

The Genetics of Human Longevity

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Abstract

Human longevity is at least partly heritable, and the progeroid syndromes of accelerated aging have genetic causes. In addition, there are human homologues to many of these genes that affect lifespan in model organisms. In people, longevity genes might slow the rate of age-related changes in cells, increase resistance to environmental stresses like infection and injury, and reduce the risk of many age-related conditions. This article reviews several genetic pathways that appear to be involved in the aging process and longevity, including genes involved in the progeroid syndromes, telomeres and telomerase, caloric restriction, stress resistance and oxidative damage, mitochondrial DNA, insulin signaling, and inflammation. It concludes with a discussion of the analytic challenges that face investigators in this area.

Genetic differences partly explain why long-lived people cluster in families. Studies comparing life expectancy in twins and other family members have found that up to 25% of the variation in human lifespan is heritable (1, 2); the remaining 75% is due to environmental exposures, accidents and injuries, and chance. Very long life, to beyond ages 90 or 100 years, appears to have an even stronger genetic basis (3). Conversely, several clinical syndromes of “accelerated aging” and death at an early age (the progeroid syndromes) have a known genetic basis (4, 5).

The rate of aging and lifespan vary greatly among species, and therefore must be under genetic control (6, 7). Recently, mutations in several genes have been found to markedly increase lifespan in nematode worms (*C. elegans*), fruit flies (*Drosophila*), and mice, sometimes up to 6-fold, apparently by slowing the aging process (8-13). There are good reasons to believe that understanding these “longevity genes” will be useful in studying human aging and lifespan. Most biologic pathways, and the genes that control them, have been conserved through evolution and there is no reason to suppose that those which regulate aging and longevity would be an exception. Indeed, several metabolic pathways that affect aging and longevity in one species of animal (e.g., fruit flies) also do so in other species (e.g., nematodes and mice). There are human homologues, with apparently similar functions, to many if not all of the genes in these pathways, although we do not yet whether these genes affect lifespan in people.

What would be the characteristics of longevity genes in humans? Such genes would function in several important ways. They might slow the rate of age-related senescent changes in cells and tissues, improve the effectiveness of repair mechanisms, and increase resistance to environmental stresses like infection and injury. Longevity genes should also affect a wide spectrum of debilitating age-related conditions. These requirements are consistent with the observation that the elderly children of centenarians have much less diabetes and ischemic heart disease, and better self-rated health, than do age-matched controls. This suggests that they have inherited a longevity gene—or more likely a set of genes—from their long-lived parent that protects against these infirmities. (In contrast, mutations in some genes, such as *BRCA1* or *apoE*, reduce lifespan by increasing the risk of a single fatal disease or a set of closely related diseases.

Genes of this sort—which do not modulate biological pathways of aging and do not influence the risks of several age-sensitive traits, disabilities, and diseases—are not considered to be longevity genes from the perspective of this review.)

It may not be obvious why longevity genes should persist in humans or any species: there appears to be little or no evolutionary pressure to select for genetic mutations whose main effects are to increase survival or fitness beyond the reproductive years. Indeed, just the opposite might be the case, since there would be selection pressure for genes that are important for reproductive success even if they have deleterious consequences in later life. However, there would be evolutionary pressure to select genes that are beneficial throughout life, and which manifest, in part, as extreme longevity.

After a brief review of terminology, this article reviews several genetic pathways (Table) that appear to be involved in the aging process and longevity, and discusses some of the analytic challenges that face investigators seeking to identify and understand the function of these pathways.

DEFINITIONS AND A FEW TECHNICAL ISSUES.

The recent sequencing and annotation of the human genome has raised the possibility of finding genetic alleles (gene variants) that are associated with complex phenotypes (traits) like longevity (50). One common way that alleles develop is through mutations in a single nucleic acid in a DNA molecule, due to a deletion, insertion, or substitution (e.g., from adenosine to thymidine). These are known as single nucleotide polymorphisms, abbreviated as SNPs and pronounced “snips.” Since SNPs are the most common type of genetic variation, they are presumed to underlie many of the biological changes in gene activity that affect traits of medical interest.

