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Mouse models of central nervous system ageing

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Ageing is accompanied by decreased overall fitness and performance. Studying brain ageing in humans is challenging due to limited or no access to healthy tissue, limited opportunities for interventions and complicated confounding factors. The generation of mouse ageing models with uniform genetic backgrounds significantly contributed to understanding (brain) ageing at the molecular level. Research has focused on evolutionarily conserved mechanisms or pathways that control ageing to facilitate data extrapolation to humans. Understanding how these pathways contribute to pathological ageing may help us understand human central nervous system (CNS) ageing and assist in the development of possible therapeutic targets. In this review, we focus on the functional consequences and pathological changes in the CNS of ageing mouse models.

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To investigate CNS ageing, a range of ageing mouse models was developed, in view of the genetic similarity between mice and humans, their relatively short life span and amenability for genetic manipulation [1]. Human and mouse brain ageing exhibit many common features. On the pathological level, brain atrophy, neuronal loss, neuronal lipofuscinosis and reactive glial cells are observed following ageing in both human and mouse brain [2]. On a functional level, both humans and mice show an age-dependent decline in learning and memory and motor performance [3]. On a transcriptional level, common sets of genes are affected by ageing in mouse and human [4]. On an epigenetic level, DNA methylation is strongly correlated with ageing [5], and age-associated DNA methylation changes are relatively well conserved between humans and mice [6].

However, it is worth noting that there is very limited correlation between age regulated gene expression changes in mouse and human, indicating that the ageing process in the CNS of human and mice might be quite different [7,8]. Given that age regulation is quite different in different tissues and species [7], research has focused on evolutionarily conserved mechanisms that control ageing to facilitate data extrapolation to humans. These conserved pathways or mechanisms include genomic instability, epigenetic alterations, telomere attrition, mitochondrial dysfunction, loss of proteostasis and nutrient sensing pathways etc. [9,10].

Introduction

Ageing is the main risk factor for many neurodegenerative diseases. Understanding how normal brain ageing transitions to pathological ageing is of vital importance to develop possible treatment for ageing associated central nervous system (CNS) pathologies.

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In this review, mouse models that have been used to study CNS ageing and ageing-related diseases will be discussed with the main focus on pathological changes during CNS ageing.

Mouse models with genomic instability

Brain ageing is characterized by loss of genomic integrity [11]. Excessive DNA damage and insufficient DNA repair both can contribute to genomic instability during the ageing process [12]. Numerous mouse models with genomic instability have been established and extensively reviewed [13,14]. Here, we only focus on models with CNS ageing phenotypes. Detailed CNS phenotypes of these mice are described in Table 1.

Mouse models with excessive DNA damage

Atm-deficient mice

Ataxia-telangiectasia (AT) is a human genetic disorder caused by mutational inactivation of the ATM gene [15]. ATM plays a major role in maintaining genomic stability and DNA strand breaks accumulate in the brain of $Atm^{-/-}$ mice [16]. ATM dysfunction resulted in increased reactive oxygen species (ROS) production, which may induce the degeneration of cerebellar neurons [17]. The histological, immunohistochemical and electrophysiological properties of Purkinje cells (PCs) were not altered in cerebellum, however, these cells showed age-dependent defects in calcium spike bursts and calcium currents [18]. Atm deficiency induced progressive loss of dopaminergic neurons in the substantia nigra (SN) and GABAergic neurons in the striatum (STR) [19]. Atm deficiency was also shown to impair astrocyte-endothelial cell interactions, which could be the underlying mechanism for neurodegeneration [20].

BubR1 deficient mice

BubR1 is a mitotic checkpoint protein that is essential for the accurate separation of duplicated chromosomes during cell division. Reduced BubR1 expression induces aneuploidy, which affects genomic stability [21]. BubR1 insufficient mice ($BubR1^{H/H}$ mice) exhibited various motor deficits, including impaired motor strength, coordination, gait patterns and reduced locomotor activity. BubR1 expression is significantly reduced with natural ageing in the mouse brain, and $BubR1^{H/H}$ mice exhibit age related decline in hippocampal neurogenesis [22]. The oligodendrocyte progenitor cell proliferation and oligodendrocyte density were markedly reduced in brain and spinal cord, which further caused axonal hypomyelination [23]. Besides, $BubR1^{H/H}$ mice also showed cerebral degeneration and accelerated gliosis in the brain [24].

DNA methyltransferase deficient mice

DNA methyltransferase 1 (Dnmt1) is the most prevalent DNA methyltransferase that maintains genomic methylation stability. Dnmt1 haploinsufficiency impaired learning and memory function in an age-dependent manner in mice [25]. In addition, conditional deletion of Dnmt1 and Dnmt3a in

neurons induced abnormal long-term plasticity in CA1 and deficits of learning and memory; however, no neuronal loss was observed [26].

DNA damage repair deficient mice

DNA damage alters the structure of DNA and most DNA damages undergo repair. Excess DNA damage is associated with ageing and cancer. There are several DNA repair pathways for different types of DNA damage. Deficiencies in DNA repair pathways cause progeria syndromes in humans and also affect the CNS [27]. Several ageing mouse models were established based on deletion or mutation of genes involved in DNA repair pathways.

Ercc1 deficient mice

Excision repair cross-complementation group 1 (ERCC1) is an essential component of multiple DNA repair pathways: nucleotide excision repair (NER), double-strand break repair and interstrand cross-link repair pathways [28]. Mice carrying a knock out and a hypomorphic allele for Ercc1 showed age-dependent motor abnormalities and cognitive decline. Further studies revealed widespread astrogliosis, microgliosis and neuronal degeneration in the brain, and motor neuron loss in the spinal cord [28,29]. The mutant mice did not show altered synapse numbers and dendritic morphology in the hippocampus. However, $Ercc1^{\Delta/-}$ mice did show age-dependent changes in the proteomic composition and synaptic plasticity in the hippocampus [30]. A similar age-related cognitive decline and neurodegeneration were also observed in conditional knockout mice ($Ercc1^{f/-} CaMKII-Cre^+$ mice), in which Ercc1 deficiency was directed to excitatory forebrain neurons [28]. For microglia, we have shown that microglia in $Ercc1^{\Delta/-}$ mice exhibit a hypertrophic morphology with thickened primary processes and larger cell bodies at the age of 16 weeks. Functionally, $Ercc1^{\Delta/-}$ microglia displayed increased phagocytosis, proliferation and ROS production. $Ercc1^{\Delta/-}$ microglia displayed an exaggerated proinflammatory response to a systemic inflammatory lipopolysaccharide (LPS) challenge, indicative of a ''primed'' state. Transcriptome analysis also confirmed $Ercc1^{\Delta/-}$ microglia were primed, with a clear phagocytic and chemotactic profile and enhanced immune state [31,32].

