BBA - Molecular Basis of Disease 1865 (2019) 1718–1744

Contents lists available at ScienceDirect

BBA - Molecular Basis of Disease

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

Review

Genetic and epigenetic regulation of human aging and longevity☆

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ARTICLE INFO

Keywords:
APOE
FOXO3
Genome-wide association studies
Transcription
Epigenetics
Histones
Network analysis
Aging
Longevity

ABSTRACT

Here we summarize the latest data on genetic and epigenetic contributions to human aging and longevity. Whereas environmental and lifestyle factors are important at younger ages, the contribution of genetics appears more important in reaching extreme old age. Genome-wide studies have implicated ~57 gene loci in lifespan. Epigenomic changes during aging profoundly affect cellular function and stress resistance. Dysregulation of transcriptional and chromatin networks is likely a crucial component of aging. Large-scale bioinformatic analyses have revealed involvement of numerous interaction networks. As the young well-differentiated cell replicates into eventual senescence there is drift in the highly regulated chromatin marks towards an entropic middle-ground between repressed and active, such that genes that were previously inactive "leak". There is a breakdown in chromatin connectivity such that topologically associated domains and their insulators weaken, and well-defined blocks of constitutive heterochromatin give way to generalized, senescence-associated heterochromatin, foci. Together, these phenomena contribute to aging.

1. Introduction

Heritability of human longevity has been estimated as 15–40% [1–9], although recent data from 5.3 million family trees of up to 13 million members generated from 86 million public profiles on an online genealogy database obtained an estimate of 16% [10]. The heritability of longevity may, however, depend on how extreme the survival probabilities used to define longevity are [11]. At younger ages, environmental factors such as infectious disease, rare conditions and externally inflicted trauma are the main causes of death. By old age (circa 70 years), individuals have partly escaped the most common causes of death in middle age, such as cancer and cardiovascular disease. Beyond age 70 the genetic component becomes increasingly important, influencing to a variable extent most common polygenic conditions that ramp up from middle-age onwards. In very old age (> 90 years) specific longevity genes emerge from the shadows and dominate over environmental influences in lifespan determination. Recent data from the Netherlands suggested paternal transmission of longevity is stronger than maternal transmission [12].

When considering the genetic basis of longevity, it is important to note that the genome is the "hardware" we are born with. Our epigenome – chemical modifications to DNA and associated proteins – is the "software" influencing gene expression. Both are important. The epigenome is malleable and its composition can be influenced by environmental factors. Whereas there is virtually nothing one can do to favourably alter our genome, there is a keen interest in understanding factors, such as dietary components, that are able to modify our epigenome in order to establish a "healthy" transcriptome. There is also an increasing interest, and major investment by entrepreneurs, in developing drugs capable of affecting the epigenome in beneficial ways to slow, and even reverse, aging. Here we will review the current understanding of the genetic and epigenetic basis of aging and longevity with a focus on humans.

2. Molecular genetic basis of longevity

2.1. Background

The modern study of the genetics of human longevity began with candidate gene studies based on major human physiological systems and diseases. The first such study focused on the human immune system and found that several human leukocyte antigen (HLA) polymorphisms were over-represented while other polymorphisms were under-represented in long-lived Okinawans (nonagenarians and centenarians)

☆ 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.2018.08.039
Received 28 May 2018; Received in revised form 2 August 2018; Accepted 28 August 2018
Available online 01 September 2018

from the Okinawa Centenarian Study, versus younger controls [13]. Based on this initial discovery, the second such study utilized the same study design and focused on the human cardiovascular system. It found that apolipoprotein A, *APOE*, and angiotensin converting enzyme gene, *ACE*, polymorphisms differed between French and German centenarians versus younger individuals [14]. As findings from model organisms began to grow, and it became evident that evolutionarily conserved biological pathways existed that impact longevity, a pathway approach emerged. The next stage of human longevity studies therefore focused on the molecular genetic basis of longevity by testing polymorphisms in genes encoding proteins involved in pathways found in model organisms to affect lifespan. Such genes have roles in mitochondrial function, oxidative stress resistance, metabolism, DNA repair, control of the cell cycle, proteostasis, telomere shortening and other functions that might potentially affect the aging process [15–19]. Such case-control studies determine the genotype frequency of polymorphisms of potential candidate genes and look for alleles enriched in long-lived individuals. As is common for genetic studies of complex polygenic conditions, many of the initial candidate associations failed to replicate in other populations or racial groups [20–22]. Part of the problem is that a large number of genetic variants with small to moderate effects contribute to the longevity phenotype. Currently, the GenAge database lists over 300 human aging-related genes and the LongevityMap database of human genetic association studies contains over 500 entries [23]. Thus, validating a true candidate variant will require enormous statistical power [24] and thus very large cohorts of long-lived individuals, something that represents a challenge given the rarity of population prevalence of extremely old people. Nevertheless, prospects will improve as the number of centenarians is set to grow from the current 0.5 million worldwide to ~3.5 million by 2050 [25]. Besides additive genetic effects, it should be noted that non-linear epistatic interactions between variants, antagonistic pleiotropy and environmental interactions can confound attempts to replicate a finding [26].

In this section, we will start with the two most prominent candidate longevity genes to have been consistently replicated in multiple studies and later refer to some of the other candidates that have shown various degrees of promise. We will then move to genome-wide association studies (GWAS) that have the advantage of merely looking for loci showing possible linkage or association with longevity – further work then being required to identify which gene(s) and variant(s) at each locus is responsible.

2.2. TOMM40/APOE/APOC1 cluster

The apolipoprotein E gene (*APOE*) was first implicated in longevity in a 1994 study of centenarians in whom frequency of the ε4 allele was low and the ε2 allele was high [14]. Subsequent studies either confirmed or failed to replicate the finding (reviewed in: [27]). *APOE* encodes one of 3 common alleles, ε2, ε3 and ε4, produced from combinations of 2 non-synonymous SNPs, *rs7412* (Arg158Cys: ε2 [28,29]) and *rs429358* (Cys112Arg heterozygote ε3; Arg112 homozygote ε4 [30–32]). The ε4 variant (allele frequency 6–37% in different populations) provides an example of antagonistic pleiotropy in which benefit and risk depends on stage of life [33]. Antagonistic pleiotropy may be an evolutionary conserved principle of aging [34]. The ε4 allele has a reproductive and survival advantage at younger ages because of its association with higher female fertility and cognitive ability in both sexes in highly infectious equatorial environments [35,36]. In contrast, in modern post-industrial environments in which sanitation is good, the ε4 isoform is associated with elevated risk of aging-related diseases.

On average, individuals with ε4 have lower plasma apolipoprotein E and C-reactive protein (CRP), accompanied by higher plasma cholesterol, low density lipoprotein cholesterol (LDL-C), apolipoprotein B, lipoprotein(a), atherosclerosis and body mass index [37,38]. This puts ε4 carriers at increased risk of cardiovascular disease [39]. A meta-analysis found that compared with the wild-type ε3/ε3 genotype, genotypes ε3/ε4 and ε4/ε4 were associated with increased risk of coronary heart disease of 22% and 45%, respectively, whereas in Caucasians only, the ε2 allele was associated with a 16% decrease in risk [40]. The ε4 allele has long been associated with increased risk of Alzheimer's disease [41]. Besides amyloid-β plaques and tau protein tangles [42], cardiovascular risk factors may be at play in this condition, owing to microhemorrhages in cerebral blood vessels, leading to damage to surrounding neural tissue that eventually presents as Alzheimer's disease in the elderly [43].

Some researchers suggest that data indicate that rather than being a longevity gene, *APOE* is in fact a “frailty gene” [44]. Over time, greater relative attrition of carriers of the ε4 allele as a consequence of cardiovascular mortality in middle to early old age, would explain the higher prevalence of ε2 carriers in very old age [44]. Japanese aged ≥105 years exhibit extremely low frequency of *APOE-ε4* alleles [45]. A study of Canadians aged 85 years who had never been diagnosed with cardiovascular disease, dementia, diabetes, cancer or major pulmonary disease found reduced prevalence of the *APOE* ε4 allele in comparison with random midlife controls [46].

Network analysis suggested age-related changes in lipid and cholesterol maintenance, particularly in the brain, may be central to healthy aging and longevity [46]. Racial differences were apparent, there being no association of any SNP with longevity in African American women [47]. A meta-analysis of data from different racial groups found a non-significantly higher association of *ε2/ε2* compared with *ε3/ε3* genotype with longevity [48]. In a subsequent rigorous meta-analysis, the *ε2/ε2* association with longevity was significant in Europeans (OR 2.39; 95% CI 0.99, 5.76), being strongest in southern European populations [49]. Variation by ethnicity was suggested as indicating gene x environment or gene x gene interaction effects.

APOE is in the 20-kb *TOMM40* (translocase of outer mitochondrial membrane 40 gene), *APOE*, *APOC1* (apolipoprotein C1 gene) cluster – *TOMM40/APOE/APOC1*. All genes in this cluster are influenced as a group. The variant responsible for contrasting *APOE* phenotypes has been suggested to be the *G*-allele of SNP *rs2075650* located in the promoter of *TOMM40*, which is positioned upstream of *APOE* and *APOC1* [50,51]. Via moderate linkage disequilibrium with the *APOE* ε4-defining SNP *rs429358*, the *TOMM40* SNP tags the deleterious effects of the ApoE ε4 isoform [52]. The *TOMM4/APOE/APOC1* locus is, however, genetically complex, with multiple *TOMM4/APOE/APOC1* locus *cis*-elements influencing both *APOE* and *TOMM40* promoter activity according on haplotype and cell type [53]. The *G*-allele may be tagging various other underlying causal variants with different effects on CAD risk and CRP [54]. A causal relationship between CRP and cardiovascular risk has been questioned [55]. *APOE* ε4 carriers showed greater cortical thinning [56]. Increasing poly-T lengths of *TOMM40* are associated with hippocampal thinning only in subjects lacking the *APOE* ε4 allele [57]. In a nutshell, the *APOE* ε2/ε3/ε4 story remains a work in progress.

2.3. FOXO3

The forkhead/winged helix box, group O (FoxO) transcription factors are crucial component(s) of the insulin/insulin-like growth factor (IGF-1) signaling (IIS) pathway. Binding of insulin and IGF-1 to their respective receptors results in activation of adenosine monophosphate-activated protein kinase (AMPK), affecting various signaling networks involved in maintaining cell metabolism in response to a reduction in cellular energy reserves, autophagy, intracellular lipid metabolism, mitochondrial function and aging [58,59]. The IIS pathway was first implicated in longevity when mutations in the *Caenorhabditis elegans* insulin/IGF-1 receptor gene (*daf-2*) were found to double lifespan [60]. Replication of this effect in other organisms, as well as of mutation of other genes in the IIS pathway, led to the suggestion that FoxO transcription factor(s) might be crucial to longevity [61]. This was because FoxO proteins regulate expression of a vast array of genes involved in

Table 1
Loci for human longevity identified by GWAS.

Study	Cohort	n	Locus	Marker	LOD	*p*	Gene(s)
Singh, 2017 [100]	LLFS	3876	**1**p13.3	*rs201856309*	–	1.67E-09	*NBPF6*; *NBPF5*
Pilling, 2017 [98]	UKB	389,166	Chr **1**	*rs602633*	–	2.7E–08	*CLESR2 … PSRC1*
			Chr **1** (rare)	*rs146254978*	–	4.6E–08	*FPGT/TNNI3K*
Singh, 2017 [100]	LLFS	3876	**2**p22.1	*rs116083259*	–	1.17E-08	*CAPN9*; *C1ORF*
Boyden, 2010 [101]	NECS	279 sibs	**3**p24.2–22.3	*rs28150*	4.02	–	*TOP2B*
Puca, 2001 [102]	Boston	137sibs	**4**q25	*D4S1564*	3.26	–	–
Sebastiani, 2017 [97]	MCC[b]	8329	4q25	*rs28391193*	–	2.0E–07	*ELOVL6*
Deelen, 2014 [92]	MCC[a]	23,850 (6 repl)	**5**q33.3	*rs2149954*	–	1.7E-08	*EBF1*
Edwards, 2011 [103]	CAMP	263 ped	Chr **6**	*rs1409014*	4.49	–	*BMP5*
Edwards, 2013 [104]	CAMP	263 ped	**6**q25–27	*rs1247322 –rs1247363*	3.2	–	*PLG/MAP3K4*
			6q25–27	*rs16892673 –rs16892700*	3.2	–	*PARK2*
Broer, 2015 [93]	CHARGE	9793	Chr **6**	*rs2802292*	–	1.85E–10	*FOXO3*
McDaid, 2017 [96]	UKB	116,279 (5 repl)	Chr **6**	*rs10455872*	–	1.60E-08	*LPA*
Pilling, 2017 [98]	UKB	389,166	Chr **6**	*rs28383322*	–	5.3E–11	*HLA-DRB1…HLA-DQA1*
			Chr **6**	*rs55730499*	–	1.7E–18	*LPA*
			Chr **6**	*rs1627804*	–	4.0–08	*BEND3*
			Chr **6** (F)	*rs3130507*	–	2.1E–10	*PSORS1C3 …*
			Chr **6** (M)	*rs3131621*	–	3.6–08	*MICA … MICB*
Joshi, 2017 [74]	UKB, CHARGE-EU	606,059	Chr 6	*rs55730499*	–	8.67E–11	*LPA*
				rs34831921	–	4.18E–08	*HLA-DQA1/DRB1*
Edwards, 2011 [103]	CAMP	263 ped	Chr **7**	*rs517258*	3.11	–	–
Pilling, 2016 [105]	UKB	75,224	Chr **7**	*rs528161076*	–	3.40–08	*AP5Z1*
Zeng, 2016 [106]	CLHLS	4965 (4 repl)	Chr **7**	*rs2069837*	–	4.05E-08	*IL6*
Sebastiani, 2017 [97]	MCC[b]	8329 (2 repl)	Chr **7**	*rs3764814*	–	5.00–15	*USP42*
Beekman, 2013 [91]	GEHA	2118 sibs	**8**p11.21 –q13.1 (M)	*rs801100 rs4368961*	3.61	–	–
Pilling, 2017 [98]	UKB	389,166	Chr **8**	*rs7844965*	–	7.7E–09	*EPHX2*
			Chr 8 (M)	*rs13262617*	–	3.1E–08	*TOX*
Boyden, 2010 [101]	NECS	279 sibs	**9**q31.3–34.2	*rs536861*	3.89 –		*TLR4*; *DBC1*
Minster, 2015 [107]	LLFS	3140 sibs (2 repl)	**9**p24.2 p23 (F)	–	3.36	–	–
Pilling, 2016 [105]	UKB	75,224	Chr **9**	*rs75824829*	–	4.00–08	*C9orf62*
McDaid2017 [96]	UKB	116,279 (5 repl)	Chr **9**	*rs1333045*	–	1.77E-08	*CDKN2B-AS1* (ANRIL)
Pilling, 2017 [98]	UKB	389,166	Chr **9**	*rs1556516*	–	4.7E–16	*CDKN2B-AS1* (ANRIL)
Singh2017 [100]	LLFS	3876 (1 repl)	**10**p15	*rs1019025*	–	4.65–08	*KLF6*
Pilling, 2017 [98]	UKB	389,166	Chr **11** (M)	*rs61905747*	–	5.5E–09	*ZW10*
			Chr **11** (rare)	*rs139137459*	–	2.7E–08	*USP2-AS1*
Boyden, 2010 [101]	NECS	279 sibs	**12**q24.31–24.33	*rs1732462*	4.05	–	–
Sebastiani, 2017 [97]	MCC[b]	8329 (2 repl)	Chr **12**	*rs7976168*	–	4.00E-09	*TMTC2*
Pilling, 2017 [98]	UKB	389,166	Chr **12**	*rs7137828*	–	3.4E–14	*SH2B3/ATXN2*
Zeng2016 [106]	CLHLS	4965 (4 repl)	Chr **13**	*rs2440012*	–	4.89E-08	*ANKRD20A9P*
Pilling, 2017 [98]	UKB	389,166	Chr **13** (F)	13:31871514	–	4.7E–08	*B3GALTL*
			Chr **13** (F)	*rs61949650*	–	2.9E–08	(intergenic)
Edwards2011 [103]	CAMP	263	Chr **14**	*rs764602*	4.17	–	*BMP4*
Beekman, 2013 [91]	GEHA	2118 sibs	**14**q11.2	*rs10484218 –rs977870*	3.47	–	
Pilling, 2017 [98]	UKB	389,166	Chr **14**	*rs61978928*	–	2.0E–08	*PROX2*
Beekman, 2013 [91]	GEHA	2118 sibs	**15**q12–q14	*rs1871009 rs580839*		3.16	–
Joshi2016 [95]	UKB	116,425 (3 repl)	**15**q24 (M)	*rs10519203*	–	4.80–11	*CHRNA3/5*
Joshi, 2017 [74]	UKB, CHARGE-EU	606,059	Chr **15**	*rs8042849*	–	3.75E–14	*CHRNA3/5*
Pilling, 2016 [105]	UKB	75,224	Chr **15**[c]	*rs1061730*	–	3.00–08	*CHRNA3/5*
McDaid, 2017 [96]	UKB	116,279 (5 repl)	Chr **15**	*rs951266*	–	4.33–10	*CHRNA5*
Pilling, 2017 [98]	UKB	389,166	Chr **15**	*rs1317286*	–	1.2E–26	*CHRNA3*
			Chr 15	*rs17514846*	–	7.1E–10	*FURIN*
			Chr 15 (M)	*rs74011415*	–	1.4E–08	*SEMA6D*
Beekman, 2013 [91]	GEHA	2118 sibs	**17q**12–q22	*rs2429990 –rs12949910*	3.47	–	–
Tanaka, 2016 [108]	HRS	5716	Chr **18**	*rs35715456*	–	2.89E-08	*SMAD7*