Some SNPs are located in exons, the regions of a gene’s DNA that are transcribed into RNA and then translated into proteins. Exonic SNPs, unless they do not result in amino acid changes (because of redundancy in the genetic code), almost certainly affect protein

structure or function. However, even SNPs located in non-coding regions of DNA may be capable of altering phenotype, for example by affecting the likelihood that an exon will be transcribed. There are also “epigenetic” changes that affect transcription but which do not involve changes at the nucleotide level, such as changes in chromatin conformation and packing, and DNA methylation.

Because genes and portions of genes are inherited in blocks, each gene variant is likely to be associated with other nearby variants. This phenomenon, known as linkage disequilibrium, means that the likelihood of two alleles being found together is directly related to how close together they are on a chromosome. Human demographic history (population expansions and migrations) also has important effects on the patterns of linkage disequilibrium. Thus genetic analyses often study haplotypes—“blocks” of DNA that tend to be inherited as a single unit.

One final introductory note: in this article, genes are *italicized*, proteins are not. Both are capitalized when referring to humans. Thus *WRN* refers to a human gene, and WRN to its protein product.

POTENTIAL LONGEVITY PATHWAYS AND GENES

Genes involved in the regulation of DNA repair and nuclear structure and function.

At a cellular level, maintenance of healthy DNA is needed for routine functions like production of proteins, as well as to ensure the genetic fidelity of daughter cells in tissues that divide. Perhaps not surprisingly, mutations in two of the genes involved in the metabolism and repair of DNA, and in nuclear structure and function, cause clinical syndromes that have features suggestive of “accelerated aging” (16, 51-54), although they do not mimic the normal aging process in its entirety.

Werner’s syndrome is caused by several different mutations of *WRN* (14), a gene that encodes a protein belonging to RecQ helicase family. The mutations result in a truncation

of the normal WRN protein. It is not known how this shortening causes the clinical manifestations of the syndrome, which include lack of an adolescent growth spurt, alopecia or graying of hair, sclerotic skin, cataracts, type 2 diabetes, hypogonadism, atherosclerosis, osteoporosis, and certain forms of cancer (in roughly chronological order) (55, 56). The median age of death is the late 40s, primarily from myocardial infarction and cancer. The effects of less severe mutations in this gene are less well documented, but one population-based analysis found that a SNP in *WRN* (the Leu allele at amino acid 1074) was more common in older subjects than in newborns (15). However, Werner's syndrome is not identical to accelerated aging (4). For example, cancers derived from mesenchymal tissues are common in Werner's syndrome, whereas Alzheimer's dementia is rare (57).

Hutchinson-Gilford progeria is caused by a mutation of *LMNA* (16), a gene that codes for a group of proteins (lamins) that are part of the filamentous network located along the inner membrane of the nuclear envelope. These proteins are believed to affect nuclear morphology, chromatin structure, DNA synthesis, and gene expression. Patients with the syndrome typically exhibit growth retardation within the first few months of life and have accelerated degenerative changes in the cutaneous, musculoskeletal, and cardiovascular systems. On the other hand, Alzheimer-type dementia is not observed, nor are there other more basic markers of aging such as large intracellular deposits of lipofuscins. The median age of death is 13.5 years, due to rapidly progressive atherosclerosis (58). Mutations in *LMNA* are responsible for at least six other disorders, including an atypical Werner syndrome in which *WRN* is not mutated (17). The effects of less severe mutations in *LMNA* on longevity are not known.

Genetic regulation of telomere length. Human chromosomes terminate in telomeres, similar to the way shoelaces end in aglets (59). Telomeres help maintain genomic integrity by preventing end-to-end fusion of chromosomes. In humans, telomeres consist of a few hundred to a few thousand copies of a uniform double-stranded DNA sequence (TTAGGG)_n, followed by a single-strand overhang of the same sequence.

Because typical DNA polymerases (the enzymes that duplicate DNA) cannot fully replicate these terminal DNA sequences, telomeres shorten with each cell division in somatic cells, like epithelial and bone marrow progenitor cells, that divide throughout life. Telomere shortening is further exacerbated by the action of nucleases, which slice off short strands of DNA. Thus, in dividing somatic cells, older adults on average have shorter telomeres than younger adults (60). In contrast, the telomeres of post-mitotic cells, like neurons, do not shorten with age. (Proliferating germ line cells solve the problem of telomere shortening by expressing telomerase, a reverse transcriptase that uses its RNA component as a template to add DNA to the overhang, thus maintaining telomere length.) Depending on the cell type, telomere shortening may trigger the loss of a cell's ability to replicate, lead to apoptosis (a form of cell death), or cause neoplastic transformation (23).