$Xpg^{/}$ mice

The premature ageing syndrome Cockayne syndrome (CS) is characterized by growth failure, abnormal sensitivity to light and impaired development of the CNS [33]. In humans with CS, the DNA repair gene XPG that is involved in NER, homologous recombination repair and base excision repair (BER) is mutated. $Xpg^{-/-}$ mice exhibit multiple progressive features of CNS ageing, such as loss of hearing and vision, cognitive decline, motor deficits and early development of tremors [34]. $Xpg^{-/-}$ mice develop wide spread astrogliosis

Table 1. Selected CNS ageing phenotypes of ageing mouse models.

Gene(s) or protein(s)	Genetic manipulation	Behavioral abnormalities	Brain size	Neuron phenotypes	Astrocyte phenotypes	Microglia phenotypes	Oligodendrocyte phenotypes	Human syndrome(s)
Atm	Knockout (KO)	Impaired motor coordination; irregular gait patterns; reduced locomotor activity [81]	Smaller brain [82]	Progressive loss of DA neurons in the SN and GABAergic neurons in the STR [19]; no neuronal loss in the cerebellum; age-dependent defects in calcium spike bursts and calcium currents in PCs [18]	Progressive structural alterations in astrocytes of the retina [20,83]; astrocytes activation in cerebellum [84]			Ataxia-telangiectasia (AT)
BubR1	Homozygous hypomorpic mutaion	Impaired motor strength, coordination and balance; irregular gait patterns; reduced locomotor activity [23]	Smaller brain [23]	Reduced in dendritic spine density in the motor cortex and cerebellum [23]; deficits in neural progenitor proliferation and maturation in hippocampus [22]	Age dependent increase of GFAP-positive astrocytes in cortex and thalamus [24]	Age dependent increase of CD11b-positive microglia in cortex, hippocampus and thalamus [24]	Reduced oligodendrocyte progenitor cell proliferation and oligodendrocyte density in brain and spinal cord [23]	Lynch syndrome; mosaic variegated aneuploidy syndrome
Dnmt1 and *Dnmt3a*	Conditional *Dnmt1* and *Dnmt3a* KO in neuron	Age-dependent decline in learning and memory [26]	Smaller hippocampi [26]	Impaired neural plasticity in CA1[26]				Cerebellar ataxia, deafness, and narcolepsy; hereditary sensory neuropathy
Ercc1	Hypomorphic mutation	Clasping of the hind-limbs, fine tremors and kyphosis, reduced motor performance and cognitive decline [29]	Smaller brain [29]	Age-dependent changes in the proteomic composition and synaptic plasticity in hippocampus [28,85]; progressive motor neuron loss in spinal cord [29]	Age-related increase in GFAP positive astrocytes in spinal cord and brain [29]	Age-related increase in Mac2-positive microglia in spinal cord and brain [29]; hypertrophic morphology with thickened primary processes and larger cell bodies; increased phagocytosis, proliferation and ROS production; priming state [31,32]		Cerebro-oculo-facio-skeletal (COFS) syndrome; xeroderma pigmentosum (XP)
Xpg	KO	Loss of hearing and vision, cognitive decline, motor deficits and early development of tremors [34]	Smaller brain [86]	Loss of PCs; abnormal dendritic morphologies and swollen proximal axon of PCs [35]	Age-related increase in GFAP positive astrocytes in spinal cord and brain [35]	Age-related increase in Iba-1 positive microglia in spinal cord and brain [35]		XP; COFS syndrome

Table 1 (Continued)

Gene(s) or protein(s)	Genetic manipulation	Behavioral abnormalities	Brain size	Neuron phenotypes	Astrocyte phenotypes	Microglia phenotypes	Oligodendrocyte phenotypes	Human syndrome(s)
Csa	KO			Increase of p53-positive neurons in neocortex, cerebellar cortex and spinal cord; non-detectable levels of neuronal degeneration at 26 weeks of age [36]	Increase of p53-positive astrocytes in neocortex, cerebellar cortex and spinal cord; increase of GFAP-positive astrocytes in the medullary reticular formation [36]	Increase of Mac2-positive microglia in the white matter [36]	Mac2-positive microglia were frequently in close proximity of oligodendrocytes in spinal cord [36]	Cockayne syndrome (CS)
Csb	KO	Mild motor coordination deficits; reduced locomotion [87]						CS; COFS syndrome
Xpd	Knockin; G602D point mutation in *Xpd* locus	Less active within the first minute of an open field test; normal motor coordination and learning capacity [88]						XP combined with CS (XPCS); trichothiodystrophy (TTD)
Csb and *Xpa*	Neuron-specific KO *Xpa* in *Csb*$^{-/-}$ mice	Seizure behavior; reduced locomotor activity; reduced ambulatory behavior in open filed test [36]	Cortex atrophy [36]	Chronic neuronal degeneration in forebrain neurons [36]	Increase of GFAP-positive astrocytes in neocortex, hippocampus and amygdala [36]			CS; XP
Sirt6	Brain-specific *Sirt6* KO	Impaired non-associative (open field test) and associative (contextual fear conditioning) learning [39]						
Terc	KO	Impaired spatial learning and memory [42]	Decreased DG volume [42]	Loss of neurons in the CA1 and frontal cortex; reduced synaptic density in frontal cortex; impaired dendritic development and neuritogenesis in hippocampus [43]	Unchanged GFAP positive astrocytes density in cortex [43]	Age dependent decrease of CD11b positive microglial number and cell body volume in DG; increased microglial density in DG [42]; increased Iba-1 positive microglia density; reduced dendritic length and branch points of microglia in cortex and CA1 [43]		Dyskeratosis congenita (DKC)