(*continued on next page*)

Table 1 (*continued*)

Study	Cohort	n	Locus	Marker	LOD	*p*	Gene(s)
		(3 repl)					
Pilling, 2017 [98]	UKB	389,166	Chr 18	*rs28926173*	–	2.3E–08	*MC2R*
Deelen, 2011 [52]	LLS	2073 (2 repl)	**19q**13.32	*rs2075650*	–	3.39E-17	*TOMM40/APOE/APOC1*
Nebel2011 [89]	German	1848 (2 repl)	Chr **19**	*rs440638*	–	1.80–10	*TOMM40/APOE/APOC1*
Sebastiani, 2012 [90]	NECS	5114 l (2 repl)	19q13.32	*rs2075650*	–	1.03E-08	*TOMM40/APOE/APOC1*
Beekman, 2013 [91]	GEHA	2118 sibs	**19**p13.3 −13.11	*rs432001 –rs919333*	3.76	–	–
			19q13.11 q13.32	*rs7250748 –rs10403760*	3.57	–	*TOMM40/APOE/APOC1*
			19q13.33–q13.41 (M)	*rs1236093 –rs1661965*	4.97	–	–
Deelen, 2014 [92]	MCC[a]	23,850 (6 repl)	**19**q13.32	*rs4420638*	–	3.4E-36	*TOMM40/APOE/APOC1*
Broer, 2015 [93]	CHARGE	9793	Chr **19**	*rs2075650*	–	2.4E-10	*TOMM40/APOE/APOC1*
Fortney, 2016 [94]	MCC[d]	25,166 (4 repl)	Chr **19**	*rs2075650*	–	2.40E-13	*TOMM40/APOE/APOC1*
Joshi, 2016 [95]	UKB	116,425 (3 repl)	**19**q13 (F)	*rs429358*	–	4.20E-15	*TOMM40/APOE/APOC1*
Joshi, 2017 [74]	UKB CHARGE-EU	606,059	Chr **19**	*rs429358*	–	1.44E-27	*TOMM40/APOE/APOC1*
McDaid, 2017 [96]	UKB	116,279 (5 repl)	Chr **19**	*rs4420638*	–	4.33E-08	*TOMM40/APOE/APOC1*
Pilling, 2017 [98]	UKB	389,166	Chr **19**	*rs429358*	–	1.4E–74	*APOE/APOC1*
			Chr **19** (M)	*rs12461964*	–	8.2–09	*EGLN2…CYP2A6*
			Chr 19 (M)	*rs74444983*	–	9.1E–09	*EXOC3L2…MARK4*
Sebastiani, 2017 [97]	MCC[b]	8329 (2 repl)	Chr **19**	*rs6857*	–	2.00E-27	*TOMM40/APOE/APOC1*
			Chr **19**	*rs769449*	–	1.00E-23	*TOMM40/APOE/APOC1*
			Chr **19**	*rs59007384*	–	5.00E-15	*TOMM40/APOE/APOC1*
Pilling, 2017 [98]	UKB	389,166	Chr **20**	*rs610784*	–	1.2E–10	*C20orf187*
			Chr **20**	*rs2273500*	–	1.5E–08	*CHRNA4*

Abbreviations in column 2: CAMP, Collaborative Aging and Memory Project; CHARGE, Cohorts for Heart and Aging Research in Genomic Epidemiology Consortium; CLHLS, Chinese Longitudinal Health Longevity Survey; GEHA, Genetics of Healthy Aging in Europe; HRS, Health and Retirement Study; LLFS, Long Life Family Study; LLS, Leiden Longevity Study; MCC, multiple combined cohorts; NECS, New England Centenarian Study; UKB, UK Biobank. Other abbreviations: Sibs, number of siblings present in study; Rep, number of replication samples in stidy; Ped, pedigrees; M, found only in male subjects; F, found only in female subjects.
The respective MCC indicated: [a]Belfast Elderly Longitudinal Free-Living Aging Study, Calabria cohort, CEPH centenarian cohort, Chinese Longitudinal Healthy Longevity Surveys, Danish longevity study I and II, deCODE, Estonian Biobank, Genetics of Healthy Aging Study, German longevity study, Leiden 85-plus study, Newcastle 85+ Study, PROspective Study of Pravastatin in the Elderly at Risk, Rotterdam Study, TwinGene. [b]New England Centenarian Study, 90PLUS Cohort. [c]Southern Italian Centenarian Study, Long Life Family Study, Longevity Gene Project, New England Centenarian Study. [c]Southern Italian Centenarian Study, Long Life Family Study, Longevity Gene Project, New England Centenarian Study. [d]35 other variants were genome-wide significant; *rs1051730* deemed most significant by the authors owing to its previous link to lower smoking and lung cancer risk.
If two genes are separated by dots the SNP is intergenic.
Parts of this Table were adapted from Hook et al. [109].

energy metabolism, oxidative stress, apoptosis, G0 to G1 and G1 to S phase progression in the cell cycle, and a diversity of other metabolic processes [61], doing so by dampening the negative effects of the IIS pathway on lifespan [62–64]. Mammals have 4 FoxO proteins – FoxO1, FoxO3, FoxO4 and FoxO6 [65].

Our group was the first to show an association of SNPs in the gene *FOXO3* with longevity in a study of American men of Japanese ancestry aged ≥95 years [66]. Since that finding, over a dozen independent studies in geographically and racially divergent populations worldwide have confirmed the *FOXO3* finding, with this gene being the next best-replicated (after *APOE*) longevity gene association [67–74]. A meta-analysis in 2014 of 11 of the studies found 5 SNPs to be associated with longevity, the strongest SNP being *rs2802292* (odds ratio [OR] = 1.36; $p = 0.005$), and which was male-specific [75]. A stratified analysis in 2015 suggested that this SNP might contribute more to longevity in Asians than Europeans [76]. In 2016, male-specific association of other *FOXO3* SNPs with longevity was seen in US [77] and Chinese [78] cohorts. In 2017, a more stringent meta-analysis confined to individuals of white ethnicity found that the genetic effect of SNP *rs2802292* decreases as more extreme definitions of longevity were considered [49]. Sebastiani and coworkers argued that *FOXO3* alleles may be associated with longevity, but not extreme longevity, at least in white males. This was supported by data from a Danish study [79]. In Japanese males, however, we found that the longevity-associated (*G*) allele of SNP *rs2802292* continued to increase in frequency beyond the age of 105 years [66].

In a recent study of 110 SNPs in *FOXO3* and 5 kb of its flanking DNA, we found 41 were associated with longevity in American men of Japanese ancestry [80]. Subsequently 17 of 107 *FOXO3* SNPs were associated with longevity in 4 European and US cohorts and allelic association with elevated hippocampal expression was seen [73]. In our study of Japanese American men, nucleotide changes in 13 of the 41 SNPs disrupted the binding sites of 18 transcription factors [80]. Two other intronic SNPs strongly associated with longevity in German, French and Danish populations exhibited allele-specific binding of CCCTC-binding factor (CTCF) and serum response factor (SRF), leading to increased *FOXO3* expression of the longevity-associated allele of each in luciferase reporter gene assays involving various human tissues [81]. It was reported recently that the transcription factor heat shock factor 1 (HSF1) binds to the enhancer sequence created by the *G* allele of *rs2802292* in *FOXO3* intron 2, so explaining why, by conferring increased resilience to stress, this SNP is so strongly associated with

longevity [82].

To determine the cause(s) of mortality that *FOXO3* protects against we performed a study involving *rs2802292* and found that *FOXO3*'s association with longevity was principally via reduction in risk of mortality from coronary artery disease (CAD) [83,84], although with a larger sample other causes may also become evident. *FOXO3* SNP *rs2802292* was associated with self-rated health in individuals aged 75–87 years, this being influenced by cardiovascular disease reduction, but not mental or cognitive status [85]. No associations were found for SNPs in *APOE* and *TOMM40* in that study [85]. The effect of *FOXO3* risk alleles on cardiovascular disease earlier in life might help explain an apparent association with vascular factors and Alzheimer's disease [86]. We found recently that the protective *G*-allele of *rs2802292* was associated with negligible telomere attrition with age in our Okinawan study population, consistent with a contribution of telomere dynamics to longevity [87]. The *FOXO3* longevity-associated intronic variant, *rs2490272*, was the strongest SNP of variants in 52 genes associated positively with intelligence in a meta-analysis of GWAS findings for white individuals of European descent [88].

FOXO1 SNPs were associated with longevity in Han Chinese centenarians [71], but no association was seen in Japanese American men [66].

2.4. Genome-wide association studies

Both the *TOMM4/APOE/APOC1* locus [52,89–98] and the *FOXO3* locus [74,99] have been validated for longevity based on their loci exceeding the $p < 5 \times 10^{-8}$ threshold for genome-wide significance in large GWAS (Table 1). GWAS of case-control cohorts and sibpair genome-wide linkage studies have also identified other loci exhibiting genome-wide significance for longevity (Table 1).

SNPs at candidate gene loci shown in Table 1 included the elongation of very long chain fatty acids protein 6 gene, *ELOVL6* [97], the intergenic region between cadherin gene, *CLESR2*, and the proline and serine rich coiled coil 1 gene, *PSRC1* [98], the intergenic region between human leukocyte antigene genes, *HLA-DRB1* and *HLA-DQA1* [74,98], BEN domain-containing 3 gene, *BEND3* [98], epoxide hydrolase 2 gene, *EPHX2* [98], prospero homeobox 2 gene, *PROX2* [98], melanocortin 2 receptor (adrenocorticotropic hormone receptor) gene, *MC2R* [98], fucose-1-phosphate guanylyltransferase gene, *FPGT/TNN13K* [98], ubiquitin specific peptidase 2 (USP2) antisense RNA 1 gene, *USP2-AS1* [98], psoriasis susceptibility 1 candidate 3 (non-protein coding) gene, *PSORS1C3* [98], thymocyte selection-associated HMG box gene, *TOX* [98], beta 3-glucosyltransferase gene, *B3GALTL* (now *B3GLCT*) [98], major histocompatibility complex (MHC) class I polypeptide-related sequence A gene, *MICA*, and B gene, *MICB* [98], zeste-white 10 gene, *ZW10* [98], semaphoring 6D gene, *SEMA6D* [98], intergenic region between egl-9 family hypoxia inducible factor 2 gene, *EGLN2*, and cytochrome P450 2A6 gene, *CYP2A6* [98], exocyst complex component 3-like 2 gene, *EXOC3L2* [98], microtubule affinity-regulating kinase 4 gene, *MARK4* [98], DNA topoisomerase gene, *TOP2B* [101], toll-like receptor 4 gene, *TLR4* [101], deleted in bladder cancer 1 gene, *DBC1* [101], bone morphogenetic protein 1 and 2 genes, *BMP4* and *BMP5* [103], plasminogen, *PLG*/mitogen-activated protein kinase kinase kinase 4 gene, *MAP3K4* [104], parkin gene, *PRKN* [104], early B cell factor 1 gene, *EBF1* [92], cholinergic receptor nicotinic α3 subunit gene, *CHRNA3* [105], *CHRNA4* [98], mothers against decapentaplegic homolog 7 gene, *SMAD7* [108], interleukin-6 gene, *IL6* [106], ankyrin repeat domain 20 family member A9 pseudogene, *ANKRD20A9P* [106], lipoprotein(a) gene, *LPA* [96,98], cyclin-dependent kinase 4 inhibitor B anti-sense gene, *CDKN2B-AS* (also known as ANRIL, a long noncoding [lnc] RNA) [96,98], neuronal acetyl choline receptor subunit α-5 gene, *CHRNA5* [96], *CHRNA3* [98], the subtilisin-like proprotein convertase, furin gene, *FURIN* [98], ubiquitin-specific peptidase 42 gene, *USP42* [24], transmembrane and TPR repeat-containing protein 2 gene, *TMTC2* [24], neuroblastoma breakpoint family 5 and 6 genes, *NBPF5* and *NBPF6* [100], and capsid protein 9 gene, *CAP9* [100]. Others, that have exhibited statistical significance but were unvalidated, were glutamate ionotropic receptor kainite type subunit 2 gene, *GRIK2* [93], inflammation and DNA repair protein gene locus, *RAD50/IL13* [110], and multiple polyphosphate polyphosphatase 1 gene, *MINPP1* [111].