Telomere length is highly heritable (61) and genetic variations that affect telomere length or function may be important determinants of human longevity and aging. For example, a rare hereditary syndrome, autosomal dominant dyskeratosis congenita, is caused by mutations in the gene (*hTR*) for the RNA component of telomerase (20) that result in shortened telomeres; the X-linked variant of the syndrome is caused by a different mutation (in *DKC1*) that affects a protein (dyskerin) which interacts with telomerase(22). Both forms of the syndrome have many features of premature aging, including graying and hair loss, cancer, poor wound healing, osteoporosis, and hypogonadism (20). These manifestations, as well as the skin and nail changes for which the syndrome is named, involve tissues that require constant cellular renewal.

A recent study found that telomere length was inversely associated with age-adjusted mortality in humans: those with shorter telomeres had worse survival, attributable in part to a three-fold greater mortality from heart disease and an eight-fold greater mortality from infectious diseases (21). Telomeres are also shorter in several age-related conditions, including coronary atherosclerosis, vascular dementia, Alzheimer's disease, and several cancers, than in healthy controls (62-65). The specific genes that affect telomere length and function in these conditions, however, have not been identified.

Genes that affect stress resistance and oxidative damage. The rate of aging in individual organisms may be affected by differences in genetically controlled resistance to potentially lethal stresses, including oxidative damage. Indeed, there appear to be parallel relations between stress resistance at the cellular level and longevity, with greater stress resistance correlating with increased life span. For example, mutations in *daf-2* and *age-1* extend longevity in *C. elegans*, and also lead to increased resistance to several forms of stress, including ultraviolet light, heat, reactive oxygen species, and heavy metals (25, 26, 66). Both of these genes have human homologues (the genes for the insulin and the insulin-like growth factor-1 [IGF-1] receptors for *daf-2*, and *PI3K*, which codes for phosphatidylinositol-3 kinase, for *age-1*). Similarly, some single-gene mutations that extend longevity in fruit flies are associated with increased resistance to many forms of acute stress. For example, a mutation in the so-called *methuselah* gene extends average life span by about 35% and increases resistance to starvation, free-radical damage, and elevated temperature (9).

A relation between stress resistance and longevity has also been observed in mammals. Analyses of cells from a variety of different species—from hamsters to humans, whose maximal lifespan varies 40-fold—have shown good correlations between resistance to cytotoxic stress and maximal life span (67). In addition, fibroblasts from small, long-lived mice are also more resistant to cytotoxic stresses (28). Other longevity-related mutation in the mouse (in *shc* and in *igflr*, the gene for the insulin-like growth factor receptor) increases resistance to oxidative stresses (27 Holzenberger, 2003 #284).

Taken together, these results support the idea that the evolution of long-lived species required pathways to mitigate many forms of intracellular damage. Early in their evolutionary history, invertebrates evolved systems for recognizing environmental conditions, such as food shortages, that favored differentiation into stress-resistant forms rather than into breeding forms that were more vulnerable to injury and toxicity. These systems for conditional differentiation may then have been adopted for developmental control pathways by more advanced organisms, including the precursors of mammals. The genes and proteins involved in regulating stress resistance in human have not been

fully characterized. There is substantial interest in superoxide dismutases, which regulate the metabolism of reactive oxygen species. Although mutations in these genes have been associated with neurological diseases like amyotrophic lateral sclerosis (68), their effects on longevity are not known.

Mitochondrial DNA, reactive oxygen species, and aging. Mitochondria, the intracellular organelles responsible for oxidative metabolism, probably originated as separate organisms that were incorporated into eukaryotes early in evolution (69). Mammalian cells have several hundred mitochondria, all of which were inherited from those in the maternal egg. Each mitochondrion has a few identical copies of its own DNA, each of which is in the form of a circular strand of 16,569 base pairs. This DNA molecule codes for 13 of the mitochondrial enzymes involved in cellular respiration (using a slightly different genetic code than does nuclear DNA), as well as a few ribosomal and transfer RNA molecules (70). In addition, nuclear genes code for other proteins involved in mitochondrial function.

