BBA - Molecular Basis of Disease 1865 (2019) 1745–1755

Contents lists available at ScienceDirect

BBA - Molecular Basis of Disease

journal homepage: www.elsevier.com/locate/bbadis

Review

Conserved signaling pathways genetically associated with longevity across the species☆

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ARTICLE INFO

Keywords:
Longevity
mTOR
AMPK
Adrenergic
Insulin/IGF-1

ABSTRACT

Advanced age is an independent risk factor for natural death and common diseases, such as cardiovascular diseases, dementia, and cancers, which are life-threatening and cause disabilities. On the other hand, individual with healthy longevity is a plausible model for successful aging. Thus, search for longevity-associated genes and pathways likely provides a unique approach to understand the genetic mechanisms underlying aging and healthspan, and emerging evidence from model organisms has highlighted the significance of genetic components in longevity. Here we reviewed the uses of model organisms including yeast, ciliate, nematode, arthropod, fish, rodent, and primate as well as human to identify the genetic determinants of longevity and discussed the genetic contributions of conserved longevity pathways, such as adrenergic system, AMPK, insulin/IGF-1, and mTOR signaling pathways.

1. Introduction

An increased age is one of the most crucial risk factors associated with wide and diverse range of diseases, such as cardiovascular diseases, neurodegenerative diseases, and cancers. The fact is, human population with age above 60 is growing at a very rapid pace worldwide, estimated to be more than 900 million now and will possibly reach two billion by the year 2050 [1]. Currently, more than 125 million people are aged 80 years worldwide. These make it an urgent necessity to understand the mechanism of aging and its contribution to the diseases and to use this knowledge to promote healthspan.

Aging is commonly described as a progressive gradual loss in physiological control with increased mortality rate and vulnerability to diseases as well as reduced adaptivity to external stimuli [2,3]. Association of hallmarks to aging, such as the genomic instability, telomere attrition, epigenetic alterations, loss of proteostasis, deregulated nutrient sensing, mitochondrial dysfunction, cellular senescence, stem cell exhaustion, and altered intercellular communication, suggests the involvement of multiple mechanisms in aging process [4]. Genetic components in aging control have been clearly evident after a number of genes are found, such as *LMNA*, *WRN*, *KL*, *SIRT1*, and *SIRT6*, contributing to human progeria syndrome or premature aging in animal models [5].

Longevity represents successful aging for a living being, and in human, some centenarians not only live longer but also healthier in their life, providing a good model for searching the genes related to longevity and healthy aging [6,7]. However, to successfully and effectively promote healthy aging and longevity, the underlying process of aging has to be well understood. That is why a great effort has been made to investigate the possible mechanisms. For instance, in addition to human, a diverse variety of model organisms ranging from yeast to non-human primate are used in studies of longevity, aging, and age-related pathologies for their shorter lifespans, easy genetic manipulations, and interventions over the past decades.

Here we inspected the characteristics and uses of model organisms including yeast, ciliate, nematode, arthropod, fish, rodent, and primate as well as human in longevity studies and discussed the conserved longevity pathways across these species.

2. Organismal models

2.1. Fungus

Yeast, *Saccharomyces cerevisiae* (*S. cerevisiae*), is the simplest,

☆ This article is part of a Special Issue entitled: Genetic and epigenetic regulation of aging and longevity edited by Jun Ren & Megan Yingmei Zhang.

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https://doi.org/10.1016/j.bbadis.2018.09.001
Received 31 May 2018; Received in revised form 26 July 2018; Accepted 4 September 2018
Available online 10 September 2018
0925-4439/

unicellular eukaryotic organism, which divides by budding resulting in two cells of unequal size and dies after 30–40 generations, hence also named as *budding yeast*. *S. cerevisiae* genome was the first eukaryotic genome to be sequenced and published in 1996 [8]. It has a genome of 12 mega basepair (Mb) in size containing approximately 6692 protein coding genes along with more than 400 other genes coding for ribosomal RNA (rRNA), transfer RNA (tRNA) and small nuclear RNA (SnRNA) [8,9]. *Saccharomyces* Genome Database is an up to date online database. So far, 47% of the *S. cerevisiae* genes have been humanized, suggestive of the functional conservation between human and yeast [10].

Having a haploid genome, *S. cerevisiae* provide the benefit of direct genotype-phenotype analysis. They have an extremely fast generation time of 3 h that speeds up the experimentation. Their easy and simple culturing requirements adds up to their uses in research, especially in aging research. Having conserved cellular processes, it is mainly targeted to study the cellular processes contributing to aging process. However, being a unicellular organism, it lacks the intercellular interactions making it unsuitable for studying the complex processes with intercellular interactions in human.

S. cerevisiae has been used to identify possibly more aging associated gene than any other model organism. *Sir2*, homologous to human *SIRT1*, was identified in *S. cerevisiae* where its overexpression is reported to be associated with extension of replicative lifespan [11,12]. Chronological aging in yeast affects nucleolar architecture and activity resultantly promoting genemic instability which limits the lifespan [13,14]. Loss of Nat4 and its associated histone H4 N-terminal acetylation mediates calorie restriction-induced longevity in *S. cerevisiae*, highlighting the role of genomic instability and epigenetic modifications in aging and longevity [15]. Calorie restriction, an important intervention for lifespan extension, is also dependent on the genetic components evident from the studies reporting the requirement of SIR2 encoding the silencing protein Sir2p, and NPT1 a gene that is involved in NAD synthesis pathway [16,17]. A number of other genes affecting longevity has been reported in yeast including *RAS1*, *RAS2*, *RPD3*, *RTG3*, *SIP2*, *SNF4*, *SIR4*, and so on [11,18–21].