A meta-analysis of 4 GWAS of 2086 cases in which longevity was defined as the oldest 1% of the 1900 birth year cohort identified 37 SNPs that attained genome-wide significance ($p < 5E–8$) [97]. Instead of using as cases the limited numbers posed by obtaining very old individuals, one of the GWAS ramped up the n value of the data set enormously by taking SNPs associated with aging-related disease and adjusting these for longevity effects in order to detect SNPs associated with longevity [96]. This led to 16 genome-wide significant SNPs, 11 of which were then validated in 5 independent population cohorts [96].

A GWAS has also been conducted in offspring of long-lived parents, finding genome-wide significance for the *SMAD7* locus on chromosome 18 [108]. Of 374 SNPs within 50 kb of 6 prior longevity loci, including *TOMM4/APOE/APOC1* and *FOXO3,* only a SNP in the early B-cell factor 1 gene, *EBF1*, region approached significance [108].

Genome-wide exon sequencing of white individuals aged 98–108 years and controls did not find amino acid mutations associated with exceptional lifespan [112]. A non-significant increase in variant burden was noted for lysosomal trafficking regulator gene, *LYST*, midasin AAA ATPase 1 gene, *MDN1*, and RNA-binding motif protein, X-linked like 1 gene, *RBMXL1*. A GWAS of copy number variants (CNV) in Danish nonagenarians and centenarians found a significant increase in mortality for every 10 kb increase in average CVN length [113]. A study of 21 hypervariable short tandem repeats spread throughout the genome found 6 that were associated with longevity [114].

Using data on genes and pathways associated with five major age-related diseases from 410 GWAS, conserved pathways of aging – in particular apolipoprotein metabolism genes – were found to simultaneously influence multiple age-related diseases [115]. Shared gene ontology terms included nutrient-sensing, signaling, translation, proteostasis, stress response and genome maintenance. Balanced proteostasis is critical for maintaining functional proteins, an adequate stress response is critical for reducing reactive molecules (e.g., superoxide) and their by-products, and genome stability is essential from a mutation load perspective as well for maintaining proper tissue-specific gene regulatory control. Table 2 lists the functions of the genes that reached genome-wide significance in GWAS.

Genetic correlations between cognitive ability and longevity have been noted [138]. A meta-analysis of education-associated variants from a GWAS [139] in 3 large UK and Estonian cohorts showed that a 1 SD higher polygenic education score was associated with a 2.7% and 2.4% lower risk of mortality for mothers and fathers of the subjects; parents in the upper third of the score lived 0.55 years longer than parents of offspring in the lower third [140].

Numerous *suggestive* loci for longevity have also been found in GWAS and genome-wide linkage studies. The number of these in respective studies was as follows: 2913 [105], 44 [97], 20 [93], 12 [96], 11 [100], 9 [106], and 6 [92]. Among these were loci that attained genome-wide significance in other longevity GWAS.

A large-scale RNA-sequencing-based expression quantitative trait locus (eQTL) study of blood from German and Danish subjects of different ages up to 104 years suggested that longevity-associated biological processes such as altered metabolism are, at least in part, a driving force of longevity, not just a consequence of old age [141]. Lack of replication in different populations may be due to variation in specific population genetic structures [26,142], between-population differences in linkage disequilibrium levels between two causal SNP loci [142], involvement of different genes in similar biological processes [143], and the large influence of non-genetic factors [141]. No biological processes were independent of a nongenetic contribution [141]. Prominent in attainment of longevity might be caloric restriction (CR) and

Table 2
Functions of genes identified by longevity GWAS.

Gene symbol	Function(s) of encoded protein	Reference(s)
ANKRD20A9P	Pseudogene; no known function.	
AP5Z1	Subunit 5 of adaptor-related protein complex; facilitates vesicle-mediated intracellular sorting and trafficking of selected transmembrane cargo proteins.	[116]
ATXN2	Autoimmune disease and blood traits.	[117]
B3GALTL	β-1,3-Glucotransferase; transfers glucose to O-linked fucosylglycans on thrombospondin type-1 repeats of several proteins.	
BEND3	Associates with chromatin remodeling complexes to modulate gene expression and heterochromatin organization.	[118]
BMP4	TGF-β superfamily member; involved in embryonic development.	
BMP5	TGF-β superfamily member; embryonic and disease development; injury response.	
C9orf62	Encodes a protein of unknown function.	
C20orf187	Encodes a protein of unknown function.	
CAPN9	Digestive tract functions; is associated with gastric cancer.	
C1ORF	Encodes a protein of unknown function.	
CDKN2B-AS1	LncRNA (ANRIL) that is in a region associated with CAD, type 2 diabetes, cancer. Regulates neighboring tumor suppressor genes *CDKN2A* and *CDKNSB*.	[98,117]
	Removal of CDKN2A-expressing senescent cells rescued aging phenotypes in mice.	[119]
	Causal mechanism suggested by countering lower ANRIL expression seen in atherosclerosis.	[120]
		[121,122]
CHRNA3/5	α-3/5 neuronal nicotinic acetylcholine receptor subunit; ligand-gated ion channel; frailty gene; associated with COPD.	
CHRNA4	Encodes α-4 neuronal nicotinic acetylcholine receptor subunit;	
CYP2A6	Member of the cytochrome P450 mixed-function oxidase system; metabolism of xenobiotics; oxidation of nicotine and cotinine.	
DBC1	Negative regulator of SIRT1 and cellular stress response.	[123]
EBF1	Controls expression of key proteins required for B cell differentiation, signal transduction and function.	
EGLN2	Control of mitochondrial function, hypoxia tolerance and apoptosis in cardiac and skeletal muscle; breast cancer.	[124]
ELOVL6	Long-chain fatty acid elongase; important role in energy metabolism and insulin sensitivity.	[125]
EPHX2	Hydrolase involved in lipid metabolism.	[126]
	Polymorphisms are associated with coronary calcification.	[127]
EXOC3L2	Interacts with EXOC4 exocyst complex component; targeting exocyst vesicles to the cell membrane; upregulated by VEGF-A.	
FOXO3	Transcription factor regulating stress resistance, DNA repair, etc.	
FPGT	Fucose-1-phosphate guanylyltransferase; involved in salvage.	
	Pathway to reutilize L-fucose from glycoprotein & glycolipid turnover.	
FURIN	Widely-expressed membrane-bound protease essential for regulatory and effector T-cell function.	[128]
	Involved in atherosclerosis.	[129]
	Polymorphisms are associated with blood pressure.	[130]
HLA-DRB1	Central role in immune system by presenting peptides derived from extracellular proteins.	
HLA-DQA1	Central role in immune system by presenting peptides derived from extracellular proteins.	
IL6	Interleukin 6; pro-inflammatory cytokine and anti-inflammatory myokine; role in innate immunity.	
KLF6	Regulates macrophage inflammatory gene expression by modulating function of NFκB and PPAR-γ.	
LPA	Lipoprotein(a); phospholipid derivate; signaling; enhances coagulation; risk factor for CAD.	
LYST	Intracellular protein trafficking from secretory lysosomes.	[131]
MAP3K4	Cell differentiation and survival, apoptosis, innate immune response and oxidative stress response.	
	Noncoding variant part of a genetic signature panel for longevity.	[90]
MARK4	Regulation of microtubule dynamics; messenger in Wnt-signaling pathway; oxidative stress and inflammation.	
MC2R	Encodes the adrenocorticotropin (ACTH) receptor crucial to cortisol-mediated stress response important in aging.	[132]
	Defects lead to subclinical Cushing's syndrome, impaired blood glucose regulation and immune system dysfunction.	[133]
MDN1	Encodes midasin, a nuclear chaperone required for maturation and export of pre-60s ribosomal subunits. Is upregulated in aging brain possibly for repair and replacement of compromised macromolecules.	[134]
MICA	MHC class I polypeptide-related sequence A precursor; antibody formation; regulated by heat shock stress pathway.	
MICB	Heavily glycosylated protein; ligand for NKG2D type II receptor; binding activates cytosolic response of natural killer cells.	
NBPF5	Neuroblastoma breakpoint family member 5; members have roles in developmental and neurogenetic disorders, as well as cancers.	
NBPF6	Neuroblastoma breakpoint family member 6; members have roles in developmental and neurogenetic disorders, as well as cancers.	
PARK2	Parkin; component of multiprotein E3 ubiquitin ligase complex, which is part of the ubiquitin proteasome targeting proteins for destruction.	
PLG	Plasminogen; plasmin precursor; degrades fibrin clots.	
PROX2	Transcription factor; gene ontology suggests involvement in cardiac muscle and neuron differentiation.	[135]
PSORS1C3	Psoriasis susceptibility 1 candidate 3 (non-protein coding); is a lncRNA expressed in stem cells and cancer cell lines.	
RBMXL1	A RNA binding protein. Other such proteins have been implication in cellular senescence and neurodegeneration.	
SEMA6D	Semaphorin 6D; stop signal for dorsal root ganglion neurons.	
SH2B3	Encodes lymphocyte adaptor protein, LNK, having a key role in linking vascular and renal inflammation to hypertension.	[136]
	CAD, blood pressure, TNF-a, cell counts, colorectal cancer	[117]
SMAD7	Belongs to TGFβ superfamily; inhibitor of TGFβ receptor type I and signaling; binds other intracellular proteins; cancer cell growth.	[137]
TMTC2	Binds calcium uptake pump SERCA2B and carbohydrate chaperone calnexin; role in calcium homeostasis.	
TNNI3K	MAP kinase kinase kinase family member; cardiac remodeling.	
TOMM40/APOE/APOC1	Cognitive functions; mitochondrial structure and function; HDL and VLDL metabolism.	
TOP2B	DNA topoisomerase II β; DNA breakage and rejoining; gene regulation.	
TOX	DNA binding; T-cell development.	
TLR4	Toll-like receptor family member; intracellular signaling pathway NF-κB and inflammatory cytokine production; innate immune system activation.	
USP2-AS1	USP antisense RNA 1; is activated by MYC.	
USP42	Ubiquitin-specific peptidase 42; ubiquitin-proteosome dependent proteolysis.	
ZW10	Centromere/kinetochore protein; functions in spindle checkpoint; chromosomal segregation.	

traditional healthy dietary intake [144,145].

A number of GWAS have used mice to validate human longevity gene findings. For example, in the case of RNA binding motif protein 6 gene, *RBM6*, the mouse ortholog showed an association of lower *Rbm6* expression in the prefrontal cortex with longer lifespan, and for sulfotransferase family 1A member 1 gene, *SULT1A1*, increased expression of *Sult1a1*was seen in CR mice [96].

Finally, an 8 million-SNP GWAS involving 2,9693 elderly Dutch Europeans, with replication in other Dutch and in UK cohorts, found perceived facial age was most strongly associated with multiple SNPs in the melanocortin receptor 1 gene, *MCR1* [146].

2.5. Case-control studies for longevity gene discovery

2.5.1. Other IIS pathway genes

Disruption in model organisms of genes in the IIS pathway can lead to an up to 2-fold increase lifespan [15,109,147]. A genome-wide meta-analysis identified 7 genome-wide significant loci, including *FOXO3*, associated with circulating IGF-1 and 4 associated with IGFBP-3 concentrations [148]. An eQTL allele of the transcriptional regulator additional sex combs 2 gene, *ASXL2*, involved in development, was associated with reduced IGF-1, lower adiposity and longevity [148]. A study of tagging SNPs in other genes in the IIS pathway, besides those for FoxOs, in American men of Japanese ancestry failed to find longevity association for activating transcription factor gene, *ATF4*, E3 ubiquitin protein ligase Cbl proto-oncogene, *CBL*, cyclin-dependent kinase inhibitor 2B gene, *CDKN2B*, exonuclease 1 gene, *EXO1* and c-jun proto-oncogene (AP-1 transcription factor subunit), *JUN* [149].

SNPs in GH/IGF-1/insulin signaling-associated genes influence both longevity and height. In a Japanese study, height-increasing genetic scores based on 30 SNPs were significantly associated with height in controls and inversely with extreme lifespan in women, but not men [150]. A study involving 4 white populations found a significant association of a GH receptor exon 3 deletion variant that increases GH sensitivity with male, but not female, longevity [151]. Homozygotes were 2.5 cm taller and lived 10 years longer. In a study of American men of Japanese ancestry an inverse association of the major longevity-associated *FOXO3* SNP, *rs2802292*, with height was found [152].

2.5.2. TORC genes

The mechanistic target of rapamycin (mTOR) is a serine/threonine kinase that forms a component of mTOR complex 1 (TORC1) and TORC2 [153]. TORC1 activates ribosomal protein S6 kinase (RPS6KA1) and inhibits eukaryotic translation initiation factor 4E-binding protein 1 (EIF4EBP1), which results in increased mRNA translation and thus protein synthesis [153]. In studies of model organisms, treatment with the mTOR inhibitor rapamycin extends their lifespan [132]. The longevity effect of CR is associated with reduced TORC1 activity [15]. Manipulation of TORC pathway genes is able to modulate lifespan [109]. A case-control study in humans of TORC components failed to find any association with longevity [154]. This involved genotyping 6 tagSNPs in mTOR gene, *MTOR*, 61 in regulatory-associated protein of mTOR gene, *RPTOR*, 7 in rapamycin-insensitive companion of mTOR gene, *RICTOR*, and 5 in ribosomal protein S6 kinase A1 gene, *RPS6KA1* [154]. Genotyping of additional SNPs in *RPTOR* revealed a marginal association with longevity [155].

2.5.3. Sirtuins

This family, comprising 7 members, is involved in epigenetic modification of multiple intracellular substrates in a NAD^+-dependent manner [17]. Sirtuins respond to CR by regulating a wide range of cellular functions that include metabolic and neuronal pathways [17]. The best characterized, sirtuin 1, controls mitochondrial function by deacetylation of FoxOs, transformation-related protein 53 (Trp53), peroxisome proliferator-activated receptor gamma coactivator 1-α (PGC-1α) and others [156]. Increased sirtuin activity helps lower aging-related metabolic dysfunction and cancer risk. While sirtuins 1, 2, 6 and 7 operate in the nucleus, sirtuin 3, 4 and 5 are located in mitochondria and affect mitochondrial proteins. Genetic variation in *SIRT1* has not been associated with longevity [157–159], whereas variants in *SIRT2* [160], *SIRT3* [72,161,162], *SIRT4* [155], *SIRT5* [72,155], *SIRT6* [72,163,164] and *SIRT7* [155] have shown associations with longevity.