There are only a limited number of genetic forms, or haplotypes, of mitochondrial DNA. For example, there are about 10 different major haplotypes in most European populations (71) and only 4 among Native Americans (72). In somatic (non-germ line) cells, mitochondrial DNA mutates about 10 to 20 times faster than nuclear DNA (73), possibly because mitochondria are the major source of reactive oxygen species, also known as free radicals, within a cell. Mutations in mitochondrial DNA accumulate with age in post-mitotic tissues, such as central nervous system neurons, and cardiac and skeletal muscle (74, 75).

The mitochondrial theory of aging states that the onset of age-related senescent changes in tissues is related to the balance between inherited healthy mitochondrial DNA and the load of age-related mutations in this DNA (76-78). Eventually, damage or loss of mitochondrial DNA prevents post-mitotic cells from regenerating new mitochondria, thereby reducing the production of ATP and leading to cell death and aging. The degree of age-induced mutation in mitochondrial DNA varies among individuals (79) and may

be under genetic control (30). It is not known whether this variation is associated with lifespan. Several studies in Europe and Japan, however, have reported that some mitochondrial DNA haplotypes are more common in centenarians than in the general population (30-35), raising the possibility that these haplotypes are associated causally with extended lifespan.

Genes that mediate the effects of caloric restriction. The most effective environmental method of increasing lifespan is caloric restriction, which increases longevity in mice, rats, fruit flies, worms, and yeast (36-38). Caloric restriction appears to operate by slowing the aging process and the onset of diseases and disorders that are associated with advancing age, perhaps by reducing the lifelong production of harmful reactive oxygen metabolites (36, 37). Thus, the senescent, regressive changes associated, for example, with skin, bone, muscle and blood vessels are retarded in their appearance, as is the incidence of tumors and their progression. (80-84). Initial experimental results with monkeys suggest that the same phenomenon will also apply to non-human primates (39, 40). The effects of caloric restriction in humans remain to be determined.

The pattern of gene expression among older animals that have been calorically restricted is similar in some respects to that seen among younger animals that had been fed ad libitum diets (85). These differences in gene expression may be useful in identifying genetic pathways whose regulation—either due to mutations or to epigenetic differences—affects lifespan.

The responses to caloric restriction and other forms of cellular stress trigger mechanisms, including activation of the sirtuin pathways, that may protect cells. Sirtuins are deacetylases, enzymes that regulate (silence) gene expression. The beneficial effects of caloric restriction in yeast require an intact sirtuin pathway(86, 87), and overexpression of *sir2* increase lifespan in *C. elegans* (88). (Resveratrol, a polyphenol compound found in red wine that activates *sir2* in yeast, mimics the effects of caloric restriction.) Yeast *sir2* has a human homologue (*SIRT1*); the effects of mutations in *SIRT1* and related genes

on human lifespan are not known. However, SIRT1 may have adverse effects in human cells on p53, a tumor suppressor (89).

Genes that regulate signaling by insulin and insulin-like growth factor-1 (IGF-1)-like molecules. Perhaps the best studied longevity pathway involves insulin/IGF-1 signaling (41). Reduced function of this pathway (Figure 1) is associated with prolonged lifespan in several species (42). In *C. elegans*, for example, a reduction-in-function mutation in *daf-2*, the homologue of the mammalian insulin and IGF-1 receptors, doubles lifespan and slows tissue aging (43-45). Mutations in many of the downstream signaling elements in this pathway, including *age-1*, *PDK1*, *daf-18*, *akt*, and *daf-16* also affect longevity. These same genes have also turned out to be involved in the response to oxidative stress (42), including the upregulation of heat shock proteins, as well as tumor suppression (45, 90, 91).

Similar effects have also been seen in fruit flies and mice. Mutations in the *Drosophila* homologue of the mammalian insulin receptor, or a loss-of-function mutation in a homologue of the insulin receptor substrate, increase lifespan (92, 93). Mice with heterozygous deletion of the IGF-1 receptor appear to have longer lifespan, although the effect may be specific to females (29). Finally, mice lacking a fat-specific insulin receptor live about 20% longer than controls (46). Thus, decreased insulin signaling in certain tissues may extend life. (By contrast, total body insulin resistance, which results in increased insulin signaling, leads to diabetes mellitus and shortened lifespan.)