Table 1 (*Continued*)

Gene(s) or protein(s)	Genetic manipulation	Behavioral abnormalities	Brain size	Neuron phenotypes	Astrocyte phenotypes	Microglia phenotypes	Oligodendrocyte phenotypes	Human syndrome(s)
Tert	KO	Impaired spatial learning and memory [49]; aggressive and depressive behavior [48];		Impaired dendritic development and neuritogenesis in hippocampus [49]				DKC
Twnk	Overexpression of *Twinkle*dup353–365 in DA neurons	Impaired motor coordination [89]		Loss of DA neurons in the SN [89]				Progressive external ophthalmoplegia; infantile-onset spinocerebellar ataxia; Perrault syndrome
Tfam	Conditional KO *Tfam* in forebrain neurons (MILON mice)	Decreased spontaneous motor activity; wobbly walking; aggressive behavior and/or hyperactivity in response to stress [90]		Massive neurodegeneration in the hippocampus, the somatosensory cortex and the piriform cortex [90]; extensive axonal degeneration in neocortex and hippocampus [91]	Increase of GFAP-positive cells in corpus callosum [91]			Mitochondrial DNA depletion syndrome
Afg3l2	Haploinsufficiency of *Afg3l2*	Impaired motor coordination; abnormal gait; clasping on tail suspension [92]		Progressive loss of PCs; morphological changes of PCs [92]	Astrocytes activation in granule layer of cerebellum [92]			Spastic ataxia; spinocerebellar ataxia
	Conditional KO *Afg3l2* in PCs	Unsteady gait [93]		Progressive loss of PCs; impaired mitochondrial protein synthesis in PCs [93]	Progressive activation of astrocytes in cerebellum; activated astrocytes are hypertrophic and express increased levels of GFAP [93]	Progressive activation of microglia in cerebellum; cellular hypertrophy and retraction of cytoplasmic processes of activated microglia [93]		
	Conditional KO *Afg3l2* in forebrain neurons			Degeneration of cortical neurons; increased pTau levels in cortical neuron [94]				
	Conditional KO *Afg3l2* in oligodendrocytes	Mild but significant impairment in motor coordination [95]					Axonal degeneration characterized by myelin thickening, vacuolization and disruption in spinal cord [95]	

Table 1 (*Continued*)

Gene(s) or protein(s)	Genetic manipulation	Behavioral abnormalities	Brain size	Neuron phenotypes	Astrocyte phenotypes	Microglia phenotypes	Oligodendrocyte phenotypes	Human syndrome(s)
Afg3l1 and *Afg3l2*	Conditional KO *Afg3l2* and *Afg3l1* in oligodendrocytes	Impaired motor coordination [95]			Upregulation of GFAP protein level in the brain and spinal cord, astrocytes activation in corpus callosum [95]	Activated amoeboid-like microglia with thick processes in corpus callosum [95]	Progressive axonal demyelination in the spinal cord and brain; death of mature oligodendrocytes followed by compensatory repopulation [95]	Spastic ataxia; spinocerebellar ataxia
Spg7	KO	Abnormal gait characterized by uncoordinated movement of the hindlimbs; progressive impaired motor coordination [96]		Progressive degeneration of long spinal axons, optic nerves and sciatic nerves; mitochondrial abnormalities in synaptic terminals in spinal cord [96]				Spastic paraplegia
Spg7 and *Afg3l2*	*Spg7* KO and *Afg3l2* haploinsufficiency	Reduced cage activity; altered coordination of the hindlimbs during gait; loss of balance, uncoordinated gait, tremor and dystonic movements of the head [97]		Progressive degeneration and abnormal dendritogenesis of PCs; degeneration of hippocampal CA3 pyramidal neurons [97]	Astrocytes activation in hippocampus [97]			Spastic paraplegia; spastic ataxia; spinocerebellar ataxia
Phb2	Conditional KO *Phb2* in forebrain	Impaired learning and memory; impaired innate fear behavior and motor coordination; excessive pathological grooming behavior [98]	Smaller brain; forebrain atrophy [98]	Loss of neurons in DG and cornu ammonis (CA); increased pTau in hippocampus; shrinkage of the cell body and loss of processes of cortex neuron [98]	Progressive development of astrogliosis in DG [98]			
Aif	*Aif* hypomorphic harlequin mutation	Altered gait pattern and rhythm; lower locomotion speed [99]	Smaller cerebella [100]	Progressive loss of cerebellar granule cells and PCs [100]	Progressive astrogliosis in thalamus, cerebellum and the STR [101]	Microglia activation [101]		Cowchock syndrome; X-linked deafness-5

Table 1 (*Continued*)

Gene(s) or protein(s)	Genetic manipulation	Behavioral abnormalities	Brain size	Neuron phenotypes	Astrocyte phenotypes	Microglia phenotypes	Oligodendrocyte phenotypes	Human syndrome(s)
PstI	Specific expression of mito-*PstI* gene in DA neurons	Reduced exploratory behavior and spontaneous activity; impaired motor coordination [102]		Progressive loss of DA neurons in SN; reduced DA neuron projection and altered neurotransmitter production in the STR [102]				Hereditary pancreatitis
	Expression of mito-*PstI* in forebrain neurons	Abnormal limb-clasping; impaired motor coordination; impaired spatial learning and memory [103]	Smaller brain; cortical atrophy [103]	Massive neurodegeneration in the STR [103]	Increased GFAP protein level in STR, hippocampus and cortex [103]			
	Specific expression of mito-*PstI* gene in oligodendrocytes	Impaired motor coordination; reduced spontaneous activity; gait alterations; trunk instability; loss of tail tone; stiff and wobbly walking; reduced rearing behavior [104]			Astrogliosis in spinal cord [104]	Microgliosis in spinal cord [104]	oligodendrocyte loss, demyelination, and axonal damage in the spinal cord [104]	
Becn1	Heterozygous KO *Becn1* in APP transgenic mice			Reduced neuronal autophagy; synaptodendritic degeneration; neuron loss [105]		Increased CD68 expression and unchanged Iba-1 expression in frontal cortex [105]		
	Conditional KO *Becn1* in PCs	Abnormal gait and ataxic behavior [106]		Swollen dystrophic axons of the PCs; rapid degeneration of PCs [106]				
	Conditional KO *Becn1* in cortical and hippocampal neurons			Reduced neuron density in CA1 [106]				