Another fungus, *Podospora anserina* (*P. anserina*), an ascomycete, having limited and short lifespan and sexually reproducing, has been developed into another aging model because of relatively easy generation of genetic mutants. Its genome is about 35 Mb [22]. Similar to the other higher organisms, it has been reported that respiration, ROS generation, apoptosis and mitochondrial DNA stability greatly influence the aging in *P. anserina* [23,24]. Loss of function mutation in the genes, COX1 and COX5, that encodes the subunit I and subunit V of the mitochondrial cytochrome *c* oxidase complex, significantly extends lifespan [25,26].

2.2. Nematode

Nematode is the phylum of smooth, unsegmented long cylindrical shaped roundworms and threadworms living in both aquatic and terrestrial environments. The most commonly studied nematode, *Caenorhabditis elegans* (*C. elegans*), is multicellular and non-parasitic, about 1 mm in length with majority of them exist as self-fertilizing hermaphrodites while some exist as males. They develop into an adult from an egg in 3 days and have a lifespan ranging from 11 to 20 days [27,28]. *C. elegans* has a genome size of 97 Mb containing more than 20,000 protein coding genes and approximately 25,000 other genes coding for rRNA, SnRNA, microRNA (miRNA), Small Cytoplasmic (scRNA), miscRNA, and others [9,29]. The fully sequenced and annotated genome provides scientific community with the advantage of access to RNAi library making it easier to generate genetic mutant strains.

C. elegans' completely sequenced, annotated, and characterized genome [29], short lifespan (2–3 week), and significant evolutionary relationship make it an ideal model organism for longevity and aging research [30]. Easy growth conditions, rapid reproduction, and development adds up to their use as model organisms [31]. *C. elegans* is the most studied model organism in longevity and drug screening. It is also a valuable model organism for studying development of biological systems including nervous, digestive and muscular systems. Despite their huge physiological and biochemical difference to humans, it has excellent characteristics to act as model organism for aging research.

C. elegans were first reported to be used in aging research in 1977 [31] with a breakthrough discovery of *age-1* providing a stepping stone into the idea that individual genes can be responsible for lifespan modulation [32,33]. The reduced expression of *acn-1* gene in *C. elegans*, orthologue of angiotensin converting enzyme (*ACE*), has been reported to delay age related phenotypes, increase stress resistance and promote longevity [34]. Recessive mutations in the daf-2 insulin receptor-like gene and da-16 that encodes a transcriptional regulator, hepatocyte nuclear factor 3 (HNF-3) are reported to extend the lifespan [35–38].

2.3. Arthropod

2.3.1. Mite

Mites and ticks represent the most diverse group within the class Arachnida with 55,000 described species [39]. Remarkable evolutionary plasticity and relatively small size enable them to colonize a wide range of terrestrial, marine, and aquatic habitats. All mites are small in an absolute sense, most of their adults are less than 1 mm in length with some mites even less than 100 μm in length as adults (~50 μm as larvae) [39]. Under the optimal environmental conditions, the developmental time from an egg to adult is less than 15 days, some species take less than 7 days. Most of them have a lifespan of 30–60 days under appropriate conditions. Genomic sampling of mites lineage remains limited so far, with 7 species including *Varroa destructor*, *Tetranychus urticae*, *Ixodes scapularis*, *Dermatophagoides farinae*, *Sarcoptes scabiei*, and *Metaseiulus occidentalis*. Their assembly length of sequenced genomes ranges from 53.5 Mb (*D. farinae*) to 1765.4 Mb (*I. scapularis*). Number of protein-coding genes are 10,473 (*S. scabiei*), 11,432 (*V. destructor*), 16,376 (*D. farinae*), 18,338 (*M. occidentalis*), 18,414 (*Tetranychus urticae*) and 20,486 (*I. scapularis*), respectively [40].

The mites have nervous, respiratory, circulatory, endocrine, digestive, excretory and reproductive systems [41]. They are easy to rear and keep with the ability of exponential population growth. The artificial breeding and industrial production of some *phytoseiid* have been achieved, while the flour mite and spider mites were reared as the prey [42]. A remarkable advantage is that gene expression can be easily regulated in mites by feeding RNAi [43]. Mite is a reasonable model for addressing questions of more generally ecological and evolutionary biological interest, including longevity and aging research.

The advances in understanding the developmental genetics of mites suggest that the size of mites is no impediment to their use as models for understanding much larger organisms [44]. Certain idiosomal setae were found to be variable in structure of *Nenteria pandioni*, suggested to be resulted from differences within the gene pool and/or from intraspecie variations associated with the process of aging [45].

2.3.2. Fly

The fruit fly, *Drosophila melanogaster*, is the most widely used fly-based model for human diseases and have a long history in genetic research beginning with discovery of sex-limited inheritance by Thomas Hunt Morgan [46]. *Drosophila* is 3–4 mm in length. It has a lifespan of 30 days with developmental time of 7 days from an egg to an adult. *Drosophila* has a sequenced genome of 142 Mb in size containing nearly 14,000 protein coding genes and more than 3000 non-protein coding genes including rRNA, tRNA, miRNA, SnRNA and others [9,47]. Despite extremely different phenotypes, comparative analysis revealed more than 75% of human disease genes have their orthologues in *Drosophila* [48].