Dwarf mice with mutations that delete the growth hormone receptor have increased lifespans (94). The function of the insulin/IGF-1 signaling pathway in these mice is also decreased (95). However, mice with genetically induced growth hormone antagonism that have normal insulin levels have a normal lifespan (96). Thus, the signaling system may act in a similar way in these mice as in *C. elegans*: decreased activity is associated with increased survival, perhaps mediated through the response to free radicals or the control of DNA repair (97, 98).

Several rare mutations in the growth hormone receptor in humans—analogueous to some of the dwarf mice mutations—lead to short stature(99), but their effects on lifespan are uncertain. A recent study from Italy identified an association between a SNP in the IGF-1 receptor gene (a G to A substitution at codon 1013) and human longevity (100); the SNP was also associated with lower circulating levels of IGF-1.

The hypothesis that genetic regulation of body size may be associated with longevity is supported indirectly by the somewhat complicated correlation between size and longevity in mammals. In general, larger species of mammals live longer, whereas within a species, the opposite is true. Thus dogs live longer than mice and rats, but not as long as horses and elephants, whereas small dogs like Chihuahuas live longer than large dogs like Great Danes (101, 102).

Genes involved in inflammation. Chronic inflammation, as manifested by high circulating levels of cytokines like C-reactive protein, tumor necrosis factor, and interleukin-6, have been associated with several age-related diseases, including atherosclerosis, cancer, and type 2 diabetes (103-106). It is not known whether genetic regulation of these cytokines affects longevity.

The inflammatory response may be an example of antagonistic pleiotropy (107), in which genes that increase the inflammatory response to infectious organisms are also associated with harmful effects, such as atherosclerosis. Inflammation has its phylogenetic origin as the innate immune system. This is also the first line of defense against microbial invasion in higher organisms like mammals, which use a class of cell-surface molecules, called toll-like receptors (TLR), to sense microbial pathogens (108). A common SNP (Asp299Gly) in the gene for one of these receptors (*TLR4*)—which reduces the inflammatory response to bacterial infections—is also associated with a reduced risk of atherosclerosis (47), as well as greatly increasing the efficacy of statin therapy (48).

Modulation of inflammation may also be responsible for some of the benefits of caloric restriction or small size. Of the 352 genes whose expression was altered to a significant

degree in calorically restricted mice, 29 were also altered in one species of dwarf mice. Of these 29 genes, only one—macrophage inhibitory factor (*mif*)—was also altered in a second dwarf mouse model of longevity (49). Macrophage inhibitory factor acts in concert with glucocorticoids to modulate the set-point and magnitude of the immune and inflammatory responses (Figure 2). Mutations in the human gene (*MIF*) have been associated with several inflammatory conditions (109-114).

THE BIOINFORMATICS/STUDY DESIGN CHALLENGE

Little is known about when and how genes exert their effects on lifespan and how they interact with each other and the environment. As a result, the best sampling strategy and design for genetic studies of human longevity are uncertain. Two types of samples are used commonly: family-based and population-based studies. Family studies can detect both genetic associations (linkage disequilibrium) and physical linkage of a trait to a particular chromosomal region (115). Thus family studies are not subject to confounding due to “population stratification,” which is discussed below. However, collecting enough families is not easy, especially for late-onset complex traits such as lifespan. Population-based sampling in unrelated persons may provide a powerful and more efficient alternative, due to recent advances in genomic and statistical techniques. They may also be more powerful than family designs for detecting gene-gene interactions (116).

Two problems—genetic heterogeneity and population stratification—can obscure, or even create, genetic effects. Genetic heterogeneity occurs when more than one genetic difference leads to the same phenotypic outcome. For a complex trait like longevity, genetic heterogeneity seems certain. Indeed, some have suggested that there are three routes to becoming a centenarian: surviving one or more potentially fatal age-related diseases, delaying their onset, or escaping them altogether (117). Population stratification refers to both the genetic admixture and the geographic clustering of genetically similar persons that historical patterns of human migration and mating have created (118, 119). The problem is that a genetic effect may not be due to the target gene, but rather to one

that is closely associated (and thus has been transmitted together in human history) with that gene (120, 121).