2.5.4. Telomere genes

Telomere attrition with age has been implicated in cell senescence and lifespan [165,166]. Most individuals do not reach a “telomeric brink” of 5 kb, denoting high risk of imminent death, during their lifetime, although this phenomenon is more likely to be seen in the oldest old [167]. A common haplotype of telomerase reverse transcriptase gene, *TERT*, has shown an association with longevity in Ashkenazi centenarians and their offspring [168]. Others found no association for *TERT* SNPs, whereas a SNP in telomerase RNA component gene, *TERC*, was associated with longevity [169]. A variant in the 3′UTR of the oligonucleotide/oligosaccharide-binding folds containing 1 gene, *OBFC1*, whose encoded protein is involved telomere maintenance, was associated with longevity [77].

2.5.5. Genes differentially expressed during CR

Among genes differentially expressed in response to CR in mice [170], most would have been responding to the CR state. Nevertheless, the possibility that the human homologs could be potential candidates for human longevity led us to perform a case-control study in American men of Japanese ancestry. Two of 12 tagging SNPs in connective tissue growth factor gene, *CTGF*, and 7 of 41 tagSNPs in epidermal growth factor gene, *EGFR*, were associated with longevity [171]. A Korean study found haplotypes of *EGFR* SNPs were associated with longevity in women [172]. Of 459 tagSNPs in 47 genes, as well as 12 other genes, association with longevity was found, after correction for multiple testing, for tagSNPs in mitogen-activated protein kinase kinase kinase 5 gene, *MAP3K5*, phosphoinositide 3-kinase regulatory subunit 1 gene, *PIK3R1*, Fms related tyrosine kinase 1 (vascular endothelial growth factor receptor) gene, *FLT1*, sirtuin 5 gene, *SIRT5*, and sirtuin 7 gene, *SIRT7* [155]. Some of the SNPs in these genes had more significant associations when assuming models of inheritance other than “minor allele recessive”, e.g., “heterozygote advantage”, which could support the concept of “antagonistic pleiotropy”.

2.5.6. Other genes

Targeted disruption of the angiotensin II type 1 receptor gene, *AGTR1*, increases mouse lifespan markedly [173]. Allelic variants of promoter SNPs were associated with lower blood pressure and extreme old age in Italian and Japanese centenarians, thus implicating *AGTR1* as a longevity gene [174]. A study in 1994 [14] examined another gene in the renin-angiotensin system, *ACE*, in which the deletion (*D*) of an insertion/deletion (I/D) polymorphism had been implicated in myocardial infarction [175] and death in subjects at elevated risk of myocardial infarction by having early onet severe essential hypertension [176]. The association of the *D* allele with longevity in French subjects [14] was then replicated in British [177], Italian [178], Portugese [179] and Uygur Chinese [180,181] centenarians, but not in many other studies. A meta-analysis found significantly higher *DD* prevalence in centenarians (OR 1.16; 95% CI 1.05–1.28; $p < 0.001$) [182]. The contrasting association could represent another example of antagonistic pleiotropy. In patients with Alzheimer's disease, those with the insertion (*I*) allele of *ACE* were less likely to develop cerebral white matter changes [183].

The minor allele of a longevity-associated SNP, *rs2149954*, at chromosome 5q33.3, identified in a GWAS [92], was associated with lower hypertension prevalence, decreased risk of myocardial infarction and heart failure, as well as increased physical functioning in long-lived individuals [184]. Genetic variation in the human bactericidal/permeability-increasing fold-containing family member 4 gene, *BPIFB4*,

impairs endothelial nitric oxide synthase activity, so reducing vasorelaxation and increasing diastolic blood pressure [185]. Under a recessive genetic model an Ile229Val polymorphism of *BPIFB4*, by modulating endothelial function and angiogenesis, was associated with longevity [186]. When overexpressed in hypertensive rats and old mice, the longevity-associated of BPIFB4 protein variant reduced blood pressure, rescued endothelial dysfunction and promoted vascular repair processes [186]. Serum BPIFB4 protein levels were higher in healthy centenarians, but lower in frail centenarians [187], as was the case for *BPIFB4* mRNA [188]. The opposite was seen for the ischemia-responding HIF-1α chemokine receptor *CXCR4* mRNA [188].

Reduction in frailty is associated with a G–395A promoter polymorphism in *KLOTHO*, a well-known longevity and aging-suppressor gene [189]. Genetic variation in *TXNRD1*, the gene encoding thioredoxin reductase, which protects against accumulation of reactive oxidants, modulates physical decline in extreme old age [190]. In other genes, variation in superoxide dismutase 3 gene, *SOD3* [72], AKT serine/threonine kinase 1 gene, *AKT1* [72] and mitochondrial DNA polymorphisms [191–195] have shown associations with longevity in various populations. A meta-analysis of multiple mitochondrial DNA association studies revealed a significant impact of Caucasian haplogroups H, J and K on longevity, type 2 diabetes, dementia and cancer [99]. Centenarians have a relatively high mitochondrial copy number, and this is evident in their F1 offspring [196]. This was likely mediated by single-stranded DNA-binding protein 4, which was highly expressed in centenarians and offspring, and was significantly associated with DNA copy number [196]. This results in adequate maintenance of energy supply.

The cholesterol ester transfer protein gene, *CETP*, whose product affects HDL metabolism, was associated with longevity in Ashkenazi Jewish and Danish [197,198], as well as Chinese [199], populations, but not in Greeks [200], American whites [20], and Italians [201]. Genetic variation in syndecan-4 gene, *SDC4*, whose encoded protein is a central mediator of cell adhesion, was associated with lipid profile and longevity [202].

Interleukin-10 modifies the inflammatory response and an *IL10* promoter polymorphism associated with elevated IL-10 production, was associated with longevity in Japanese [203], Italian [204] and Jordanian [205] men, and in both sexes in Bulgaria [206]. Recently, multiple SNPs in the major histocompatibility complex, class II, including the DQ β1 gene, *HLA-DQB1*, have shown associations with longevity at the $p = 10^{-8}$ level [207]. Interestingly, HLA genes were the first reported longevity-associated genes in humans [13]. Longevity-associated alleles in 2 SNPs were associated with plasma triglycerides and LDL:HDL ratio. A GWAS of self-rated health involving the UK Biobank found association with 13 independent loci [208]. Most prominent of these were *HLA-DQB1*, as well as *HLA-DQA1*, *HLA-DRA1* and *HLA-DDRB5*, and Kruppel-like factor 7 gene, *KLF7*. The tumor necrosis factor (TNF) superfamily of genes is located in the central class II HLA region. TNF-α is pro-inflammatory, which is opposite to IL-10 which is anti-inflammatory. *TNFA* variants are not associated with longevity. Targeting of known immune-associated loci using an immunochip identified a novel SNP in the extended region of the inflammation and DNA repair gene locus, *RAD50/IL13*, with longevity in German, French and Danish long-lived individuals (OR 1.20; 95% CI 1.12–1.28; $p = 5.4 \times 10^{-7}$) [110].

Variation in genes involved in DNA repair, such as *LMNA* [209], *WRN*, *CDKN2A* and *CDKN2B* [74,210], as well as *FOXO3* (discussed earlier), are associated with longevity. Longevity associations were reported for haplotypes of aldehyde dehydrogenase 2 gene, *ALDH2*, proprotein convertase subtilisin/kexin type 1 gene, *PCSK1*, V-yes-1 Yamaguchi sarcoma viral related oncogene homolog gene, *LYN*, and several other genes in Korean nonagenarians [172]. It is often difficult to understand or predict how genes such as these might influence longevity, since all of the pathways a gene influences may not be currently known.

Antagonistic pleiotropy may apply to the spermatogenesis associated 31 gene, *SPATA31* [211], which belongs to the core duplicon families important in hominid evolution and is one of the fastest evolving in human evolution [212]. Increased copy number likely helped in protection from UV damage when hominids became diurnal and lost body hair, but at the cost of activation of senescence pathways and DNA repair processes risking elevation in somatic mutations and cancer. While *SPATA31* overexpression causes premature senescence by interfering with aging-related transcription pathways, fewer copies are seen in Germans aged > 96 years as compared with younger individuals, consistent with a fitness benefit during the reproductive period of life, but a negative influence on lifespan [211].

An intronic variant of the solute carrier family 1, member 5 gene, *SLC1A5*, encoding the major glutamine transporter, ASCT2, influences longevity via an effect on splicing [213]. Amino acid transporter gene SNPs have also been shown to be associated with age-related physical decline and survival in the elderly, likely via TORC1 signaling [214].

Longevity associations seen for *SIRT2* involved SNPs in microRNA (miRNA) target sites in the 3′untranslated region (3′-UTR), as was also the case for dopamine receptor 2 gene, *DRD2* [160]. Disruption of miRNA binding to the 3′-UTR often alters mRNA stability and thus levels of encoded protein synthesized. A rare loss-of-function mutation in the serpin family E member 1 gene, *SERPINE1* (c.699–700dupTA), which encodes plasminogen activator inhibitor-1, was associated with longevity in an Amish community, as well as longer telomere length, lower fasting glucose and less type 2 diabetes [215]. Evidence of epistasis exists. For example, an association of fibronectin type III domain-containing 5 gene, *FDNC5*, with longevity appears to depend on the presence of the *FOXO3 rs2802292 T* allele and *APOE* ε2/ε4 [216]. A weak association was found between polymorphisms in the vitamin D receptor gene, *VDR*, and longevity, as well as health parameters, in centenarians [217].

SNP-SNP interaction analyses have been proposed recently for investigation of the genetics of human longevity [218]. Synergistic interaction by SNPsyn was applied to 3 candidate pathways – IIS, DNA repair, and pro/antioxidant – using 1058 tagSNPs in 140 genes and subjects from the Danish 1905 Birth Cohort Study. The strongest involved specific SNPs in the IGF receptor 1 gene, *IGF1R*, the tyrosine-protein phosphatase non-receptor type 1, *PTPN1* (otherwise known as the protein-tyrosine phosphatase 1B gene, *PTP1B*), DNA repair pathway gene, *TP53*, and the excision repair cross complementing gene, *ERCC*. Epistatic interactions were seen between *TP53* and pro-oxidant pathways gene *TXNRD1*, as well as between *TP53* with *ERCC2*, another gene involved in the DNA repair pathway. The growth hormone secretagogue receptor gene, *GHSR*, interacted with IIS and DNA repair partner genes, pregnancy-associated plasma protein A gene, *PAPPA*, protein tyrosone phosphatase, non-receptor type 1 gene, *PTPN1*, Parkinsonism associated deglycase gene, *PARK7*, and meiotic recombination 11 homolog gene, *MRE11A*, involved in homologous recombination, telomere length maintenance, and DNA double-strand break repair.

2.5.7. The “gerontome”

In a large systems-level analysis of the genetics of aging, and that discriminated between pro- and anti-longevity genes, it was shown that genetic links between aging and aging-related diseases appeared to be due to a small fraction of aging-related genes that tend to have a high network connectivity and that aging-related disease genes have faster molecular evolution rates [219]. Aging genes tend to be at network hubs, where, via protein-protein interactions and co-expression networks, communication takes place among different functional modules or pathways, indicating high connectivity [220] (Fig. 1). Close interactions among aging hubs may make aging subnetworks vulnerable, so contributing to aging. There were strong interactions between aging genes through biological sub-networks such that aging genes weremore likely to collaborate with one another than with background, essential, transcription factor, and housekeeping genes (Fig. 2).

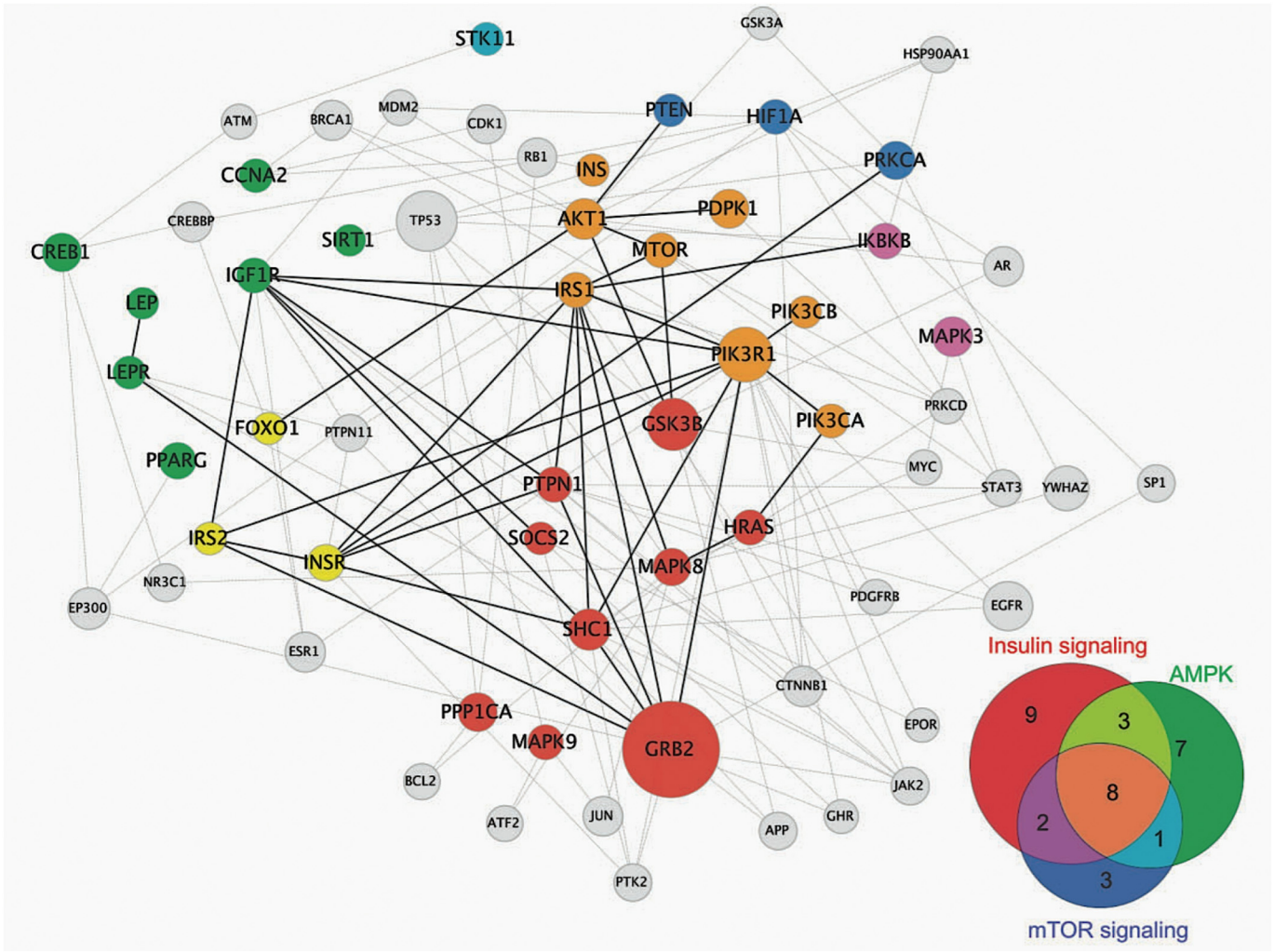

Fig. 1. Aging-related protein interaction subnetwork for three well-known aging-related pathways: insulin signaling, AMPK and mTOR signaling. (From Zhang et al. [220])

2.6. Gene neighborhoods in longevity

We have found recently that *FOXO3* is located at the hub of an early-replicating neighborhood of 46 genes with which it interacts via CTCF, a transcription factor that regulates chromatin architecture, attracting tissue-specific transcriptional activators, repressors, cohesin and RNA polymerase II [80]. The 46 neighboring genes encode proteins that, like FoxO3, are involved in various processes that contribute to cell resilience, such as autophagy, stress response, energy/nutrient sensing, cell proliferation, apoptosis and stem cell maintenance. Together they may work as a "gene factory" for healthy aging. In response to stress, we showed that *FOXO3* moved physically closer to its neighboring genes, the shift being stronger for carriers of the longevity-associated *G*-allele of *FOXO3* SNP *rs2802292* compared with homozygotes of the common, *T*, allele (Fig. 3) [80]. *FOXO3* mRNA expression in response to stress was more pronounced for *FOXO3 G*-allele carriers, as were two other genes in the cluster so far tested. These findings highlight the fact that genotype-phenotype correlations commonly reported in the study of complex traits often focus on single protein-coding genes but ignore gene neighborhoods. It has been suggested [3] that physical interactions between genes themselves might be an additional contributory factor in the omnigenic model proposed recently to explain the "missing heritability" evident from large-scale genome-wide association studies of complex polygenic traits [4]. Confirmation of this will require further research.

