the induction of autophagy in yeast, nematodes, and flies (Bjedov et al., 2010; Rubinsztein et al., 2011). However, similar evidence does not yet exist for the effects of rapamycin on mammalian aging, and other mechanisms, such as inhibition of the ribosomal S6 protein kinase 1 (S6K1) implicated in protein synthesis (Selman et al., 2009), could contribute to explain the longevity effects of rapamycin (see "Deregulated Nutrient Sensing"). Spermidine, another macroautophagy inducer that, in contrast to rapamycin, has no immunosuppressive side effects, also promotes longevity in yeast, flies, and worms via the induction of autophagy (Eisenberg et al., 2009). Similarly, nutrient supplementation with polyamine preparations containing spermidine or provision of a polyamine-producing gut flora increases longevity in mice (Matsumoto et al., 2011; Soda et al., 2009). Dietary supplementation with ω-6 polyunsaturated fatty acids also extends lifespan in nematodes through autophagy activation (O'Rourke et al., 2013).

In relation to the proteasome, activation of EGF signaling extends longevity in nematodes by increasing the expression of various components of the ubiquitin-proteasome system (Liu et al., 2011a). Likewise, the enhancement of proteasome activity by deubiquitylase inhibitors or proteasome activators accelerates the clearance of toxic proteins in human cultured cells (Lee et al., 2010) and extends replicative lifespan in yeast (Kruegel et al., 2011). Moreover, increased expression of the proteasome subunit RPN-6 by the FOXO transcription factor DAF-16 confers proteotoxic stress resistance and extends lifespan in *C. elegans* (Vilchez et al., 2012).

### *Overview*

There is evidence that aging is associated with perturbed proteostasis, and experimental perturbation of proteostasis can precipitate age-associated pathologies. There are also remarkable examples of genetic manipulations that improve proteostasis and delay aging in mammals (Zhang and Cuervo, 2008).

## Deregulated Nutrient Sensing

The somatotrophic axis in mammals comprises the growth hormone (GH), which is produced by the anterior pituitary, and its secondary mediator, insulin-like growth factor 1 (IGF-1), produced in response to GH by many cell types, most notably hepatocytes. The intracellular signaling pathway of IGF-1 is the same as that elicited by insulin, which informs cells of the presence of glucose. For this reason, IGF-1 and insulin signaling are known as the "insulin and IGF-1 signaling" (IIS) pathway. Remarkably, the IIS pathway is the most conserved aging-controlling pathway in evolution, and among its multiple targets are the FOXO family of transcription factors and the mTOR complexes, which are also involved in aging and conserved through evolution (Barzilai et al., 2012; Fontana et al., 2010; Kenyon, 2010). Genetic polymorphisms or mutations that reduce the functions of GH, IGF-1 receptor, insulin receptor, or downstream intracellular effectors such as AKT, mTOR, and FOXO have been linked to longevity, both in humans and in model organisms, further illustrating the major impact of trophic and bioenergetic pathways on longevity (Barzilai et al., 2012; Fontana et al., 2010; Kenyon, 2010) (Figure 4A).

Consistent with the relevance of deregulated nutrient sensing as a hallmark of aging, dietary restriction (DR) increases lifespan or healthspan in all investigated eukaryote species, including nonhuman primates (Colman et al., 2009; Fontana et al., 2010; Mattison et al., 2012).

### *The Insulin- and IGF-1-Signaling Pathway*

Multiple genetic manipulations that attenuate signaling intensity at different levels of the IIS pathway consistently extend the lifespan of worms, flies, and mice (Fontana et al., 2010). Genetic analyses indicate that this pathway mediates part of the beneficial effects of DR on longevity in worms and flies (Fontana et al., 2010). Among the downstream effectors of the IIS pathway, the most relevant one for longevity in worms and flies is the transcription factor FOXO (Kenyon et al., 1993; Slack et al., 2011). In mice, there are four FOXO members, but the effect of their overexpression on longevity and their role in mediating increased healthspan through reduced IIS have not yet been determined.