Several approaches have been used to identify genes affecting aging and longevity in human populations. In the absence of an *a priori* hypothesis about the location and number of target (candidate) genes, a genome-wide search using linkage can be used. This requires identifying genetic markers (like SNPs) at approximately evenly placed locations across the genome to find those that occur more frequently in long-lived people (122). In family studies, for example, 400 to 1,000 such markers are used to look for regions of interest. This positioning helps narrow the search to a specific chromosomal region, which can then be mapped more finely or sequenced to look for the responsible mutation. A population-based genome scan, however, would require hundreds of thousands of genetic markers, which is not feasible presently. This technical limitation may soon be circumvented if the HapMap project, which will provide a list of common haplotypes and blocks of haplotypes that have been inherited together, is successful (123). The HapMap findings will enable the development of haplotype-tagging SNPs (markers that identify specific haplotypes) for both population- and family-based studies.

Another population-based approach to identifying genes important in aging and longevity involves testing for genetic associations between candidate genes and specific phenotypes of interest, like lifespan. However, the variants that alter a gene's activity are unknown for the vast majority of genes. Some have advocated selection of SNPs in candidate gene studies based on the haplotype structure of the gene, while others have advocated prioritization based on the likelihood that variants affect biological function.

A DOSE OF REALITY

Generalizing results from lower organisms like worms to humans—“nematomorphizing” the aging process—may not be appropriate. Worms do not develop pneumonia, have myocardial infarctions, fall and break their hips, or become demented; indeed, they do

not even have lungs, coronary arteries, bones, or brains. Protein products that may have very similar functions at the cellular level in different animal phyla may have very different effects at the level of the organism.

Human aging is also influenced by cultural factors, such as habits and social support. The conditions under which longevity genes developed—either in humans or in non-human species—are not the conditions under which we now age. Genes that are associated with longevity in our current environment and culture, in which death from predation, exposure, starvation, and many infectious diseases is uncommon, may be very different from those associated with longevity in animals and earlier humans. Current causes of cellular stress are likely to differ substantially from those 20,000 years ago. The human diet now has an excess of, not a deficit in, available calories. The leading cause of death in the developed world—atherosclerotic vascular disease—has only become an important cause of mortality within the past few generations. Many conditions, such as injuries and infections, were much more likely to be lethal throughout human history than they are today. Nutrition, public health, access to shelter, primary and secondary prevention, and medical care have likely changed the genetic make-up of the elderly from what would have been selected earlier in mammalian and human history.

Nevertheless, the identification of longevity genes or gene pathways may enable the development of treatments to increase lifespan. The search is not for targets for gene-replacement therapy—there are too many cells that would require “fixing”—but for the development of non-genetic therapies, such as small molecules that activate or deactivate these genes or their protein products, thereby slowing the aging process and extending the human lifespan.

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Table. Genes and genetic pathways that may be involved in human longevity.

<i>Genetic pathways</i>	<i>Potential candidate genes in humans*</i>	<i>Evidence from model organism(s)</i>	<i>Selected references</i>
Regulation of DNA repair and nuclear structure and function (progeroid syndromes)	<i>WRN, LMNA</i>	Progeria in mice	(14-19)
Telomeres and telomerase	<i>hTR, DKC1</i>	Dyskeratosis and neoplasia in mice	(20-24)
Stress resistance and oxidative damage	Genes for superoxide dismutases, and the insulin and IGF-1 receptors; phosphatidylinositol-3 kinase	<i>C. elegans</i> , <i>drosophila</i> , mice	(9, 25-29)
Mitochondrial DNA	Mitochondrial haplotypes		(30-35)
Response to caloric restriction	<i>SIRT1</i>	Yeast, <i>C. elegans</i> , <i>drosophila</i> , mice, rats, monkeys	(36-40)
Insulin signaling	Genes for the insulin and IGF-1 receptor; insulin receptor substrate; and others (see Figure 1)	<i>C. elegans</i> , <i>drosophila</i> , mice,	(41-46)
Inflammation	Genes for toll-like receptor 4, macrophage inhibitory factor, interleukin 6, C-reactive protein, and others (see Figure 2)	Mice	(47-49)

* As discussed in the text, mutations in these genes, or epigenetic changes that affect these genes, may be associated with aging and longevity.