Table 1 (Continued)

Gene(s) or protein(s)	Genetic manipulation	Behavioral abnormalities	Brain size	Neuron phenotypes	Astrocyte phenotypes	Microglia phenotypes	Oligodendrocyte phenotypes	Human syndrome(s)
Atg7	Conditional KO *Atg7* in CNS	Abnormal limb-clasping reflexes; tremor; impaired motor coordination [107]	Cortex atrophy [107]	Loss of PCs; neuron loss in hippocampus [107]	Increased GFAP expression in the cerebral cortex [107]			
	Conditional KO *Atg7* in motor neurons of SOD1^{G93A} mice	Hindlimb tremor [108]		Progressive loss of motor neurons [108]	Decreased GFAP expression in spinal cord compared to SOD1^{G93A} mice [108]	Decreased Iba-1 expression in spinal cord compared to SOD1^{G93A} mice [108]		
	Conditional KO *Atg7* in PCs	Impaired locomotion and motor coordination [109]		Axonal dystrophic swelling; degeneration of PCs [109]				
	Conditional KO *Atg7* in forebrain neurons	Impaired contextual fear memory and cued fear memory [110]		Progressive degeneration of hippocampal CA1 neurons; increased pTau-positive inclusions in neurons [110]				
	Conditional KO *Atg7* in DA neurons	Impaired locomotion [111]		Delayed DA neuron degeneration in midbrain; early degeneration of nigrostriatal axons; reduction in striatal DA levels; dystrophic dendrites; accumulation of alpha-synuclein in presynaptic terminals [111]				
FIP200	Conditional KO FIP200 in CNS	Impaired motor coordination; tremors and stiff movement; abnormal limb-clasping reflexes [112]	Smaller cerebella [112]	Progressive loss of neurons, spongiosis, and neurite degeneration in the cerebellum [112]				Hereditary breast-ovarian cancer syndrome
Smpd3	KO	Age-dependent decline of motor, coordination, and cognitive ability [54]		Increased neuron-specific marker *Mapt* and *Ttbk* expression; age-dependent neuronal dysproteostasis characterized by increased APP, amyloid-beta and pTau protein levels; age-dependent increase of neuronal apoptosis [54]	Unchanged astrocytes-specific markers *Eaac1* and *Glast1* gene expression level in brain [54]		Increased oligodendrocyte-specific *Plp* gene expression in brain [54]	

Table 1 (*Continued*)

Gene(s) or protein(s)	Genetic manipulation	Behavioral abnormalities	Brain size	Neuron phenotypes	Astrocyte phenotypes	Microglia phenotypes	Oligodendrocyte phenotypes	Human syndrome(s)
Bip	Knock-in; *Bip* heterozygous mutation	Impaired motor coordination; paralysis and tremor; loss of righting reflex [56]		Increased ER stress, protein aggregation and neurodegeneration in the motoneurons of spinal cord [56]				
Igf-1	Conditional *Igf-1* KO in liver	Impaired spatial memory learning [58]			Increased number of GFAP positive cells in DG [58]			Insulin-like growth factor 1 deficiency
Igf1r	Astrocyte-specific KO of *Igf1r*	Impaired working memory [59]			Impaired mitochondrial function; deficient in glucose and amyloid-beta uptake in astrocytes [59]			IGF-1 resistance
Foxo1/3/4	KO			Axonal degeneration [60]	Extensive astrocytes activation in the brain and spinal cord [60]	Extensive microglial activation in the brain and spinal cord [60]		Alveolar rhabdomyosarcoma
Foxo1/3/4	Neuron-specific KO of *Foxo 1/3/4*	Auditory startle reflexes, the voluntary wheel-running activity, impaired locomotion and motor coordination; increased leg clasping behavior [60]			Astrocytes activation in the cerebellum [60]	Microglial activation in the cerebellum [60]		

Abbreviations: KO, knockout; DA, dopamine; SN, *substantia nigra*; GABA, gamma-aminobutyric acid; PCs, Purkinje cells; AT, Ataxia-telangiectasia; GFAP, glial fibrillary acidic protein; CA, *cornu ammonis*; ROS, reactive oxygen species; COFS, cerebro-oculo-facio-skeletal; XP, xeroderma pigmentosum; Iba-1, ionized calcium-binding adapter molecule 1; CS, Cockayne syndrome; XPCS, xeroderma pigmentosum combined with Cockayne syndrome; TTD, trichothiodystrophy; DG, *dentate gyrus*; DKC, dyskeratosis congenita; pTau, phosphorylated Tau; STR, *striatum*; APP, amyloid precursor protein; ER, endoplasmic reticulum.

and microgliosis in brain and spinal cord, starting at 4 weeks of age. At 14 weeks of age, astrogliosis was severe and associated with axonal swellings and loss of PCs in the cerebellum. The genotoxic stress marker p53 was detected in neurons, astrocytes and oligodendrocytes. Terminal deoxynucleotidyl transferase dUTP nick end labeling (TUNEL) showed a significant increase in apoptotic cells in the cerebrum at 4 as well as 14 weeks of age [35].