It would now appear that modulation of *FOXO3* activity could have an amplifier effect on genes in its neighborhood. This would complement the transcriptional effects that FoxO3 has on expression of a wide array of specific genes across the genome. Other gene clusters, such as the *TOMM4/APOE/APOC1* locus merit similar scrutiny for gene-gene interactions in complex polygenic conditions, including longevity.

2.7. Genes for healthy aging

Healthy aging appears to be a phenotype distinct from exceptional longevity. This was the finding of a whole-genome sequencing study of 1354 individuals in the UK aged 80–105 years reporting no chronic diseases, and termed the "wellderly", compared with a control group [221]. No locus reached genome-wide significance, but among the top hits were variants associated with cognitive function that were significantly over-represented, most notably in a linkage block at the MHC locus 6p22.1 ($p = 6 \times 10^{-7}$), followed by 5q31.1 containing solute carrier family 22 member 4 gene, *SLC22A4*, that affects carnitine and carnitine-related metabolite levels, then 2q36.1, containing potassium voltage-gated channel subfamily E regulatory subunit 4 gene, *KCNE4*, that has a nearby SNP affecting cognitive decline. No association could be found with well-known longevity loci in this cohort, although borderline significance with healthy aging was seen for the major longevity-associated *FOXO3* SNP *rs2802292* and there was depletion of the *APOE*-ε4 frailty allele in the "wellderly". A decreased genetic risk score

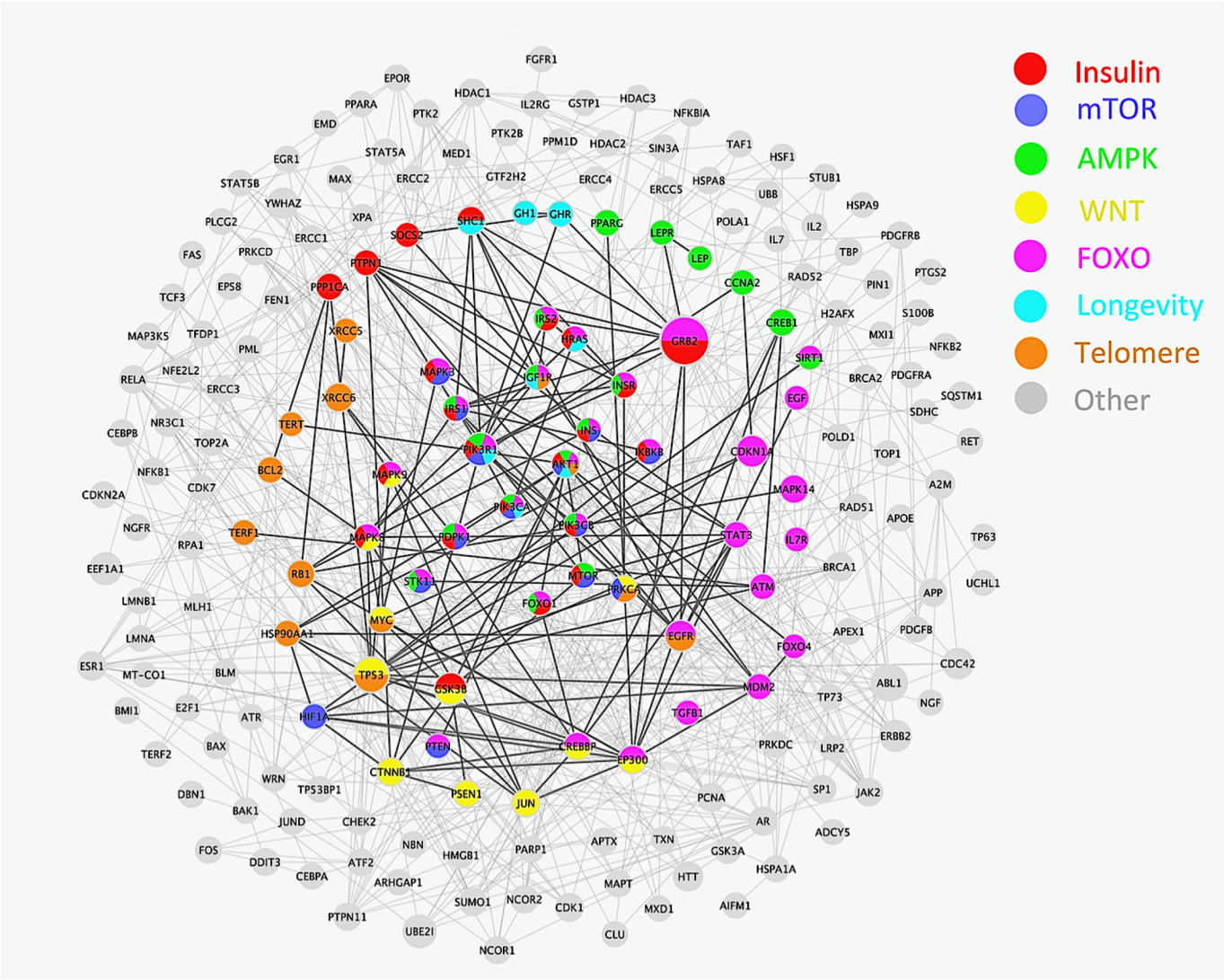

Fig. 2. The aging subnetwork consists of 192 aging genes and 561 direct interactions among these. The sizes of the nodes are proportional to their degrees of interaction in the entire protein-protein interaction network. Aging genes involved in aging-related pathways and interactions among them are both highlighted. (From Zhang et al. [220])

for Alzheimer's disease and CAD was seen, but not for type 2 diabetes or cancer. The authors suggested that healthy lifestyle might be the main driver of familial clustering of exceptional good health. This factor would help propel individuals into achieving extreme old age.

Variability in red blood cell (RBC) volumes (RBC distribution width: RDW) increases with age and is a strong predictor of mortality, incident CAD and cancer. In a study of 116,666 UK Biobank volunteers, genetic variants explained 29% of RDW individuals aged over 60 years and 33.8% of RDW in those aged < 50 years [222]. RDW was associated with 194 independent genetic signals (119 intronic), 71 implicated in autoimmune disease, body mass index, Alzheimer's disease, longevity, age at menopause, bone density, myostasis, Parkinson's disease and age-related macular degeneration. Pathway analysis showed enrichment for telomere maintenance, ribosomal RNA and apoptosis.

3. Transcriptomics

The transcriptome of centenarians differs from that of septuagenarians [223]. In centenarians 1721 genes were differentially expressed compared with septuagenarians and young people. The most statistically significant associations with biological processes were immune response, followed by cell adhesion and MHC class 1 receptor activity, transport processes, antigen processing and presentation of peptide antigen via MHC class 1, response to drug, ion transport, signal transduction, cell surface receptor linked signaling pathway, small GTPase mediated signal transduction, intracellular signaling pathway, response to wounding, presentation of endogenous peptide antigen. Response to hypoxia, apoptosis, protein transport, T cell activation and processes integral to the plasma membrane [223]. Sub-network analysis converged on 6 genes – interferon-γ gene, *IFNG* (Fig. 4) – T-cell receptor gene, *TCR*; tumor necrosis factor gene, *TNF*; SP1 transcription factor gene, *SP1*; TGF-β1 gene, *TGFB1*; and interleukin 32 gene, *IL32* – to influence B-cell lymphoma-extra large (Bcl-xL) gene, *BCL2L1*, Fas and Fas ligand, all involved in the control of apoptosis – Bcl-xL by inhibiting the intrinsic, mitochondrial pathway to apoptosis, and Fas and FasL by controlling the extrinsic pathway to apoptosis. As well as being involved in apoptosis, Bcl-xL is involved in mitochondrial damage protection [224], control of mitochondrial respiration [225], modulation of the immune response [226] and DNA repair [227], all of which are associated with healthy aging. Genes upregulated in centenarians tended to be downregulated in septuagenarians, consistent with activation of those networks in exceptional aging. In Spanish and Sardinian cohorts, *BCL2L1* mRNA expression and protein were higher in centenarians than in septuagenarians, but were similar to young

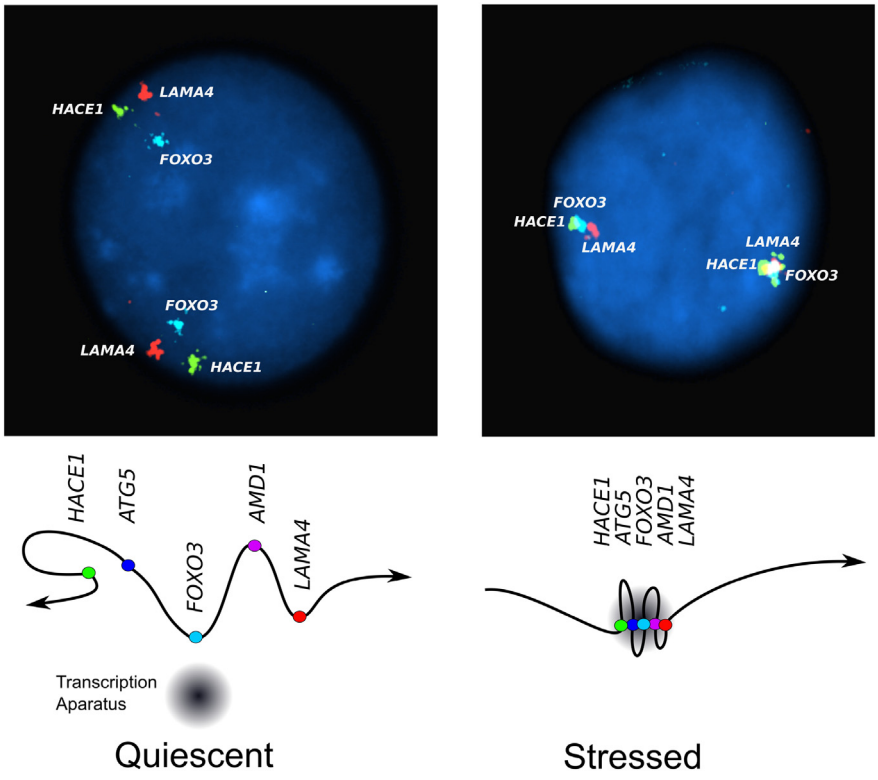

Fig. 3. The gene *FOXO3* interacts with its neighbors in a 46-gene cell resilience "gene factory" on chromosome 6q21 [80]. *Upper panel:* fluorescent in situ hybridization experiments showing, on the *left*, position of fluorescently-labeled *FOXO3* (pale blue), *HACE1* (green) and *LAMA4* (red) in quiescent lymphoblastoid cell lines; and on the *right*, change in position of the genes in cells after activation by stress, induced by serum deprivation and H_2O_2 treatment. *Lower panel:* schematics showing the effect; for simplicity only 5 of the 46 neighborhood genes are shown. The sphere denotes a presumed transcription center. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

individuals, suggesting a major role in healthy aging [223]. In support, transfection of Bcl-xL into mouse embryo fibroblasts and septuagenarian lymphocytes suppressed cell cycle inhibitors, increased cell proliferation, protected against oxidative damage, and delayed the accumulation of senescent cells. A constitutively active mutant of the *Caenorhabditis elegans BCL2L1* ortholog, *ced-9*, increased survival [223]. These findings revealed an important role for *BCL2L1* in human aging.

A transcriptomic prediction model was developed from whole-blood gene expression data for 14,983 individuals of European ancestry from 6 independent cohorts [228]. The 1497 genes differentially expressed with chronological age will be discussed in the epigenetics section below.

RNA profiles of young vs. old human muscle were able to distinguish the age of multiple tissue types [229]. Regulators of the 150 genes identified were identified by reverse genetics and pharmacological methods [230]. Rapamycin perturbed the healthy aging gene expression signature. A degree of direct coordination and a link with mTOR activity pointed to a link between a healthy neuromuscular age biomarker and a major axis of lifespan [230].

4. Epigenetics

4.1. Background

Epigenetics is the study of heritable changes in gene function that do not involve changes in the DNA sequence [231]. The expression of a gene depends not only on the specific sequences but also how it is packaged. DNA can be packaged differently in several ways: (i) DNA is firmly attached to proteins (e.g., histones) responsible for regulating the expression of genes present in this DNA. As a result, half of these proteins end up in the daughter cells after cell division. (ii) DNA can be modified (most commonly at the 5-position of cytosine [C]) and half of these modified sequences end up in the daughter cells following cell division if the hemimethylated DNA is not fully methylated by maintenance methylases following DNA synthesis. DNA modification (e.g., CpG methylation) generally leads to a change in the way the DNA is packaged. As a result, the daughter cells, unless modified in their new environment, will exhibit a similar pattern of gene expression as their mother cells.

Most genes have CpG islands in their promotors that when methylated are fully turned off. When unmethylated, the genes can be active. In the transition from one state to the other there is a cascade of events that occur that involve a host of proteins involved in modifying or maintaining a specific state of chromatin that allows differential access of the DNA to regulatory elements. We now know that the latter process involves not only specific proteins but also RNA that can serve as a "scaffold" to various regulatory proteins. Curiously, several transcription factors preferentially bind CpG methylated sequences [232].