Drosophila is easy to breed. An embryo develops in to adult fly in approximately 10 days, and a fly lay approximately 100 eggs in a day making it relatively easy to produce a large population of flies or embryos as per requirement of the experiment [49]. *Drosophila* is used in gene mapping studies and identifying the role of individual genes related to specific biological functions. With a long and rich history, it is being proved to be an excellent model system to understand the genetic and environmental contribution to the age associated decline in biological processes leading to advanced therapeutics and strategies promoting longevity and healthy aging.

Age associated decline in heart physiology is also well studied in *Drosophila* [50]. It has led to the identification of longevity controlling genes including insulin-like peptides and Target of Rapamycin (*TOR*) signaling molecules [51,52]. Recently, a study reported that the overexpression of genes involved in heterochromatic maintenance including *Sir2*, *Su(var)3–9* (a histone H3K9 methyltransferase) and *Dicer-2* reduced the age-related elevated expression of transposable elements (TEs), furthermore, enhanced expression of *Su(var)3–9* or *Dicer-2* has also been linked to longevity [53]. Mutational analysis and quantitative trait locus analysis have led to the identification and discovery of a number of genetic determinants of lifespan including Chico, dTOR, dilp, ds6k, inR, dSir2, and so on [54–58].

2.4. Fish

Zebrafish, *Danio rerio (D. rerio),* is a fresh water fish and have distinct, pigmented, horizontal stripes on the side of its body. It belongs to the family of freshwater fishes *Cyprinidae*. It can grow to 6.4 cm in length and has a lifespan of 3.5–5 years with a short generation time of 3–4 months [59]. *D. rerio* has a genome of 1464 Mb in size containing nearly 26,000 protein coding and 6000 non-protein coding genes [9,60]. Comparative analysis revealed that 70% of human genes have their orthologues in zebrafish [60].

Zebrafish is the most promising fish model for aging research. The characteristics like experiencing senescence, fully sequenced genome and easy genetic modification makes it an excellent choice for a model organism [60]. Wellcome trust Sanger Institute has founded a *"Zebrafish Mutation Project"* that aims to create a knockout model for each protein-coding gene in zebrafish genome through whole exome enrichment and Illumina next generation sequencing, and has generated 36,284 knockout disease models so far. Their inexpensive maintenance and optical transparency at embryonic and larval stages or adults (in some cases) prove to be of great interest for researchers [61]. However, their highly efficient regenerative system compared to humans complicates their use [62].

Using *D. rerio* as a model organism, it has been reported that abnormal expression of Lamin A gene leads to impaired development of mesenchymal lineage, providing evidence for the involvement of Lamin A in aging mechanisms [65]. Using a telomerase reverse transcriptase (*tert*) gene mutant *D. rerio*, termed as hu3430 line, lack of telomerase activity has been reported to be associated with telomere shortening, lifespan reduction and premature aging [66].

The African turquoise killifish, *Nothobranchius furzeri (N. furzeri)*, is a naturally short-lived vertebrate. The computational estimates revealed that the genome of *Nothobranchius furzeri* is upto 1.3–2.2 Gb in size and so far, 28,494 protein-coding while nearly 6000 non-protein coding genes have been identified through *de novo* gene prediction and sequence homology analysis [63]. Despite of its short lifespan, it exhibits all the mammalian aging related phenotypes including sensory and fertility decline [64,65]. With short lifespan, shorter life cycle and rapid sequencing of its genome [66,67], *N. furzeri* is developing into a suitable candidate for model organism for longevity and aging research.

2.5. Rodent

Rodents, belongs to class Mammalia of phylum Chordata, characterized by a pair of incisors in both upper and lower jaws, are found in diverse terrestrial habitats. Rats and mice are the most widely studied and used laboratory animals.

2.5.1. Mouse

Mus musculus (M. musculus) are characterized by a pointed snout, small rounded ears, and a long naked, hairless tail. It has a body length of 7.5–10 cm with a tail of length 5–10 cm. The mice gestation period is 19–21 days reproducing 5–6 offspring on average that attain sexual maturity in 5–7 weeks. Mice has an average lifespan of about 2–3.5 years [68]. *M. musculas* has a genome of 3482 Mb in size containing nearly 23,000 protein coding while approximately 14,000 non-protein coding genes [9,69]. Comparative analysis among mice and human genome revealed that 80% of genes have single orthologue in other while less than 1% of the genes were found that don't have their orthologue in the other [70].

M. musculus, has become a premier model for genetic research over the past century because of its physiological and genetic similarities to humans and the ability to modify its genome with ease. They have a lifespan of 2–3 years. Inbred mice as a model organism in aging research is not only providing us with insights into aging pathogenesis but also the use of genetically modified mice models including gene knockout, mutant and transgenic mice have been proving useful in identifying the targets for therapeutic interventions to delay or reverse aging phenotypes and pathogenesis [71–74]. Although Fungi (yeasts), Nematodes *(C. elegans*) and flies *(Drosophila)* are very useful models for studying the biological processes, mice provide us with even better tools to study complex mammalian processes. Mice require minimal maintenance and it is easier to get large population in short time period.