Csa$^{/}$ and Csb$^{-/}$ mice

Csa and *Csb* are genes involved in transcription-coupled excision repair (TCR) In $Csa^{-/-}$ and $Csb^{-/-}$ mice, activated microglia and astrocytes are detected in the white matter. However, microglia activation was not observed in NER-deficient $Xpa^{-/-}$ and $Xpc^{-/-}$ mice. Therefore, next, TCR-deficient mice were generated with selective NER deficiency targeted to forebrain neurons. $Csb^{-/-}/Xpa^{c/-}/CamKII\alpha$-Cre mice displayed dramatic age-related neuronal loss, behavioral abnormalities, and brain atrophy in the forebrain [36].

Sirt6 deficient mice

Sirtuins (SIRT1–SIRT7) are an evolutionarily conserved family of NAD$^+$-dependent deacetylases, and play a critical role in brain ageing and neurodegenerative diseases [37]. SIRT6 promotes DNA repair and its activity declines with age. Sirt6 overexpression expanded life span in male mice [38]. *Sirt6* knockout mice exhibit an accelerated ageing phenotype and die prematurely. *Sirt6* specific depletion in the brain results in increased DNA damage, Tau phosphorylation and learning defects [39].

3xTg/Pol$\beta^{+/}$ mice

DNA polymerase beta (Polβ) is a primary polymerase involved in BER. Disruption of Polβ induced growth retardation and post-natal lethality in mice. A 50% reduction in Polβ levels (heterozygous for *Polβ* gene) aggravated the phenotypes of 3xTg Alzheimer's Disease (AD) mice. Neuronal dysfunction, cell death and memory impairment were also shown to be more severe than in the 3xTg AD mice or $Pol\beta^{+/-}$ mice. Pathway comparison analysis of human and mouse microarray data revealed that the combined 3xTg/$Pol\beta^{+/-}$ transgenic mouse is more similar to human AD patients than the 3xTgAD or $Pol\beta^{+/-}$ mice [40].

Telomere attrition mouse model

Telomere shortening is observed in all eukaryotes [41]. Mice carrying a homozygous germ line deletion for the telomerase RNA component gene (*Terc*) showed complete loss of *Terc* expression and telomerase activity. For the $Terc^{-/-}$ mice, the telomeres become shorter during successive generations of mating due to the replication end-point problem, usually resulting in phenotypic changes after the third generation. Third generation T$erc^{-/-}$ mice showed impaired spatial learning memory, and accordingly, the dentate gyrus (DG) volume

and brain weight were decreased in the $Terc^{-/-}$ mice [42]. Further study revealed reduced neurogenesis in the DG and loss of neurons in the hippocampus and frontal cortex in third generation $Terc^{-/-}$ mice [43]. Telomere dysfunction also led to reduced microglial numbers and cell body volume in DG, nevertheless, telomere shortening did not affect microglial proliferation or induce an ageing phenotype [42,43]. $Terc^{-/-}$ microglia also exhibited an enhanced pro-inflammatory response to peripheral LPS stimulation. However, unlike $Ercc1^{\Delta/-}$ microglia, this enhanced response is correlated with brain infiltration and blood–brain barrier dysregulation rather than age-related microglia priming [44]. *Terc* deficiency was also studied in combination with several age-related disease mouse models. Telomere shortening was shown to accelerate the amyotrophic lateral sclerosis (ALS) phenotypes in SOD1^{G93A} transgenic mice and Parkinson's disease (PD) phenotypes in (Thy-1)-h[A30P] α-synuclein transgenic mice [45,46]. Surprisingly, telomere shortening reduced AD amyloid pathology in APP23 transgenic mice [43].

Telomerase reverse transcriptase (TERT) is the catalytic subunit of the telomerase complex. Its deficiency also induced ageing phenotypes quite similar to T$erc^{-/-}$ mice [47]. What differed is that TERT deficiency induced aggressive and depressive behaviors in a mouse brain structure-specific manner [48]. *Tert* gene knockout mice also display impaired spatial memory, dendritic development and neuritogenesis [49]. Detailed CNS phenotypes of these mice are described in Table 1.

Mouse models with mitochondrial dysfunction

It is well accepted that mitochondria play a central role in ageing and neurodegenerative diseases [50]. Commonly used mouse models with mitochondrial dysfunction include dopaminergic neuron specific Twinkle transgenic mice, mitochondrial late-onset neurodegeneration (MILON) mice, mitochondrial quality control gene *Afg3l2*, *Spg7*, *Phb2* and *HtrA2/Omi*-deficient mice, apoptosis-inducing factor *Aif* deficient mice and mito-PstI transgenic mice all showed substantial brain ageing and neurodegeneration phenotypes [51]. Detailed CNS phenotypes of these mice are described in Table 1. Due to premature death of *HtrA2/Omi* deficient mice, this mouse model is not discussed here [52].

Mouse models with deficits in proteostasis

Loss of proteostasis is observed in many neurodegenerative diseases such as AD and PD. In mammals, proteostasis is maintained by chaperones and two proteolytic systems, the ubiquitin-proteasome and the lysosome-autophagy systems [10]. Autophagy-deficient mice showed ageing related changes and neurodegenerative changes that resemble those associated with ageing [53], among them, *Becn1*, *Atg7* and FAK family-interacting protein of 200 kDa (FIP200) deficient mice showed neurodegeneration phenotypes (see Table 1).

Defects in the sphingomyelinases gene *Smpd3* resulted in age-dependent neuronal dysproteostasis in *Smpd3*$^{-/-}$ mice, causing accumulation of APP, Aβ, and phosphorylated Tau (pTau) in neurons. The deficient mice also showed age-dependent decline of motor activity, coordination and cognitive ability [54]. Endoplasmic reticulum (ER) is important to maintain proteostasis, as approximately 30% of proteins are synthesized and processed there. ER stress is also a common pathological signature in a variety of diseases, including neurodegenerative disease [55]. Binding immunoglobulin protein (BiP) is central for ER function and mutant BiP mice exhibited motor disabilities during ageing. Degeneration of motoneurons and accumulations of ubiquitinated proteins were also found in the spinal cord [56].