Epigenetic regulation involves posttranslational modification of core histone proteins. This involves the acetylation, phosphorylation, methylation, phosphorylation, sumoylation, ubiquitination and citrullination of histone tails [233,234]. A "histone code" is formed. This involves various combinations of these histone modifications, which differ between organisms. The particular combination influences the pattern of recruitment of transcription factors and coactivators/cosuppressors responsible for regulation of chromatin structure and transcriptional activity of genes. Methylation and acetylation of histone tails appear to be the modifications having the most important effects on gene expression. Histone modifications affect transcriptional activity via two major mechanisms: (i) by changing the structure and conformation of chromatin; (ii) by alerting particular enzymes to recruit transcriptional activators or suppressors. This is a dynamic process. Histone modifications can be added and removed by specific enzymes that target acetyl groups on lysine residues present in the histone N-terminal tails. Addition involves histone acetyltransferases (HATs) and methyltransferases, and removal involves histone deacetylases (HDACs) and lysine demethylases [234–238] (Fig. 5). As a result, transcription of genes can be either activated or repressed.

Histone modifications affect the structure of the nucleosome, which consists of 146-base pairs of DNA wrapped around a histone octamer comprising two sets of H2A, H2B, H3 and H4 monomers [239]. Changes in nucleosome configuration affects the status of chromatin between

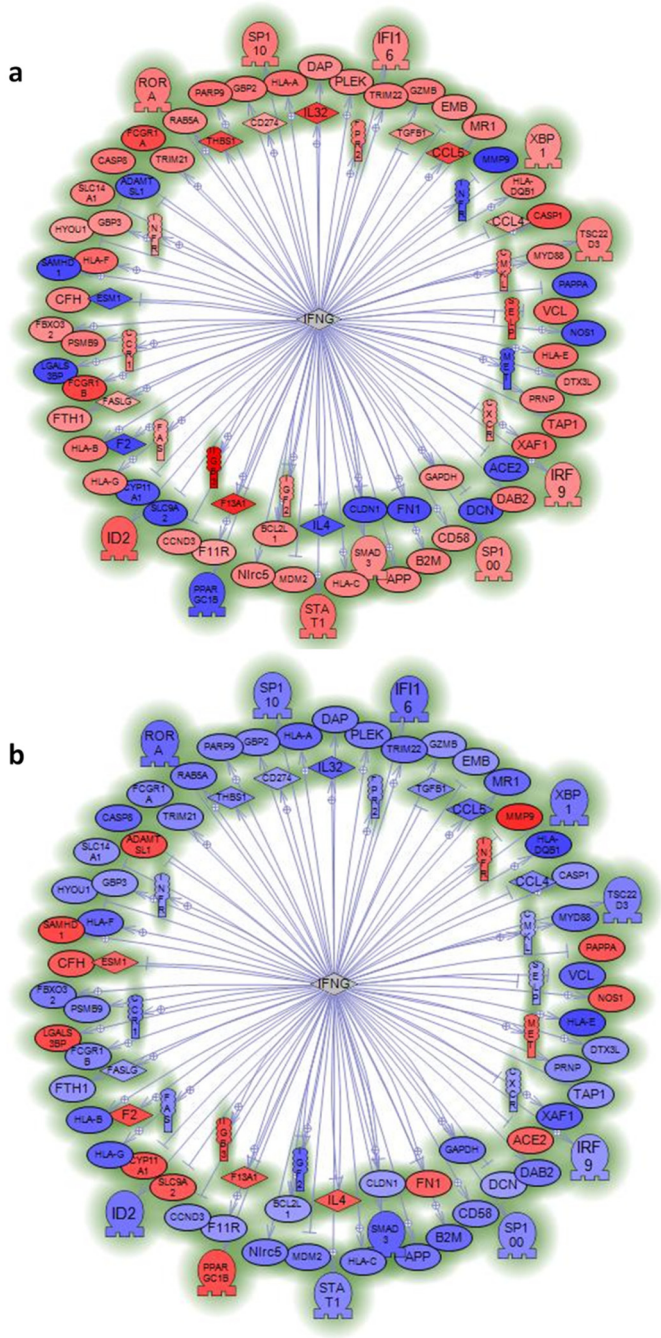

Fig. 4. Example of sub-network analysis result for one of the 6 genes that were prominent in the analysis. Shown are genes regulated by interferon-γ gene, *IFNG*, in mononuclear cells from (a) centenarians and (b) septuagenarians as compared with young individuals.
(From Borras et al. [223])

either compacted (tight-close) or relaxed (loose-open) [236]. The level of chromatin openness affects the degree of gene activity within a DNA region. When lysine residues on histones are deacetylated they have a positive charge, which attracts the negatively charged DNA strand, so resulting in a compact chromatin state that is associated with repression of transcription. On the other hand, when acetylated, the positive charge is lost. This results in an open chromatin structure, so leading to transcriptional activation.

The HDAC family is comprised of at least four classes: class I HDACs (HDAC1, HDAC2, HDAC3 and HDAC8) that are most closely related to the yeast Rpd3 HDAC; class II HDACs (HDAC4, HDAC5, HDAC6, HDAC7, HDAC9 and HDAC10) that share homology domains with the yeast Hda1 enzyme; class III HDACs that comprise sirtuins 1, 2, 3, 4, 5, 6 and 7, which are homologs of the yeast Sir2 enzyme; and lastly, HDAC11, which is the only member of class IV HDACs and is closely related to class I HDACs [238].

In addition to performing deacetylation reactions, HDACs regulate various cellular functions and gene expression by interacting with hundreds of different transcription factors [236,240].

4.2. DNA methylation and aging

DNA methylation data have been used as biomarkers of aging ("epigenetic clocks"), enabling accurate age estimates for any tissue across the lifespan [241]. DNA methylation patterns appear to be gene- and tissue-specific. Globally, DNA in leukocytes has generally been reported to be hypomethylated with age while specific CpC sites in gene promoters tend to be hypermethylated [242,243]. A method has been developed to determine biological age based on the methylation patterns of specific sites in three genes, with an average accuracy of ± 5.2 years [244]. Based on the methylation status of 353 CpGs, accuracy was then improved to an error of ± 3.6 years, with a correlation of 0.96 [245]. Of the 353 CpG sites, 193 became hypermethylated and 160 became hypomethylated with age. The genes are involved in cell death and survival, cell growth and proliferation, organismal and tissue development, and cancer. NAD^+-mediated activation of sirtuin-1 deacetylates, and thereby activates, clock-controlled genes as part of circadian expression changes [246]. In the elderly, *SIRT1* expression is elevated, possibly as a compensatory response to increased oxidative stress [247].

While monozygous twins are epigenetically indistinguishable during the early years of life, older twins exhibit differences in their overall content and genomic distribution of 5-methylcytosine DNA and histone acetylation, consistent with epigenetic drift with age [248]. Recently, a highly multiplexed mass cytometry analysis was able to show the markedly different cell-type and hematopoietic-lineage-specific chromatin modification patterns in single cells [249]. With aging, chromatin modifications exhibited a marked increase in heterogeneity between individuals and elevation in cell-to-cell variability. Twin studies revealed a genetic component of 30% in variation in chromatin marks, with 70% driven by non-heritable influences. Peripheral blood mononuclear cells of Italian semi-supercentenarians (age 105–109 years) had an 8.6-year younger epigenetic profile than expected, and their offspring (aged 50–89 years) had a 5.1 year lower epigenetic age than age-matched controls [250].

The aging cell is exposed to ROS that can increase inflammation, induce DNA damage and influence DNA methyltransferase (DMT) activity. The damage results in an increase in mutation frequency and affects the DNA methylation of nearby cytosine bases. Hydroxylation of guanine (to yield 8-hydroxy-guanine) causes a > 90% decrease in methylation of neighboring cytosine [251]. It was suggested that this process may help to explain the age-related drift in hypomethylation.

The methylation patterns are distinct in the innate and adaptive arms of the human immune system during hematopoiesis [252]. A progressive loss of CG methylation was found in developing lymphocytes and there was consistent occurrence of non-CG methylation (i.e., C hydroxymethylation) in specific cell types, such as T-cells.

There are many examples of specific genes in the innate immunity pathway that are dysregulated by aging and/or methylation. For example, differential methylation (hypo- vs. hyper-methylation) was seen in 1859 genes in rheumatoid arthritis [253].

A whole-blood gene expression meta-analysis identified 1497 genes that were differentially expressed with chronological age [228]. These genes were enriched for potentially functional CpG methylation sites in enhancer and insulator regions that were associated with both chronological age and gene expressions levels. Gene expression profiles were used to calculate "transcriptomic age" of individuals. Differences

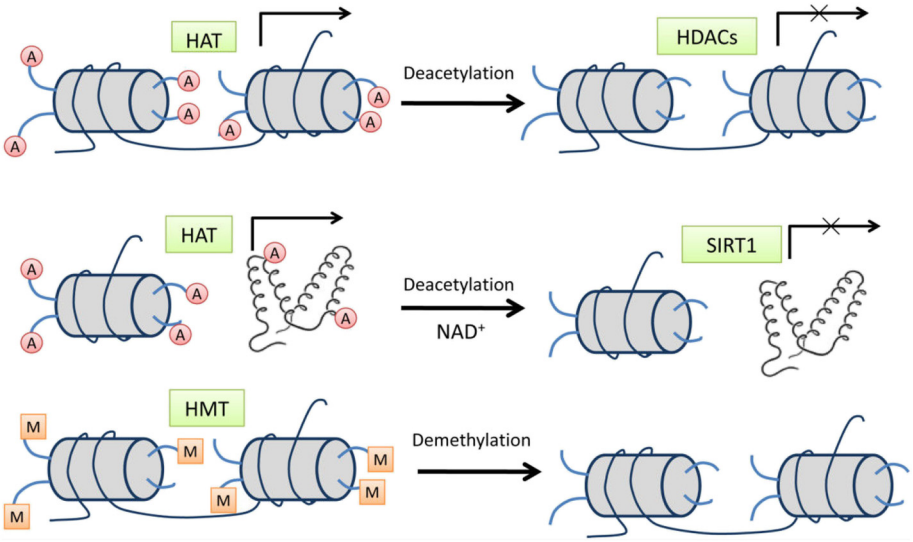

Fig. 5. Histone modification pathways.
(From Li et al. [238])

between transcriptomic and chronological age were associated with aging-related biological parameters such as blood pressure, total and HDL cholesterol levels, fasting glucose, body mass index, hand grip strength, and mini mental state test score. Transcriptomic prediction complemented epigenetic prediction of age [228]. DNA methylation profile difference between Chinese female centenarians and middle-aged controls revealed 626 differentially methylated regions, within which was enrichment of age-related disease genes [254].

4.3. Chromatin modification and aging

Histone methylation has a great impact on whether a region is active or repressed and depends on the exact location (amino acid) and degree of methylation (mono-, di, tri-). It is dynamically regulated by histone methyltransferases and histone demethylases (see review: [255]). Histone acetylation influences how the DNA will interact with histones. Fig. 6 shows the changes in chromatin state with aging [256].

Histone methylation H3K4me3 is believed to be activating to genes, while H3K27me3 is repressing to genes, and this pattern has been directly linked to lifespan regulation in mice [257], *Drosophila melanogaster* [258] and *C. elegans* [259], wherein these bivalent sites become hypomethylated with age. Life extending treatments such as CR and rapamycin suppress this hypomethylation [257]. Aging in *C. elegans* results in a global decrease in somatic H3K27me3. Treatments that increase global levels of H3K27me3 extend lifespan in *C. elegans*, but not consistently in other organisms, so is controversial.

Core histone proteins are known to diminish with age in yeast [260], nematode [261] and human [262] cells. The level of core histone variant, macroH2A, a splice variant of histone H2A, has been reported to increase with age during replicative senescence in cultured human fibroblast cells and in aged mice and primates [263]. MacroH2A is assumed to be a transcriptional repressor [264]. The sirtuin 1 ortholog, Sir2, decreases and subtelomeric locations of histone H4 lysine 16 acetylation increase, along with histone loss, with age in yeast [260]. CR and genetic models of longevity in mice result in a common transcriptional signature that includes mitochondrial energy metabolism, inflammation and ribosomal structure in multiple mouse tissues [265]. In response to CR, mice lacking Sirt3 fail to induce mitochondrial and anti-inflammatory elements of this signature, whereas the inverse of this signature is seen in response to a high fat diet, obesity and metabolic disease [265].

In aging, there is a general loss and disorganization of histones that is assumed to lead to the dysregulation of underlying genes. Evidence for this is an abnormal phasing of histones and induction of repressed genes in yeast [266]. This would suggest an abnormality or limited supply of the components that control gene regulation (i.e., promoter-recognizing proteins/transcription factors).

Age-related DNA hypermethylation has been reported to be enriched at the genomic regions carrying bivalent histone marks (i.e., both H3 K4me3 and H3 K27me3) at promoters, whereas DNA hypomethylation colocalizes with the histone modification marks H3 K9Ac, H3 K27Ac, H3 K4me1, H3 K4me2, and H3 K4me3 that are found largely in enhancer regions [267].

Global H3K27me3 levels increase with age in some organisms [268], while they decrease with age in others [261]. Identifying the locus- and cell-type-specific dynamics will be critical to obtain a better understanding of factors that influence lifespan.

Fig. 7 highlights the physiological processes affected by epistatic changes to the genome during aging [256].

4.4. Epigenetics and longevity

Caloric restriction of 30% extends lifespan of a small primate model by 50% [269]. Aging-related diseases were decreased, white matter was preserved, and although there was a claimed decrease in gray matter (neuronal cell bodies) in the cerebrum, there was no change in cognitive performance, behavior and motor function. With aging, there is a marked drift in both gains and losses of DNA methylation that correlates with lifespan and is attenuated by CR [270]. CR is accompanied by increased HDAC activity. This suggests that in response to nutritional stress global deacetylation may serve to protect cells and thereby influence the aging processes [271]. Two key genes implicated in aging – the $p16^{INK4a}$ gene, *CDKN2A*, and the human telomerase reverse transcriptase gene, *TERT* – are upregulated during CR. This is accompanied by enrichment in HDAC1 on the promoters of each, which contributes to longevity [238,271]. During senescence, methyl-CpG-binding protein hypermethylates the *SIRT1* promoter and causes histone modification, leading to dysfunction of endothelial progenitor cells, increased apoptosis and reduced angiogenesis [272]. The importance of HDACs in CR point to the potential of drugs or other strategies for modulation of cell epigenetics in order to slow aging and treat diseases of aging.