Klotho, a gene encoding a membrane protein involved in suppressing age-related phenotypes including short lifespan, was identified in *Klotho* mutant mice leading to its widespread use as a model organism for longevity and aging research [75]. High levels of oxidative stress lead to DNA damage pushing the cell into an irreversible senescent phase and accumulation of these senescent cells over the time has been associated with accelerated aging in mice [74,76]. *SIRT6*-deficient mice grows to be smaller with various abnormalities including severe metabolic defects leading to early death at the age of about 4 weeks [77,78]. Furthermore, overexpression of *SIRT6* in male mice results in median and maximum lifespan extension by 14.5% and 15.8% respectively [79].

More recently, mice of genus *Peromyscus* were used in aging research as they have longer lifespan as compared to *Mus musculus. Peromyscus* have a lifespan of 4–5 years on average [80]. Decreased ROS generation coupled with enhanced resistance to different metabolic stresses increased the lifespan potential of *Peromyscus*, providing evidence in support of the oxidative stress hypothesis of aging [81,82].

2.5.2. Rat

Rattus norvegicus (R. norvegicus), a brown or grey rodent, are 25 cm long, and have a similar tail length. They have a gestation period of 21 days, reproducing 7 litters on average that attain sexual maturity in 5 weeks. Rats have an average lifespan of 1.5–2 years. *R. norvegicus* has a genome of 3042 Mb in size containing 22,250 coding genes, 8934 non-coding genes, 1688 pseudogenes, and 41,078 gene transcripts [9,83,84]. Almost all the genes related to human diseases have been reported in rats [84].

R. norvegicus, because of its close similarities to human genome, is a very useful laboratory model organism. They are easier to maintain and a large population can be produced in a short time. A lot of wild-type, inbred, induced, and genetically engineered rat strains mimicking human diseases are available for research. It is an excellent model for cardiovascular diseases including hypertention and stroke. Comparitively larger in size, it is easier to handle during surgical procedures and serial blood draws in case of drug screening studies.

The use of rats in longevity and aging research dates back to 1975,

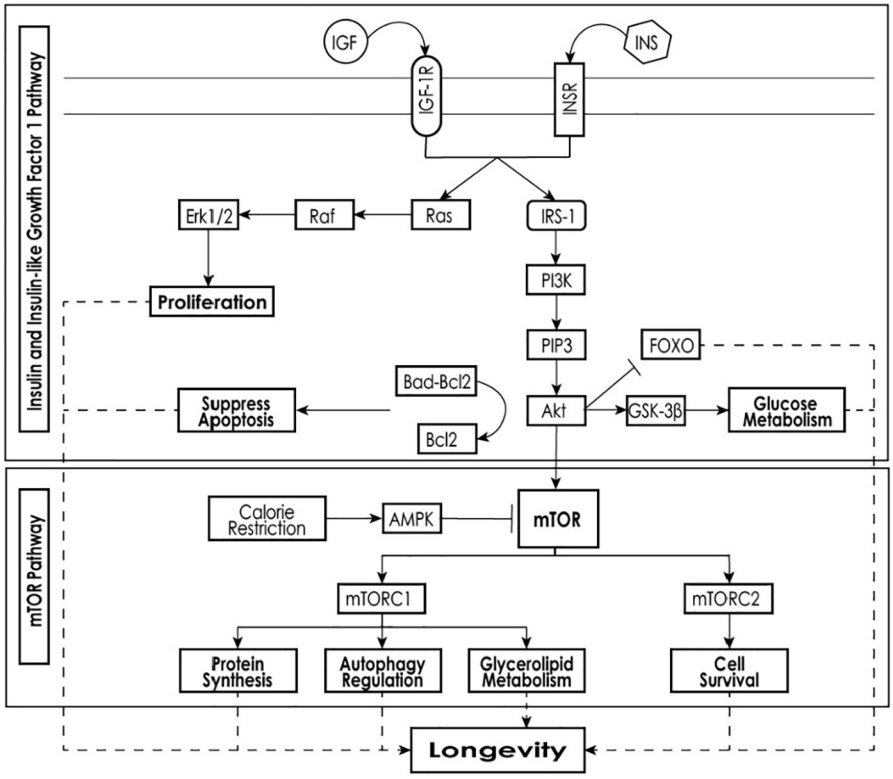

Fig. 1. Conserved Signaling Pathways associated to longevity suggests energy control plays a vital role in longevity and aging: The nutrient sensing pathways, namely IIS (insulin/insulin-like growth factor 1 pathway) and TOR (target-of- rapamycin), are conserved across species. Genetic downregulation of these pathways is reported to significantly increase the health span and lifespan of the model organisms. The effects of calorie restriction on lifespan extension are associated with reduced activities of the TOR and Ras/PKA pathways and require various transcription factors including FOXO, DAF-16, and others. These transcription factors regulate the activation of genes involved in resistance to oxidative stress, energy metabolism, DNA damage repair, glucose metabolism, autophagy, and protein synthesis promoting health span and longevity. IGF: Insulin-like growth factor; IGF-1R: Insulin Like Growth Factor 1 Receptor; INS: Insulin; INSR: Insulin Receptor; ERK1/2: Extracellular Signal-Regulated Kinase1/2; Raf: Rapidly Accelerated Fibrosarcoma (Proto-Oncogene, Serine/Threonine Kinase); IRS-1: Insulin Receptor Substrate; PI3K: Phosphatidylinositol-4,5-Bisphosphate 3-Kinase; PIP3: Phosphatidylinositol-4,5-Bisphosphate 3-Kinase; Akt: Serine/Threonine Kinase; FOXO: Forkhead Box O1; GSK-3β: Glycogen Synthase Kinase 3 Beta; Bad: BCL2 Associated Agonist of Cell Death; Bcl2: B-cell lymphoma 2; AMPK: Adenosine Monophosphate-Activated Protein Kinase; mTOR: Mechanistic Target of Rapamycin Kinase; mTORC1: mammalian target of rapamycin complex 1; mTORC2: mammalian target of rapamycin complex 2.