Mouse models with deficits in nutrient sensing

The insulin/insulin-like growth factor 1 (Insulin/IGF1) signaling pathway is evolutionarily conserved and involved in growth, development, metabolic homoeostasis and also CNS ageing [57]. IGF1 is a neuroprotective hormone that is mainly produced in the liver. Conditional, liver-specific inactivation of the *Igf1* gene induced an age-associated decline in learning memory. Further study identified astrocytosis and increased neurochemical disturbances in the DG area [58]. Reduced hippocampal IGF-1 receptor (IGF1R) expression is associated with age-related decline in learning, and astrocyte-specific knockout of IGF1R was demonstrated to induce impairments in working memory [59]. Forkhead box O (FOXO) transcription factors play a pivotal role in the IIS/PI3K/Akt signaling pathway. They are important determinants of ageing and longevity [60]. FOXO expression progressively increases in ageing human and mouse brains [61]. Conditional knockout of *Foxo* 1, 3, and 4 in neurons and glia cells induced an accelerated ageing phenotype in mice, manifested by axonal tract degeneration and gliosis [61].

Senescence accelerated mouse-prone (SAM-P) mice

The SAM-P mice are naturally occurring mouse lines that display a series of accelerated ageing phenotypes. At present, there are eight strains of SAM-P. It is noteworthy that each SAM-P strain has relatively strain-specific pathological phenotypes [62]. Since SAM-P/8 and SAM-P/10 display deficits in learning and memory, these strains were extensively used to investigate CNS ageing. A variety of age-associated alterations involving neurons, glia and blood brain barriers have been identified in SAM-P/8 and SAM-P/10 mice brain. SAM-P/8 could also serve as an animal model for AD and other dementias as age-related increases in pTau and amyloid accumulation were also observed in the hippocampus of SAMP8 mouse brains [63]. The 3xTg-AD transgenes in a SAM-P/8 background showed deficits in spatial memory and female-specific aggravation of AD pathology characterized by activation of astrocytes and increased accumulation of pTau and amyloid in the brain [64]. Some epigenetic alternations associated with ageing and neurodegeneration were also identified in the SAMP-P/8 brain [65,66].

Promising therapeutic targets

Although ageing itself is an inevitable process, interventions could be applied to extend both lifespan and health-span. A longevity study in monozygotic twins indicated that life span is determined largely by environmental factors rather than genetic factors [67]. Work on mouse models of ageing has not only contributed to the identification of many of the molecular pathways involved in ageing, but also have provided possible targets for the treatment of age-related CNS decline. Epigenetic signatures are proposed to function as biomarkers of ageing, for example, the DNA methylome can help to measure human ageing rates [5]. Epigenetic modifications are considered to be dynamic and reversible, making it an attractive therapeutic target. Chromatin modifying compounds such as sirtuin modulators and histone deacetylase inhibitors are thought to provide a promising treatment for neurodegenerative diseases [68,69].

In recent years, senescent cells are recognized as a new target for age-related disease. In mouse, clearance of p16Ink4a-positive senescent cells was shown to delay ageing-associated phenotypes in *BubR1*$^{H/H}$ mice [70]. Fuhrmann-Stroissnigg et al. established a drug-screening platform to identify senolytic compounds using *Ercc1*$^{-/-}$ primary murine embryonic fibroblasts. Through this platform, they successfully identified an HSP90 inhibitor, 17-DMAG, which could extend health-span and delay the onset of several age-related symptoms in *Ercc1*$^{Δ/-}$ mice [71]. Microglia are shown to undergo age-dependent degeneration, increasingly displaying a primed or hyperreactive, pro-inflammatory phenotype and a deficiency in phagocytosis and chemotaxis. Senescent microglia are believed to be involved in switching normal brain ageing to pathological ageing [72]. The rejuvenation of senescent microglia was already shown to be a potential druggable target [73]. However, so far, there is no evidence whether microglia senolysis could restore normal function and revert or halt CNS ageing phenotypes.

Dietary restriction increases lifespan or health-span in all investigated eukaryote species [10]. A similar effect is seen when the activity of nutrient-sensing pathways is reduced by mutations or chemical inhibitors [74], indicating that nutrient-sensing pathways could provide promising targets to slow ageing. For example, the Insulin- and IGF-1-signaling pathway, the mammalian target of rapamycin (mTOR) pathway and the AMPK pathway are involved in nutrient sensing. And, manipulation of these pathways could increase lifespan and delay multiple aspects of ageing [10,75,76].

Conclusions

Studying brain ageing in humans is challenging due to very limited or no access to healthy tissue, limited opportunities

for interventions and human ageing in general is complicated by confounding factors like environment, nutrition, medical history, medication, education etc. The generation of mouse models with uniform genetic backgrounds significantly contributed to our understanding of ageing at the molecular level. However, conclusions must be drawn with caution because the results obtained from inbred mice may not represent the species as a whole [77]. Also, the mouse models cannot recapture all the brain ageing phenotypes in human, nor reliably predict age-related changes in humans owing to differences in the ageing process in human and mouse.

Though the mouse models described here have been used to identify molecular mechanisms of ageing, and to identify possible therapeutic targets, their use in the development of therapies and in particular the translation to the human situation is still not well developed [78]. In case of AD, for example, gene mutations that lead to AD-like phenotypes in young animals do not fully mimic human AD in older patients and therefore the predictive value of testing drugs in such models is limited [79].

Nonhuman primates are more similar to humans in how they experience ageing processes, which include ageing related pathologies like cancer, diabetes, arthritis, cardiovascular disease, and neurological decline. However, their substantial size, long lifespan, and the associated expense are prohibitive factors in their large scale-use for research into ageing. Nonetheless, they could provide a crucial component between the bench and the bedside [80]. In this review, we mainly focused on the functional consequences and pathological changes resulting from conserved pathways dysfunction in brain ageing. Understanding how these conserved pathways contribute to pathological ageing may help us to get a better understanding of brain ageing and develop possible treatment strategies. Finally, it is worth noting that the ageing process involves multiple organs and tissues, and the influence of peripheral organs on CNS ageing cannot be ignored.

Conflict of interest

The authors have no conflicts of interest to declare.

Acknowledgements

References

[1] Vanhooren V, Libert C. The mouse as a model organism in aging research: usefulness, pitfalls and possibilities. Ageing Res Rev 2013;12(1):8–21.