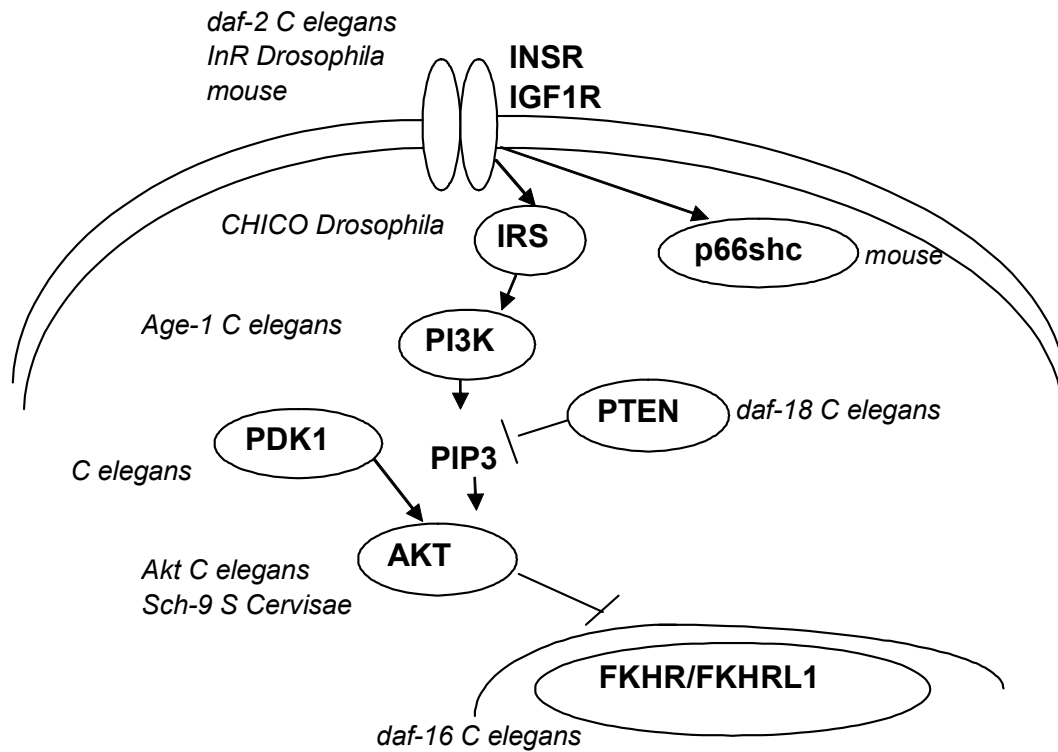


Figure 1. Genes involved in the insulin/IGF-1 signaling pathway that are known to affect lifespan in model organisms. Abbreviations: INSR: insulin receptor; IGF1R: IGF-1 receptor; IRS: insulin receptor substrate; PI3K: phosphatidylinositol-3 kinase; PTEN: phosphatase and tension homolog; PDK1: 3 phosphoinositide dependent protein kinase 1; AKT: AKT oncogene/protein kinase B; FKHR: forkhead transcriptional factor.