Table 1
Orthologue of key components involved in nutrient sensing pathways across the species.

Homo sapiens	*Macaca mulatta*	*Rattus norvegicus*	*Mus musculus*	*Danio rerio*	*Drosophila melanogaster*	*Caenorhabditis elegans*	*Saccharomyces cerevisiae*
INSR	INSR	Insr	Insr	insra/b	NA	NA	NA
IGF-1R	IGF-1R	Igf1r	Igf1r	Igf1ra/b	InR	daf-2	Gpr1
IRS-1	IRS-1	Irs1	Irs1	irs1	CHICO	IST1	NA
Ras	Ras	ras	ras	rasa	NA	NA	Ras2
PI3K (PIK3CA)	PIK3CA	Pik3ca	Pik3ca	LOC561737	PIK3CA	Age-1	NA
Akt	Akt	Akt	Akt	Akt	Akt	Akt	NA
FOXO	FOXO	foxo	foxo	foxob	dFOXO	DAF-16	FKH1/2

Table 2
Longevity associated gene enrichment analysis through KOBAS 3.0.

Pathways	Organisms	Input number	Background number	Corrected *p-value*
Insulin signaling pathway	*Homo sapiens*	24	139	4.86E-23
	Mus musculus	11	142	6.74E-11
mTOR signaling pathway	*Homo sapiens*	21	154	1.79E-18
	Mus musculus	10	156	2.64E-09
	C. elegans	26	76	5.74E-21
	Drosophila	14	93	2.16E-10
Beta-adrenergic signaling	*Homo sapiens*	13	149	1.07E-09
	Mus musculus	5	152	0.000632
AMPK signaling pathway	*Homo sapiens*	24	125	5.91E-24
	Mus musculus	12	129	1.73E-12

Input Number: Number of input genes.
Background Number: Number of total genes involved in the pathway.

when the first reports of calorie restriction inducing extended lifespan, were published [85]. A small molecule, Tetrahydroxystilbene-2-O-β-D-glucoside (*THSG*), showed anti-aging properties through regulation of the expression of longevity gene, *Klotho*, expression [86]. Calorie restriction is also reported to increase the expression of FOXO1, FOXO3, and FOXO4 to prevent aging and promote longevity [87]. DNA damage and oxidative stress have been associated with decreased age in high sucrose diet fed rats [88]. Rapamycin is reported to extend the ovarian lifespan through suppression of mTOR signaling and increased expression of sirtuins including SIRT1 and SIRT6 [89,90]. Inhibition of angiotensin II function through angiotensin II type I receptor (AT1R) antagonists also extends lifespan in rats [91].

2.6. Primate

Primates belong to class *Mammalia* of phylum *Chordata.* They are characterized by distinct hands, feet and a relatively large brain as compared to other mammals.

2.6.1. Non-human primate

The rhesus macaque *(Macaca mulatta, M. mulatta)* monkey is the most widely used non-human primate model for aging research. They are 19–21 inches in length. They have an average lifespan of 26 years with a maximum of 40 years [92]. *M. mulatta* has a genome of 3146 Mb in size containing more than 21,000 protein coding while approximately 11,000 non-protein coding genes [9]. It shares 93% sequence identity with human genome [93].

Advantage of using *M. mulatta* as model organism for aging includes their long lifespan. They have the closest phylogenetic relationship with humans and exhibit close similarities in regard of physiology, neurological and cognitive functions, genetics, and aging. They also develop