[2] Harkema L, Youssef SA, de Bruin A. Pathology of mouse models of accelerated aging. Vet Pathol 2016;53(2):366–89.

[3] Yeoman M, Scutt G, Faragher R. Insights into CNS ageing from animal models of senescence. Nat Rev Neurosci 2012;13(6):435–45.

[4] de Magalhaes JP, Curado J, Church GM. Meta-analysis of age-related gene expression profiles identifies common signatures of aging. Bioinformatics 2009;25(7):875–81.

[5] Hannum G, Guinney J, Zhao L, Zhang L, Hughes G, Sadda S, et al. Genome-wide methylation profiles reveal quantitative views of human aging rates. Mol Cell 2013;49(2):359–67.

[6] Spiers H, Hannon E, Wells S, Williams B, Fernandes C, Mill J. Age-associated changes in DNA methylation across multiple tissues in an inbred mouse model. Mech Ageing Dev 2016;154:20–3.

[7] Zahn JM, Poosala S, Owen AB, Ingram DK, Lustig A, Carter A, et al. AGEMAP: a gene expression database for aging in mice. PLoS Genet 2007;3(11):e201.

[8] Loerch PM, Lu T, Dakin KA, Vann JM, Isaacs A, Geula C, et al. Evolution of the aging brain transcriptome and synaptic regulation. PLoS One 2008;3(10):e3329.

[9] Bishop NA, Lu T, Yankner BA. Neural mechanisms of ageing and cognitive decline. Nature 2010;464(7288):529–35.

[10] Lopez-Otin C, Blasco MA, Partridge L, Serrano M, Kroemer G. The hallmarks of aging. Cell 2013;153(6):1194–217.

[11] Chow HM, Herrup K. Genomic integrity and the ageing brain. Nat Rev Neurosci 2015;16(11):672–84.

[12] Maynard S, Fang EF, Scheibye-Knudsen M, Croteau DL, Bohr VA. DNA damage, DNA repair, aging, and neurodegeneration. Cold Spring Harb Perspect Med 2015;5(10).

[13] Specks J, Nieto-Soler M, Lopez-Contreras AJ, Fernandez-Capetillo O. Modeling the study of DNA damage responses in mice. Methods Mol Biol 2015;1267:413–37.

[14] Friedberg EC, Meira LB. Database of mouse strains carrying targeted mutations in genes affecting biological responses to DNA damage version 7. DNA Repair (Amst) 2006;5(2):189–209.

[15] Shiloh Y, Lederman HM. Ataxia-telangiectasia (A-T): an emerging dimension of premature ageing. Ageing Res Rev 2017;33:76–88.

[16] Stern N, Hochman A, Zemach N, Weizman N, Hammel I, Shiloh Y, et al. Accumulation of DNA damage and reduced levels of nicotine adenine dinucleotide in the brains of Atm-deficient mice. J Biol Chem 2002;277(1):602–8.

[17] Kamsler A, Daily D, Hochman A, Stern N, Shiloh Y, Rotman G, et al. Increased oxidative stress in ataxia telangiectasia evidenced by alterations in redox state of brains from Atm-deficient mice. Cancer Res 2001;61(5):1849–54.

[18] Chiesa N, Barlow C, Wynshaw-Boris A, Strata P, Tempia F. Atm-deficient mice Purkinje cells show age-dependent defects in calcium spike bursts and calcium currents. Neuroscience 2000;96(3):575–83.

[19] Eilam R, Peter Y, Groner Y, Segal M. Late degeneration of nigro-striatal neurons in ATM-/- mice. Neuroscience 2003;121(1):83–98.

[20] Raz-Prag D, Galron R, Segev-Amzaleg N, Solomon AS, Shiloh Y, Barzilai A, et al. A role for vascular deficiency in retinal pathology in a mouse model of ataxia-telangiectasia. Am J Pathol 2011;179(3):1533–41.

[21] Baker DJ, Dawlaty MM, Wijshake T, Jeganathan KB, Malureanu L, van Ree JH, et al. Increased expression of BubR1 protects against aneuploidy and cancer and extends healthy lifespan. Nat Cell Biol 2013;15(1):96–102.

[22] Yang Z, Jun H, Choi CI, Yoo KH, Cho CH, Hussaini SMQ, et al. Age-related decline in BubR1 impairs adult hippocampal neurogenesis. Aging Cell 2017;16(3):598–601.

[23] Choi CI, Yoo KH, Hussaini SM, Jeon BT, Welby J, Gan H, et al. The progeroid gene BubR1 regulates axon myelination and motor function. Aging (Albany NY) 2016;8(11):2667–88.

[24] Hartman TK, Wengenack TM, Poduslo JF, van Deursen JM. Mutant mice with small amounts of BubR1 display accelerated age-related gliosis. Neurobiol Aging 2007;28(6):921–7.

[25] Liu L, van Groen T, Kadish I, Li Y, Wang D, James SR, et al. Insufficient DNA methylation affects healthy aging and promotes age-related health problems. Clin Epigenetics 2011;2(2):349–60.

[26] Feng J, Zhou Y, Campbell SL, Le T, Li E, Sweatt JD, et al. Dnmt1 and Dnmt3a maintain DNA methylation and regulate synaptic function in adult forebrain neurons. Nat Neurosci 2010;13(4):423–30.

[27] McKinnon PJ. Maintaining genome stability in the nervous system. Nat Neurosci 2013;16(11):1523–9.

[28] Borgesius NZ, de Waard MC, van der Pluijm I, Omrani A, Zondag GC, van der Horst GT, et al. Accelerated age-related cognitive decline and neurodegeneration, caused by deficient DNA repair. J Neurosci 2011;31 (35):12543–53.

[29] de Waard MC, van der Pluijm I, Zuiderveen Borgesius N, Comley LH, Haasdijk ED, Rijksen Y, et al. Age-related motor neuron degeneration in DNA repair-deficient Ercc1 mice. Acta Neuropathol 2010;120(4): 461–75.