Sirtuin 1 has an important impact on aging and extension of lifespan in response to CR [17,273,274]. Sirtuin 1 activity is tied to metabolic

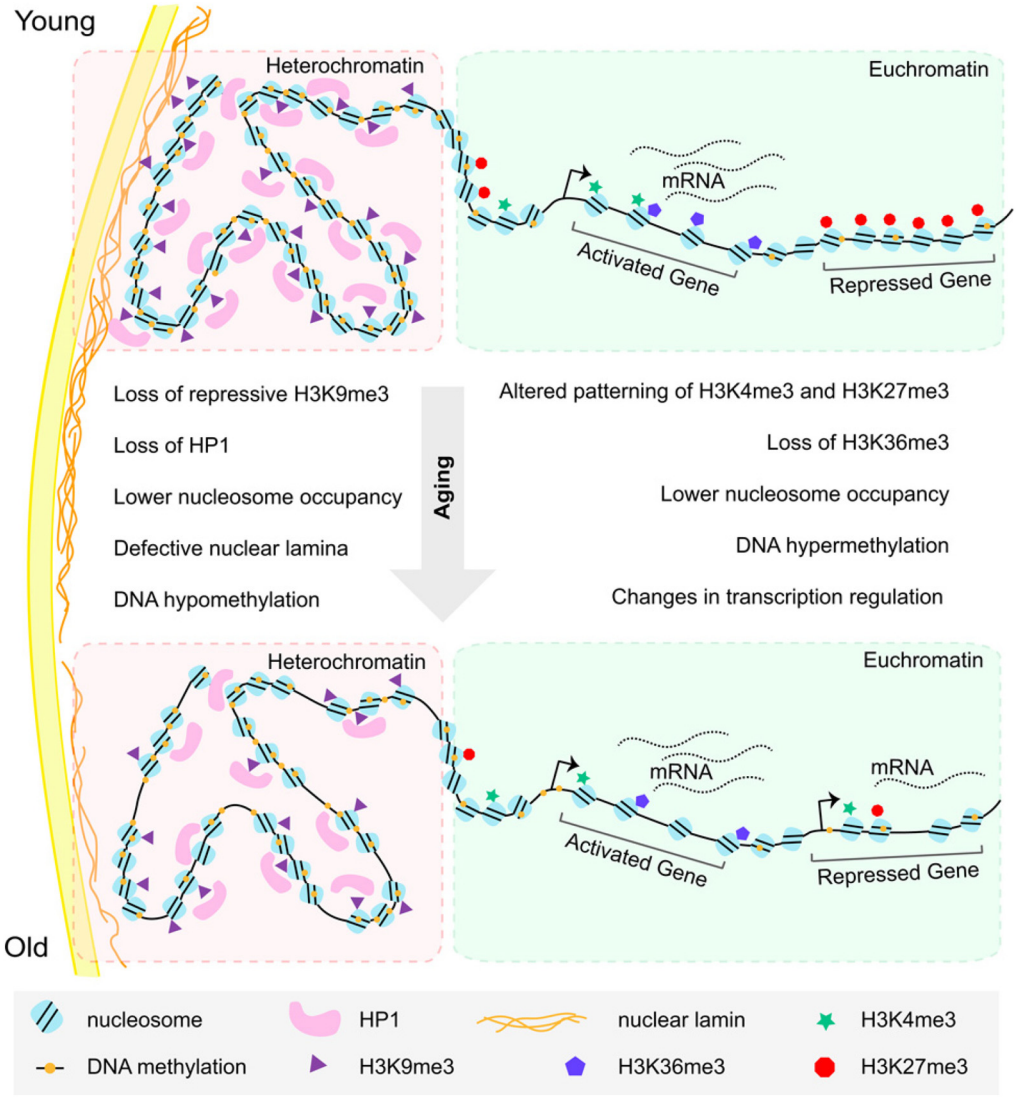

Fig. 6. The changes in chromatin states with aging. Increased cellular senescence results in a loss of heterochromatin caused by the factors depicted in the diagram. (From Booth and Brunet [256])

activity of cells by its dependence on intracellular NAD/NADH ratio, which reflects oxygen consumption, respiratory chain activity and metabolic rate. Histone acetylation is associated with an open chromatin status leading to gene activation. In contrast, histone methylation has differential effects on the binding of various proteins to histones, leading to either activation or silencing of gene expression [235] (Fig. 8). Lysine residues on histones can be mono-, di- or trimethylated, and either activation or repression is dependent upon the particular lysine residue that is modified [275,276]. Such histone modifications modulate *CDNK2A* and *TERT* expression, so affecting their expression and thus aging and longevity of human cells [238].

During normal aging, changes in gene expression and epigenetic modification occur in a tissue-specific manner. In mammals, 80% of all CpG sites are methylated [277]. Clusters of CpG dinucleotides (CpG islands) are often located near transcription start sites (TSS) of genes [278]. Most CpG islands are normally unmethylated, but during healthy aging of tissues methylation changes occur in a small subset of genes. Such age-related methylated genes have been seen in human whole blood [279–281] and can be used as a biomarker of biological (epigenetic) age [244,280,282]. DNA methylations seems to largely reflect the passage of chronological time, being inferior to a frailty index composed of 34 health items as a predictor of mortality [283]. The epigenetic clock is based on the 353 specific CpG sites spanning the genome [245,284,285].

Erosion of highly organized methylation patterns ("methylation drift") is negatively correlated with lifespan and is strongly conserved across species [270]. Chronic inflammation, which shortens lifespan, accelerates methylation drift [286]. CR delays aging-related methylation drift in mouse, rhesus monkey and human blood cells and other tissues, and results in a significantly younger "methylation age" [270]. The rate of drift correlated with lifespan. Thus, methylation drift is an excellent biomarker of aging and lifespan. Since methylation drift correlates with changes in gene expression it is most probably a mediator of age-related functional decline and disease. In support, the aging-associated increase in hypomethylation at super-enhancers of highly expressed genes crucial for liver function in ad libitum fed mice was suppressed in CR and Ames dwarf mice, with methylation changes occurring more selectively, but less specifically, in rapamycin-treated mice [257]. Hypermethylation was enriched at CpG islands marked with bivalent activating and repressing histone modifications and resembled hypermethylation seen in liver cancer. Genome-wide methylation profiling in nonagenarians identified 19 mortality-associated CpG sites that mapped to genes whose functions were clustered around the nuclear factor κB complex, indicating an important role for this complex in human longevity [287].

During aging, dynamic changes in DNA methylation in the brain

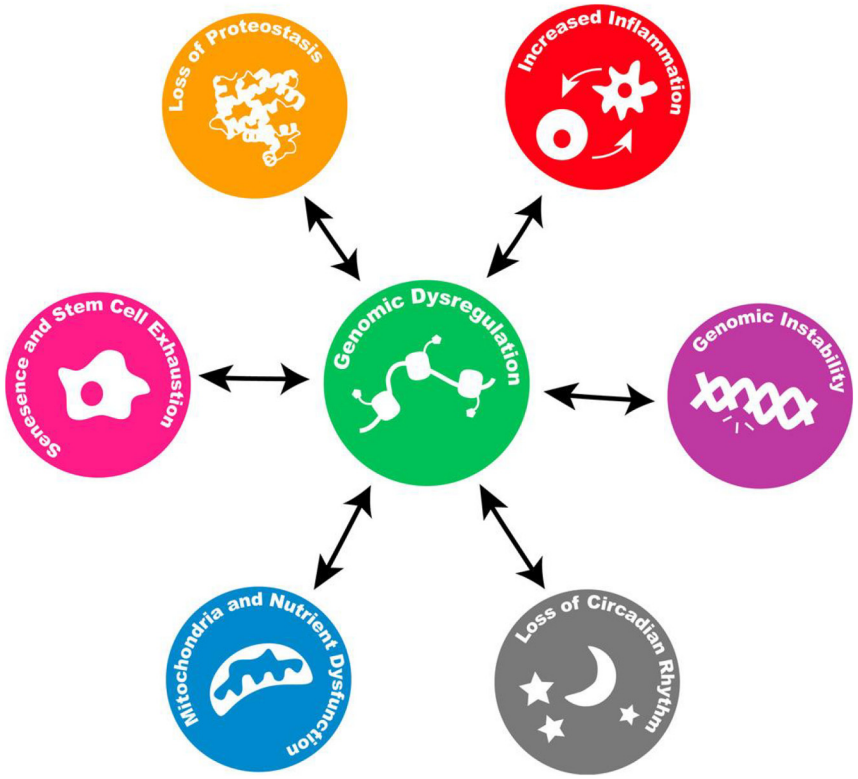

Fig. 7. Epigenomic changes result in dysregulation of gene expression in aging.
(From Booth and Brunet [256])

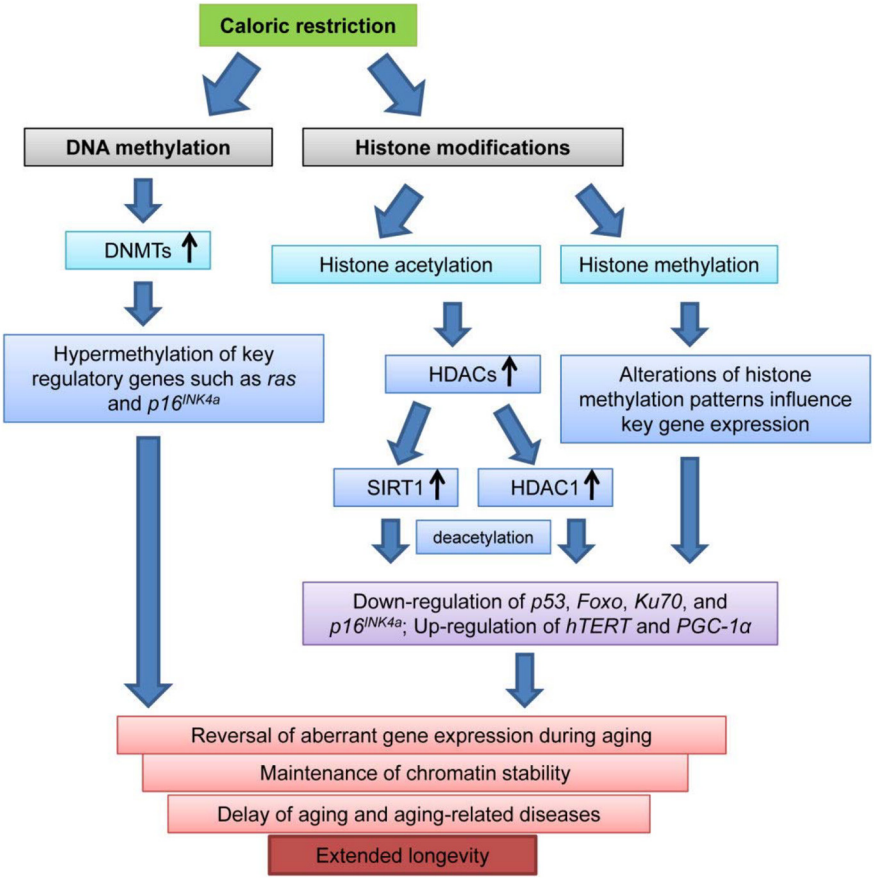

Fig. 8. Caloric restriction regulates epigenetic processes by DNA methylation and histone modification. Via the pathways shown, this helps increase lifespan.
(From: Li et al. [238])

include global hypomethylation [288–291] and site-specific hypermethylation predominantly in promoter regions [292,293]. Many of the genes hypermethylated in the aged brain are involved in neurodevelopment [294,295]. Most hypermethylation correlates with gene silencing [296]. Transcriptional repression rather than induction is seen in the cerebral cortex with aging [292]. The global hypomethylation of the aging brain is associated with decrease in DMT activity [297]. In cortices from Alzheimer's patients 5-methyl cytosine is reduced [298]. Such a reduction correlates with increased neurofibrillary tangle formation [298]. Diminished capacity for re-establishment of normal methylation pattern after DNA demethylation likely affects long-term neuronal survival and degeneration with age [299]. Potential interactions of DMTs with histone modifications could further contribute to the regulation of neuronal function and survival during aging.

Certain regions of the genome are imprinted differently between mother and father, via chromatin modifications that include DNA methylation [300,301]. While it was assumed that all marks were erased during these phases, some methylation marks are not fully erased, and persist. There is epidemiological evidence for intergenerational and transgenerational inheritance of longevity and lifespan-limiting conditions in human populations [302]. Long-lived individuals exhibited a young epigenetic profile compared with their chronological age in the Sydney Centenarian Study [303]. Unique DNA methylation patterns and low overall variability in DNA methylation was observed in high life expectancy region of Costa Rica [304].

Using RNA-seq data sets for 21 somatic cell types and tissues whose cellular turnover (lifespan) ranged from 2 days (monocytes) to lifetime (neurons), the gene expression profile of neurons showed reduced protein metabolism, consistent with survival and CR [305]. A gene expression signature of turnover was negatively correlated with the energetically high-cost cell cycle and factors supporting genome stability. These are risk factors for aging-associated pathologies. Expression of the tumor-suppressor p53 gene (*TP53*) was 5–30 times lower than in other cells and tissues. The reduced p53 expression in neurones was associated with reduced cell-cycle related proteins. Low p53 expression may contribute to the exceptional lifespan of low-turnover cells and tissues such as neurons, heart muscle and skeletal muscle, and perhaps human longevity.

4.5. Chromatin modification and cell compartmentalization

Heterochromatin is present in the cell in several forms. Constitutive heterochromatin is highly condensed, is composed of highly repetitive sequences. It is found primarily adjacent to chromosome centromeres and positioned near the nuclear membrane during interphase. In contrast, facultative heterochromatin is less condensed, is capable of transitioning between condensed and decondensed states, generally consists of condensed domains interposed with euchromatin and these condensed regions, too, are near the nuclear periphery. The inactive X chromosome in females is an example of facultative heterochromatin, most of the genes being transcriptionally inactive. Most chromosomes comprise combinations of heterochromatin and euchromatin.

Histone modification can act to silence transcription via the formation of facultative heterochromatin (i.e., H3K9me3 and H4K20me2) and to regulate genome stability (involving H3K56ac and H3K14ac). The patterns and changes in histone modification are highly tissue- and gene-specific [306]. Active histone modification H3K4me3 (a mark of promoter accessibility) occurs during aging and in cellular senescence [261].

Lamins and their associated proteins help to form the nuclear lamina which maintains the structural integrity of the nucleus, organizes chromatin, facilitates nuclear assembly/disassembly during mitosis, and acts as a scaffold for DNA repair [307]. Chromatin that is in close proximity to the nuclear lamina, is largely heterochromatic, and is characterized by low gene density, a repressive chromatin configuration, and is flanked by insulator protein (CTCF) binding sites [308]. When mouse embryonic stem cells are induced to differentiate into either astrocytes or adipocytes, many genes that are normally present at the nuclear periphery locate to the nuclear interior where they are primed for expression at a later differentiation state [309,310]. This transition relies on histone methyltransferases and deacetylases [311].