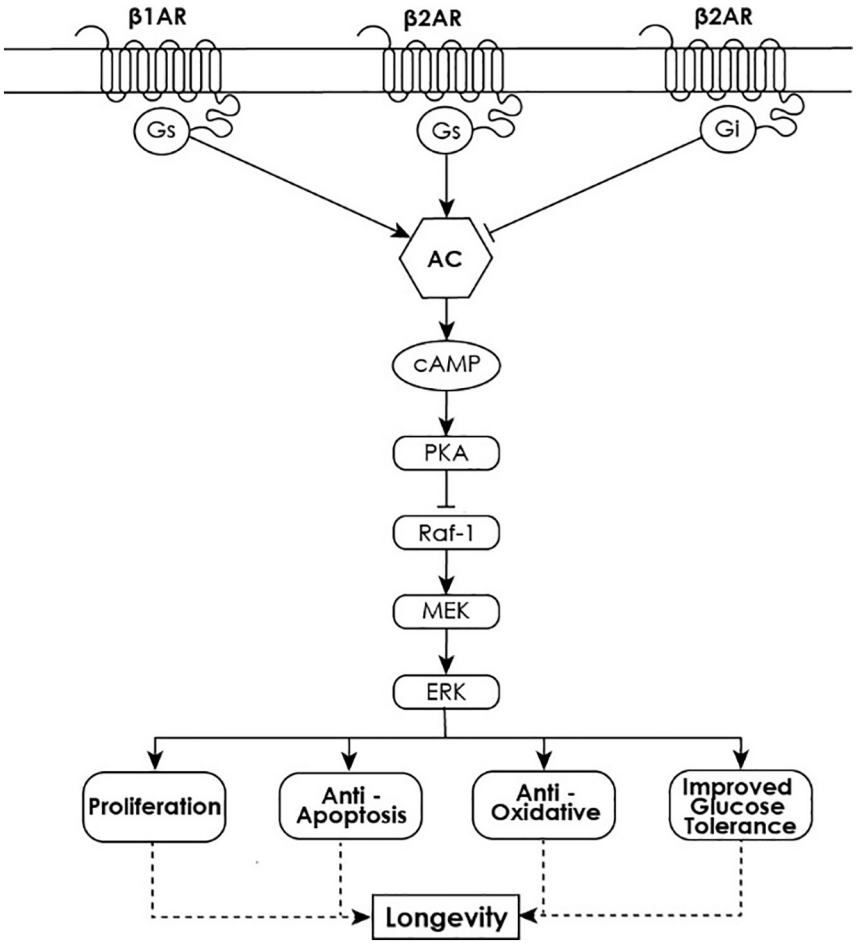

Fig. 2. β-adrenergic system modulating longevity: The activation of beta-adrenergic system, β1 and β2 receptors, found in the heart, lung, and peripheral tissues, causes positive inotropic and chronotropic responses, cardiac myocyte growth, and cardiac toxicity. AC5-KO mice model showed increased protection against oxidative stress, apoptosis, and osteoporosis leading to longevity through the activation of the Raf/MEK/ERK signaling pathway suggesting βAR suppression as a therapeutic intervention for lifespan and health span extension.
β1AR: Beta-1 Adrenergic Receptor; β2AR: Beta-2 Adrenergic Receptor; Gs: G protein stimulatory; Gi: G protein Inhibitory; AC: Adenylyl cyclase; cAMP: Cyclic adenosine monophosphate; PKA: Protein kinase A; ERK: Extracellular Signal-Regulated Kinase.

age-related pathologies like humans including cardiovascular diseases, bone degradation and decline in metabolic activities among others [94,95]. Their strong and large body, unpredictive behavior, special environmental requirements and relatively expensive maintenance are some of the challenges to their use in research [96].

Over the past three decades, overwhelming evidence has been reported by Wisconsin National Primate Research Center (WNPRC) in a long running research study started in 1989, affirming the key role of calorie restriction in promoting longevity, health span, and delay in aging [92,97–99].

2.6.2. Human

Homo sapiens (H. sapiens), belongs to class *Mammalia* of phylum *Chordata.* Human has a genome of 3554 Mb in size and contains 20,310 coding genes, 22,529 non-coding genes, 14,589 pseudogenes, and 199,234 gene transcripts [9]. The genetic contribution of human aging is predominantly investigated using retrospective studies rather than interventions. Longevity, defined as a typical length of life, is a perfect natural model for human aging. The genetic predispositions of longevity are being uncovered using various genetic tools such as fine mapping of candidate genes, genome wide association study (GWAS), whole exome sequencing (WES), and even whole genome sequencing (WGS) [100]. The clues obtained from the recent studies reveal that longevity is affected by genetic, epigenetic as well as environmental factors [100–106].

Genome wide association studies have led to the discovery of a number of genes associated to longevity trait in human [100,107]. Population evidence of candidate genes for longevity have been carried out using candidate strategies. Polymorphisms in *APOE, ACE, SIRT, IL6, IGF* are also investigated for their association to longevity [100,108,109]. Progeria, characterized by premature aging, includes Hutchinson-Gilford Progeria Syndrome (HGPS), Werner syndrome and Bloom's syndrome. These syndromes provide valuable insights into the mechanisms of aging process and accelerated senescence. *FOXO* family are widely replicated in distinct populations [110]. FOXO family members, *FOXO1A* and *FOXO3A*, were reported to be associated with longevity in Han Chinese Population [103–106,110]. We previously reported the interactions between a habit of tea drinking at the age of 60 or at present age and carrying FOXO1A-266 or FOXO3-310 or FOXO3-292 were significantly associated with lower risk of cognitive disability at advanced ages and reduced mortality [103,104]. Strong association of *FOXO1A* to female longevity further extends the evidence of gender dependent effects on longevity [110,111]. We previously reported that the genetic variations in the β2-adrenergic receptors encoding gene *ADRB2* leading to its increased production is inversely associated to lifespan [112].

All these findings point to a genetically programmed background for the aging process. Human based population studies are considered to be a backbone of human aging research, leading to extensive findings ranging from individual genetic factors to the complex pathways, affecting longevity and aging.

3. Pathways associated with longevity

It is a well-established fact that genetic background along with environmental factors modulate the aging process and longevity. On genetic front, the genome and epigenome maintenance, regulation of proteostasis and the nutrient sensing pathways including Insulin/Insulin-like Growth Factor 1 (insulin/IGF) pathway, the mechanistic target of rapamycin (*mTOR*), *AMP* Kinase signaling are found to be

Table 3
Organismal models for longevity and aging research.