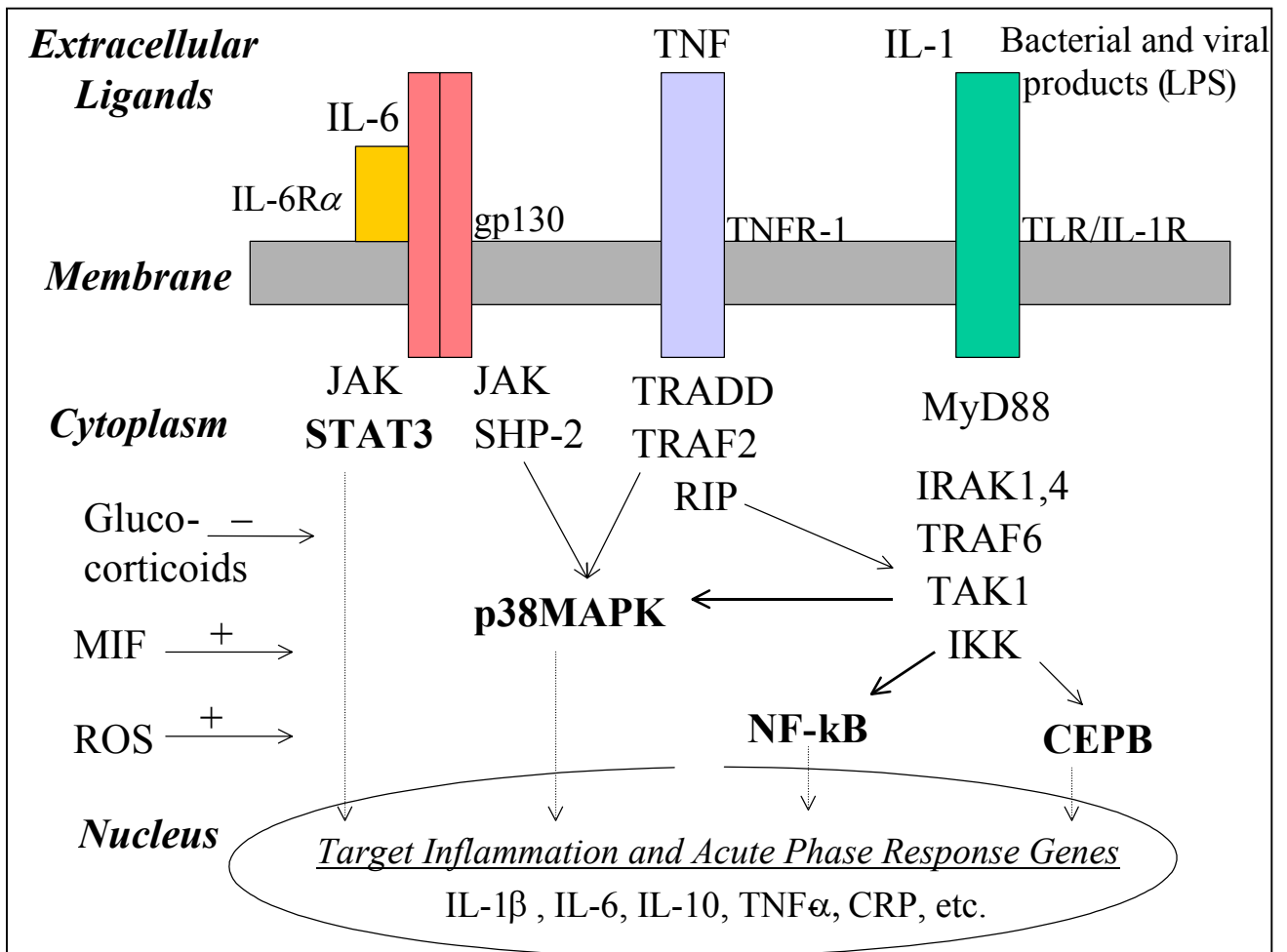


Figure 2. Regulation of inflammatory and acute-phase responses. Lipopolysaccharide (LPS)-binding to interleukin-1 (IL-1) and toll-like receptors (TLR), represented schematically at the upper right of the figure, stimulate a shared intracellular pathway involving several cytoplasmic molecules, including MyD88, IL-1R-associated kinases (IRAK1 and IRAK4), tumor necrosis factor (TNF) receptor-associated factor 6 (TRAF-6), and transforming growth factor β -activated kinase (TAK1). These in turn activate I κ B proteins by I κ B kinase complex (IKK), which allows nuclear factor kappa-B (NF- κ B) to translocate into the nucleus, where activation of various inflammation-response genes occurs. TNF receptor-1 signaling (upper middle) induces several cellular responses that overlap with lipopolysaccharide-mediated TLR signaling, including NF- κ B activation. IL-6 (upper left) activates two major intracellular signaling cascades: JAK/Stat3 (Janus kinase/signal transducer and activator of transcription-3) and MAPK (mitogen-activated protein kinase). The NF- κ B complex regulates many genes involved in cellular stress, immune, and inflammatory responses, including cell adhesion molecules, antimicrobial peptides, cytokines, and chemokines, all of which recruit monocytes, neutrophils, and other effector cells to sites of

infection or injury. NF- κ B and CCAAT enhancer-binding protein (C/EBP) act cooperatively to modulate liver-specific expression of acute phase proteins, such as C-reactive protein (CRP). Macrophage inhibitory factor (MIF), in concert with glucocorticoids and oxidative stress-induced pathways (reactive oxygen species [ROS]), controls the set point and magnitude of the immune and inflammatory response.

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