There is a general loss and redistribution of heterochromatin in senescent cells [312]. This leads to cellular dysfunction with age. In the senescent cell > 30% of the chromatin is associated with senescence-associated heterochromatin foci (SAHF), which are regions of highly condensed chromatin associated with heterochromatic histone modifications (H3K4me3 and H3K27me3), heterochromatic proteins, histone variant macroH2A, high-mobility group A (HMGA) proteins and are late replicating regions in the genome [313]. The latter are generally localized over lamin-associated domains. Breakdown of the nuclear lamina is believed to cause a loss of heterochromatin organization, in which there is a transposition of euchromatin, facultative heterochromatin (fHC), and constitutive heterochromatin (cHC), with cHC moving away from the nuclear lamin and to the center of chromosomal territories [313]. While most mutations cause a variety of autosomal dominant disorders, specific mutations in the lamin A gene, *LMA*, are known to cause the premature aging syndrome Hutchinson-Gilford progeria syndrome (HGPS) [314], in which a point mutation in a cryptic splice site leads to a truncated protein [315]. The same molecular mechanism responsible for HGPS is also active in healthy cells [315]. Age-related changes in histone modification and increased DNA damage have been attributed to sporadic use of this cryptic splice site as inhibition of this site reversed the associated nuclear defects [315].

By high-throughput conformation capture (Hi-C), age-associated differences were demonstrated in local chromatin connectivity between embryonic stem cells, somatic cells, and senescent cells, suggesting that senescence is an endpoint of the continuous nuclear remodeling process during differentiation [316]. With age-related breakdown of the nuclear lamin there was a loss of local interactions within topologically-associated domains (TADs) and an increase in distant interactions between TADs in the senescent state, thus supporting the premise that senescence is associated with a change in physical chromatin compaction. Neighboring genes that were transcriptionally isolated from one another could become co-regulated. It was also found that the regions of the genome that changed the most were the least accessible and were high in AT content. These characteristics are descriptive of “satellite DNA” that is highly repetitive and contains a high concentrations of centromeric constitutive heterochromatin [317]. Fig. 9 depicts changes that occur with cell senescence.

5. Non-coding RNA and aging

Only 1.5–1.8% of the mammalian genome is transcribed to yield proteins. The rest is transcribed into noncoding RNAs (ncRNAs) that mostly include small (20–30 nt sncRNAs) and long (> 200 nt lncRNAs) [318,319]. Noncoding RNAs represent a vast pool in the mammalian genome that may provide some of the missing links in the aging process [320].

SncRNAs are comprised mainly of inhibitory RNAs such as microRNAs (miRNAs), small inhibitory RNAs (siRNAs) and piwi-interesting RNAs (piRNAs) involved mainly in post-transcriptional gene regulation, mediated by mRNA degradation or disruption of translation. These have been studied in aging [321–325]. PCR arrays of serum samples from Baltimore Longitudinal Study of Aging subjects identified multiple differentially expressed miRNAs, including 6 miRNAs that correlated with subsequent longevity [326]. Five of these miRNAs targeted 24 aging-associated mRNAs which included *PARP1*, *IGF1R* and *IGF2R* mRNAs.

LncRNAs are transcribed from the intergenic and intronic regions of the mammalian genome [319,327,328]. While the transcriptional regulatory sequences of lncRNAs are evolutionarily conserved, many lncRNAs are species- (including primate-) specific. Just as for mRNA,

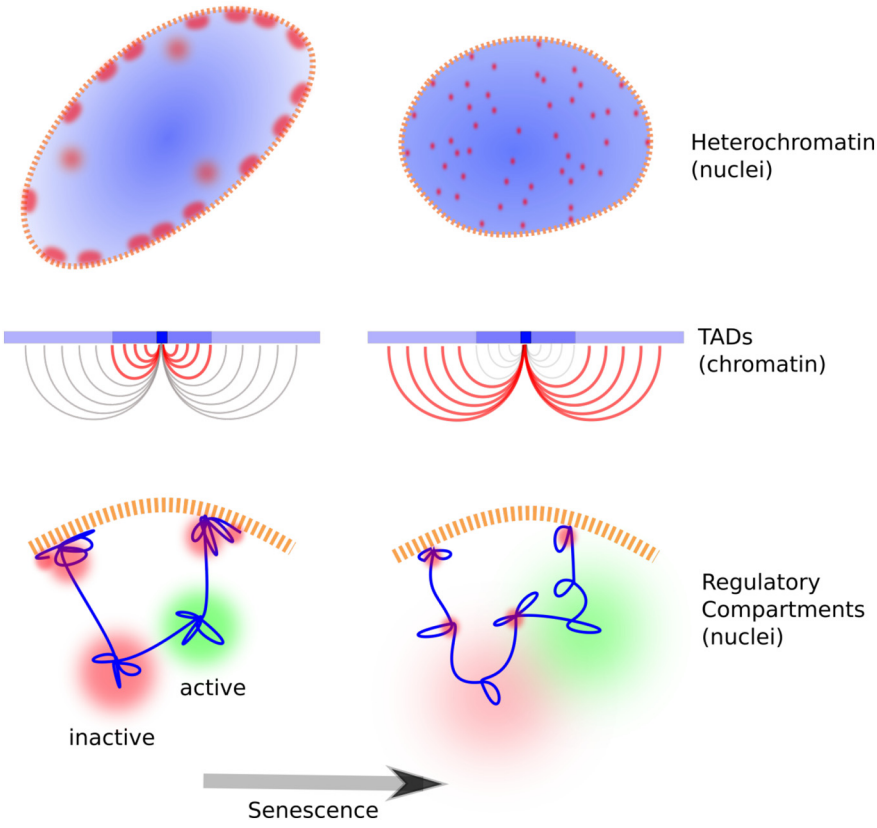

Fig. 9. Breakdown of the nuclear lamina, heterochromatin, and chromatin connections in senescence. With senescence comes a dissolution of the tight control of gene regulation as the inactive chromatin becomes dissociated from the nuclear envelope, topological-associated domains (TADs) lose neighboring connections in exchange for long-range interaction, and the distinction between active and inactive chromatin domains becomes blurred.

lncRNAs are transcribed by RNA polymerase II, then introns are removed, 5'methyl-capping takes place, and poly-adenylation occurs. They are characterized by well-defined transcriptional landmarks (histone H3-lysine 4 (H3K4) and H3K36 tri-methylation, H3K9 acetylation and CpG DNA methylation), and are regulated by common transcription factors such as p53, Oct and Nanog [328–330]. Based on their genomic location, orientation and mode of transcription, lncRNAs are arbitrarily classified further into sense, antisense, bi-directional, promoter-associated, enhancer-associated, pseudogene-associated, telomere-associated, circular and repeat-rich lncRNAs in a nonexclusive manner [319,327,331,332]. Most lncRNAs exhibit specific subcellular, cell, tissue and developmental expression patterns in mammals, which supports them having important biological functions such as development and differentiation, cell survival, cell proliferation and apoptosis, dosage compensation and gene imprinting, reprogramming of differentiated cells and maintenance of stem cells [320].

Most of the characterized lncRNAs are nuclear localized and act as enhancer RNAs (eRNAs), chromatin modifiers via recruitment of various DMTs, and histone modifiers via polycomb repressive complexes or histone methyltransferases [320]. Many lncRNAs affect key cellular processes such as proliferation, differentiation, quiescence, senescence, stress and immune response, and many other cellular functions related to aging [333].

A list of lncRNAs involved in regulation of cellular senescence and aging has been compiled [320]. Some are antisense transcripts complementary to mRNA transcripts of the same gene [320]. Among these are lncRNAs differentially expressed in senescent cells [334] and that suppress mRNA expression [320]. Other lncRNAs are encoded by pseudogenes and act to negatively regulate the expression levels of the corresponding mRNA for cell adhesion molecules and translation machinery components in senescent cells. These effects could affect cell morphology, growth and division, as well as expression of various senescence-associated proteins, so contributing to cellular senescence and aging [320]. Yet other lncRNAs are encoded in intergenic DNA and affect a multitude of different intracellular processes, some of which may contribute to senescence and aging [320]. A class of heterogeneous 5′-UUAGGG-3′ repeat-containing lncRNAs – telomere repeat containing RNA (TERRA) – is partly associated with telomeric heterochromatin [335–337]. When strongly upregulated, TERRA can promote telomere dysfunction such as shortening, decreased stability and heterochromatin formation [320].

Genetic variants in noncoding RNAs have the potential to differentially influence aging processes and lifespan. The lncRNA ANRIL, was implicated in longevity in a GWAS [96]. Understanding genetic variants in the noncoding genome is a current challenge. Constrained regions in the noncoding genome associate with the most essential genes and are enriched for pathogenic variants [338].

The immune system changes over time, increasing pro-inflammatory activity by innate immune cells such as monocytes and macrophages, and decreasing the immune response [339]. A progressive change in expression of 69 non-coding RNAs (56 microRNAs and 13 snoRNAs) is seen with chronological age [340]. The age-related miRNAs were found to regulate genes involved in immune, cell cycle and cancer-related pathways.

A number of miRNAs have been reported to have increased expression with age in mouse [341] and rat [342] livers. Up-regulated miRNA targets are associated with detoxification activity and regeneration capacity – functions known to decline in old liver, consistent with the negative regulatory roles of miRNAs [341]. By measuring expression patterns in mouse liver following CR it was found that: (i) the expression of miRNAs, lncRNAs and transposable elements were largely repressed; (ii) the protein-coding mRNAs that demonstrated increased expression in CR are highly targeted by miRNAs; and (iii) the miRNA-targeting sites were enriched for genes having chromatin-related functions. One such gene is chromodomain helicase DNA binding protein 1 gene, *Chd1,* which is instrumental in chromatin remodeling [343].

6. Longevity gene networks

To understand the genetic and epigenetic landscape of human aging a meta-analysis was performed of 6600 human longevity genes from 35 datasets comprising 8 curated aging data sets (1154 genes), 10 age-related diseases (1207 genes), 4 gene expression sets (2130 genes), and 13 methylation sets (3498 genes) [344]. From this, biological relationships between aging-associated genes were investigated by producing a protein interaction network and characterizing network neighborhoods. Most genes only appeared in a single category, whereas 1050 were associated with two, 159 with three, and 7 with all four categories. Those 7 were *APOE*, chaperonin containing TCP1 subunit 7 gene, *CCT7*, erb-b2 receptor tyrosine kinase 1 gene, *ERBB2*, protein kinase C alpha gene, *PRKCA*, Ras association domain family member 1 gene, *RASSF1*, sterol regulatory element binding transcription factor 1 gene, *SREBF1*, and tumor necrosis factor gene, *TNF*. The TNF receptor family member ectodysplasmin A receptor (EDAR) associated death domain gene, *EDARADD*, and lymphocyte activating 3 gene, *LAG3*, exhibited the strongest evidence for aging-associated DNA methylation changes. Of the 6600 aging-associated genes, 5949 had at least one interaction. There were 1079 human aging clusters in the combined interaction network. The interaction network provided an additional layer for linking proteomic and genomic data. On the basis of "guilt by association", a previously unsuspected gene may be a candidate if its encoded protein is found to physically interact with a protein known to be involved in the condition or pathway. Clusters with a strong aging association included one containing mTOR signaling pathway members, and one in which Werner syndrome RecQ like helicase gene, *WRN*, was one of 16 members. Another lacked genes associated previously with aging, but linked 8 genes differentially methylated with age, and 7 differentially expressed in response to CR.

7. Potential anti-aging interventions

Because CR delays aging and ameliorates risk of aging-related diseases, but adherence in human populations is burdensome, attempts have been made to identify natural or synthetic compounds that mimic the effects of CR [238]. "Epigenetic diets" that favourably influence the epigenetic profile of individuals have been described, together with natural compounds able to mediate effects of such diets [345]. Prominent among these is resveratrol, a sirtuin 1 activator, able to promote healthy aging and increase longevity [346–354]. Others include spermidine, the antidiabetic drug metformin, selenium, synthetic sirtuin-activating compounds such as SRT1720 and SRT2104, senolytics (e.g., dasatinib plus quercetin), and the NAD^+ booster nicotinamide mononucleotide. Dietary components such as green tea, broccoli sprouts and soybeans, and the bioactive compounds extracted from these diets have received extensive attention due to their ability to favourably alter the epigenetic landscape in cancer cells [355–358]. Long-term consumption of epigenetic diets may alter chromatin profiles, slow aging and reduce risk of degenerative diseases of aging such as cancer, cardiovascular disease, type 2 diabetes and neurodegenerative disorders [359–366], suggesting that these bioactive diets may affect aging processes by altering chromatin profiles that also occur in CR [367]. Global gene expression profiling methods have been developed to identify CR mimetics able to delay aging [368].

A potent specific thiazoquin(az)oli(one)e CD38 inhibitor, 78C, reverses age-related NAD^+ decline and improves various aging-related physiological and metabolic parameters [369]. The elevation in NAD^+ led to activation of pro-longevity and health-span-related factors such as sirtiuns, AMPK and PPARs, and inhibition of pathways such as mTOR-S6K and ERK, having a negative impact on health span.

8. Future directions

Despite the extensive findings described in this review, contrary to many complex, age-related diseases, consensus on the ultimate set of multi-biomarker aging or lifespan-related phenotypes for genetic and genomic studies has not yet been reached [370]. Awareness is needed of racial differences, sex-specificity of longevity associations, variation in results depending on the definition used for longevity [11], choice of controls, such as whether to use a random population sample or individuals who have died before a certain age [49]. The fact that most studies of human longevity involve long-lived cases and younger controls, has resulted in risk of obtaining false positive or false-negative findings from population stratification artifact and cohort effects, among other epidemiological biases. Large cohort studies with prospectively collected data are optimal since cases and controls come from similar birth cohorts, but such studies are expensive and few in number because they require decades-long follow-up and large biorepositories for the study of the mechanisms of aging and aging-related phenotypes.

There is an interplay between genetic and behavioral risks. Individuals aged ≥75 years with multiple adverse alleles (such as those involving *TOMM40/APOE/APOC1*, insulin-degrading enzyme gene, *IDE*, and PI3K catalytic subunit β gene, *PI3KCB*) had a 62% higher mortality rate than those with none, whereas people with a low-risk behavioral profile had a 65% lower mortality rate than those with a high-risk behavioral profile [371]. A challenge will be interpretation of vast volumes of genetic data that will continue to emerge [26].

More research is needed on interventions able to forestall the "telomere brink", given the opposing association of short leukocyte telomere length (LTL) and alleles associated with LTL with increase coronary risk, and long LTL being associated with increased cancer risk [167,372].

Epigenetic factors include environmental influences and lifestyle choices, but also the microbiome [373]. The latter in particular merits further research. Dysregulation of transcriptional and chromatin networks is likely a crucial component of aging [256]. Epigenomic changes during aging profoundly affect cellular function and stress resistance [256]. Further work aimed at understanding age-dependent epigenomic changes should lead to key insights into the aging process and development of means of delaying or even reversing the changes and countering age-related diseases.

Transparency document

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

Acknowledgements

We thank the National Heart, Lung, and Blood Institute, the National Institute on Aging, and the Hawaii Community Foundation for support.

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