Species	Average lifespan (year)	Genome size (Mb)	Protein coding/non-protein coding genes	Genes related to aging/longevity	Usage	References
Saccharomyces cerevisiae	30–40*	12	6692/400	899	Functional analysis of genes involved in cellular processes modulating aging and longevity	[8,9,156]
Caenorhabditis elegans	11–20**	97	20,000/25,000	798	Identification and physiological impact of genes on aging and longevity	[9,29,157]
Metaseiulus occidentalis	30–60**	152	18,338/NA	NA	Ecological and evolutionary differences in age among different species	[40,42,44]
Drosophila melanogaster	30**	142	14,000/3000	175	Identification and functional analysis of genes associated to aging and longevity	[9,47,53]
Danio rerio	3.5–5	1464	26,000/6000	NA	Identification and functional analysis of genes associated to aging and longevity	[9,60]
Mus musculus	2–3.5	3482	23,000/14,000	134	Gene identification, functional analysis and therapeutic interventions improving healthspan and lifespan	[9,69,72]
Rattus norvegicus	3	3042	22,250/8934	NA	Gene identification, functional analysis and therapeutic interventions improving healthspan and lifespan	[9,83,84]
Macaca mulatta	26	3146	21,000/11,000	NA	Epigenetic regulation of gene expression and their impact on aging and longevity	[9,92,93]
Homo sapiens	80–100	3547	20,441/22,219	306	Population based association analysis for the identification of genetic factors affecting aging and longevity	[9]

*Divisions; **Days; *Genes related to aging/longevity were obtained from a database, Human Ageing Genomic Resources (accessible at http://genomics.senescence.info/).*

conserved and involved in human, mice, *C. elegans*, and *Drosophila.* Nutrient sensing pathways modulating longevity, are graphically represented in Fig. 1. The key components involved in these pathways are conserved across the species ranging from yeasts to human. The orthologues of the key components of the pathways are listed in Table 1. An enrichment analysis of the genes reported to be involved in longevity and aging in different organisms, performed using a web-based module KOBAS 3.0 to these pathways, is summarized in Table 2.

Insulin signaling is involved in glucose homeostasis though stimulation of glucose uptake by cells and blockade of glycogenolysis and gluconeogenesis in liver. Binding of insulin or *IGF-1* to the insulin or *IGF-1* receptors activates the insulin/IGF-1 signaling cascade leading to the cellular glucose uptake, activation of *NF-κB*, and activation of mTOR complex [113,114]. There is an accumulating evidence that genetic manipulations attenuating the insulin/IGF-1 singnaling tends to extend the lifespan across the model organism [115–117]. The insulin/IGF-1 pathways is reported to modulate the transcription factors, for instance, *FOXO3A*, which is found to be associated to longevity in one of our previous study [110]. Reduced insulin/IGF-1 like signaling, increased AMPK signaling and sirtuins extend lifespan in *C. elegans* through activation of the conserved transcription factor DAF-16, a sole orthologue of human FOXO family [118]. dFOXO, an orthologe of mammalian FOXO3A and *C. elegans'* DAF-16 in *Drosophila,* delay aging and promote longevity [119]. Furthermore, reduced expression of insulin like peptides [51], insulin receptors [120], and receptor substrates [121] extend lifespan in *Drosophila*. A recent study in rats suggested that calorie restriction, a potential intervention to promote longevity, induced benefit on insulin stimulated glucose uptake depends upon increased Akt-2 phosphorylation, a component of insulin signaling pathway [122].

mTOR pathway, a highly conserved pathway from yeast to higher organisms, lies at the heart of nutrient sensing and is involved in the regulation of cellular growth and metabolism including synthesis and degradation of proteins. mTOR can be activated through various pathways including insulin/IGF-1 pathway, and respond to the presence of high amino acid concentrations. In mammals mTOR is a part of two different structural and functional complexes; (i) mTORC1; senses higher amino acid concentration and modulates the protein, lipid, nucleotide synthesis, and autophagy [123,124]; and (ii) mTORC2; involved in cell proliferation and survival [125,126]. Inhibition of mTOR signaling has been reported to extend the minimal and maximal lifespan in mice [127,128]. In rats, rapamycin is reported to extend the ovarian lifespan through suppression of mTOR signaling and increased expression of sirtuins including *SIRT1* and *SIRT6* [89,90]. *C. elegans* with a null mutant at LET-363, orthologue of mTOR in *C. elegans*, and RNAi induced suppressed expression of let-363 showed extended lifespan [129]. In *Drosophila*, TSC1 and TSC2 (Tuberous Sclerosis Complex genes 1 and 2) act together to inhibit TOR [130], and overexpression of dTsc1, dTsc2, or dominant-negative forms of dTOR or dS6K promoted longevity [131]. Calorie restriction induced lifespan extension has been linked to reduced TOR signaling in *S. cerevisiae* [132].

The AMPK and sirtuins sense low energy states through detection of higher AMP and NAD^+ levels. AMPK leads to restoration of the energy balance through catabolic responses including proteolysis, fatty acid oxidation, and inhibition of cell growth and proliferation [133]. AMPK has been reported to inhibit mTOR signaling [134], and has synergistic effects to calorie restriction [135] extending the health span and lifespan. Sirtuins have been reported to regulate the aging process and are essential for the calorie restriction induced longevity in *S. cerevisiae, C. elegans*, *D. melanogaster* and mice [118,136]. AMPK has been reported to be involved in differential expression of proteins in metabolic pathways through regulation of coactivators and transcription factors including *C. elegans*' DAF-16 and the human homologue FoxO3 [137,138]. Genomewide expression profiling and functional analysis revealed a link between CEP-1/p53 and CEH-23 suggesting their role downstream of AAK2 and the AMPK catalytic subunit homologue in *C.*

Table 4
Eight major organ systems, lifespan, and model organisms.

Species	Circulatory system	Nervous system	Respiratory system	Skeletal system	Muscular system	Digestive system	Reproductive system	Excretory system	Lifespan	References
Saccharomyces cerevisiae	−	−	−	−	−	−	−	−	+	[11–14]
Caenorhabditis elegans	+	+	+	−	+	+	+	+	+	[31–34]
Metaseiulus occidentalis	+	+	+	−	−	+	+	+	+	[40–42,44,45]
Drosophila melanogaster	+	+	+	−	−	+	+	+	+	[50–53]
Danio rerio	+	+	+	+	+	+	+	+	+	[158–160]
Mus musculus	+	+	+	+	+	+	+	+	+	[73–75]
Rattus norvegicus	+	+	+	+	+	+	+	+	+	[85,86,88,90]
Macaca mulatta	+	+	+	+	+	+	+	+	+	[92,97–99]
Homo sapiens	+	+	+	+	+	+	+	+	+	[110,111,152,161]

(−) Not available; (+) Available.

elegans, in promoting stress resistance and longevity [139]. An antioxidant, chicoric acid, stimulated activation of AMPK pathways extends lifespan in *C. elegans*. Tissue specific upregulation of AMPK catalytic subunit, including neuronal-specific or intestinal, also increases lifespan in *Drosophila* [140]. A heterozygous mutation in AMP biosynthetic enzymes causing the increased AMP/ATP and ADP/ATP ratios, and transgenic overexpression of AMPK in the fly's fat body or muscle increased the lifespan, while RNAi-mediated AMPK knockdown in these tissues decreased the lifespan in *Drosophila* [141]. A decline in AMPK activation has been observed in different tissues with age in rats [142]. In mice, AMPK is involved in inhibition of TOR activity either directly through phosphorylation of the Raptor subunit, or indirectly through phosphorylation of an upstream kinase, tuberous sclerosis protein 2 (TSC2) [143,144]. Another target of AMPK phosphorylation includes the *FOXO* family of transcription factors, which is involved in lifespan extension through reduced insulin/insulin-like growth factor (IGF) signaling [145].

The beta-adrenergic system consists of β1 and β2 receptors that are found in the heart, lung, and peripheral tissues [146]. The activation of any of the two receptors causes positive inotropic and chronotropic responses, cardiac myocyte growth, and cardiac toxicity. Transgenic mice overexpressing β-adrenergic receptor 2 (β2AR) showed increased incidence of death resulting from cardiomyopathy and heart failure as early as 8.5 months with maximum age of 15 months [147]. Adenylyl cyclases (AC) are membrane bound enzyme that catalyze the synthesis of cAMP from ATP and play a vital role in β-adrenergic signaling. The cardiac tissue-specific overexpression of AC6 resulted in restoring myocyte AC function, improved heart function, increased cAMP generation, and abrogated myocardial hypertrophy leading to increased lifespan in the mice with cardiomyopathy background [148]. AC5-KO mice showed increased protection against oxidative stress, apoptosis, and osteoporosis, leading to longevity through the activation of the Raf/MEK/ERK signaling pathway [149]. Moreover, overexpression of mammalian ERK2 extended lifespan and improved resistance against heat shock and oxidative stress in budding yeast [149]. Pharmacological inhibition of β1AR through βAR blockers, metoprolol or nebivolol, resulted in the extension of lifespan in *Drosophila* and mice [150]. Recently, β2AR inhibition was reported to diminish the age-related accumulation of hepatic triglyceride, increased body weight and improved glucose tolerance in mice [151]. Consistent with the reports from animal models, our previous study provided the clues of involvement of β-adrenergic system in longevity, which was evident from genotyping and Single Nucleotide Polymorphism (SNP) association study in Han Chinese Population and backed by transfection studies using *HEK293A* cells [152]. β2AR has been reported to be associated with gender dependent human longevity supporting the well documented sexual dimorphism exhibited by longevity, as two SNPs (rs1042718 and rs1042719) of β2AR coding gene *ADRB2* and their haplotypes leading to the reduced translation efficiency of *ADRB2* were reportedly associated with longevity in men [110,152]. Together these results provided the evidence of the conservation of β-adrenergic system across the species, its involvement in promoting longevity, and suggest βAR suppression as a therapeutic intervention for lifespan and health span extension (Fig. 2).

4. Conclusion

In this review, we summarized the various models commonly used in longevity and aging research, focusing on their genetic background, key findings, and their advantages/disadvantages in study of organismal (Table 3) and systemic aging (Table 4). These suggestions are helpful to select the suitable models to understand aging and longevity.

In addition, we discussed about the evolutionary conservation of pathways associated with longevity, including Insulin signaling, mTOR, AMPK, and beta-adrenergic pathways. Among these, the beta-adrenergic system is mentioned to be the conserved pathway associated to longevity for the first time. Interestingly, all these conserved pathways link to energy metabolism, suggesting that the energy control plays an essential role in longevity and aging. Supportively, caloric restriction is widely accepted intervention to prevent degenerative diseases and extend lifespan and/or healthspan [92,141,153–155]. Aging is an unescapable stage in life cycle. Like other stages, aging may be initiated programmatically (reversible), however, it becomes disordered (irreversible) at the end, which eventually leads to death. How these pathways function during these processes remains to be further investigated.

Transparency document

The Transparency document associated with this article can be found, in online version.

Acknowledgements

This study was supported by grants from the National Basic Research Program of the Chinese Ministry of Science and Technology (973 Grants 2013CB530700 and 2007CB512103) and the National Natural Science Foundation of China (81630034 and 81130003) to Xiao-Li Tian.

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