[30] Vegh MJ, de Waard MC, van der Pluijm I, Ridwan Y, Sassen MJ, van Nierop P, et al. Synaptic proteome changes in a DNA repair deficient ercc1 mouse model of accelerated aging. J Proteome Res 2012;11(3):1855–67.

[31] Raj DD, Jaarsma D, Holtman IR, Olah M, Ferreira FM, Schaafsma W, et al. Priming of microglia in a DNA-repair deficient model of accelerated aging. Neurobiol Aging 2014;35(9):2147–60.

[32] Holtman IR, Raj DD, Miller JA, Schaafsma W, Yin Z, Brouwer N, et al. Induction of a common microglia gene expression signature by aging and neurodegenerative conditions: a co-expression meta-analysis. Acta Neuropathol Commun 2015;3:31.

[33] Karikkineth AC, Scheibye-Knudsen M, Fivenson E, Croteau DL, Bohr VA. Cockayne syndrome: clinical features, model systems and pathways Ageing Res Rev 2017;33:3–17.

[34] La Fata G, van Vliet N, Barnhoorn S, Brandt RMC, Etheve S, Chenal E, et al. Vitamin E supplementation reduces cellular loss in the brain of a premature aging mouse model. J Prev Alzheimers Dis 2017;4 (4):226–35.

[35] Barnhoorn S, Uittenboogaard LM, Jaarsma D, Vermeij WP, Tresini M, Weymaere M, et al. Cell-autonomous progeroid changes in conditional mouse models for repair endonuclease XPG deficiency. PLoS Genet 2014;10(10):e1004686.

[36] Jaarsma D, van der Pluijm I, de Waard MC, Haasdijk ED, Brandt R, Vermeij M, et al. Age-related neuronal degeneration: complementary roles of nucleotide excision repair and transcription-coupled repair in preventing neuropathology. PLoS Genet 2011;7(12):e1002405.

[37] Satoh A, Imai SI, Guarente L. The brain, sirtuins, and ageing. Nat Rev Neurosci 2017;18(6):362–74.

[38] Kanfi Y, Naiman S, Amir G, Peshti V, Zinman G, Nahum L, et al. The sirtuin SIRT6 regulates lifespan in male mice. Nature 2012;483 (7388):218–21.

[39] Kaluski S, Portillo M, Besnard A, Stein D, Einav M, Zhong L, et al. Neuroprotective functions for the histone deacetylase SIRT6. Cell Rep 2017;18(13):3052–62.

[40] Sykora P, Misiak M, Wang Y, Ghosh S, Leandro GS, Liu D, et al. DNA polymerase beta deficiency leads to neurodegeneration and exacerbates Alzheimer disease phenotypes. Nucleic Acids Res 2015;43(2):943–59.

[41] Blasco MA. Telomere length, stem cells and aging. Nat Chem Biol 2007;3 (10):640–9.

[42] Khan AM, Babcock AA, Saeed H, Myhre CL, Kassem M, Finsen B. Telomere dysfunction reduces microglial numbers without fully inducing an aging phenotype. Neurobiol Aging 2015;36(6):2164–75.

[43] Rolyan H, Scheffold A, Heinrich A, Begus-Nahrmann Y, Langkopf BH, Holter SM, et al. Telomere shortening reduces Alzheimer's disease amyloid pathology in mice. Brain 2011;134(Pt 7):2044–56.

[44] Raj DD, Moser J, van der Pol SM, van Os RP, Holtman IR, Brouwer N, et al. Enhanced microglial pro-inflammatory response to lipopolysaccharide correlates with brain infiltration and blood-brain barrier dysregulation in a mouse model of telomere shortening. Aging Cell 2015;14(6):1003–13.

[45] Linkus B, Wiesner D, Messner M, Karabatsiakis A, Scheffold A, Rudolph KL, et al. Telomere shortening leads to earlier age of onset in ALS mice. Aging (Albany NY) 2016;8(2):382–93.

[46] Scheffold A, Holtman IR, Dieni S, Brouwer N, Katz SF, Jebaraj BM, et al. Telomere shortening leads to an acceleration of synucleinopathy and impaired microglia response in a genetic mouse model. Acta Neuropathol Commun 2016;4(1):87.

[47] Strong MA, Vidal-Cardenas SL, Karim B, Yu H, Guo N, Greider CW. Phenotypes in mTERT(+)/(−) and mTERT(−)/(−) mice are due to short telomeres, not telomere-independent functions of telomerase reverse transcriptase. Mol Cell Biol 2011;31(12):2369–79.

[48] Zhou QG, Wu HY, Zhou H, Liu MY, Lee HW, Liu X, et al. Reactivation of Tert in the medial prefrontal cortex and hippocampus rescues aggression and depression of Tert(-/-) mice. Transl Psychiatry 2016;6(6): e836.

[49] Zhou QG, Liu MY, Lee HW, Ishikawa F, Devkota S, Shen XR, et al. Hippocampal TERT Regulates Spatial Memory Formation through Modulation of Neural Development. Stem Cell Rep 2017;9(2):543–56.

[50] Hekimi S, Lapointe J, Wen Y. Taking a ''good'' look at free radicals in the aging process. Trends Cell Biol 2011;21(10):569–76.

[51] Iommarini L, Peralta S, Torraco A, Diaz F. Mitochondrial diseases part II: mouse models of OXPHOS deficiencies caused by defects in regulatory factors and other components required for mitochondrial function. Mitochondrion 2015;22:96–118.

[52] Jones JM, Datta P, Srinivasula SM, Ji W, Gupta S, Zhang Z, et al. Loss of Omi mitochondrial protease activity causes the neuromuscular disorder of mnd2 mutant mice. Nature 2003;425(6959):721–7.

[53] Rubinsztein DC, Marino G, Kroemer G. Autophagy and aging. Cell 2011;146(5):682–95.

[54] Stoffel W, Jenke B, Schmidt-Soltau I, Binczek E, Brodesser S, Hammels I. SMPD3 deficiency perturbs neuronal proteostasis and causes progressive cognitive impairment. Cell Death Dis 2018;9(5):507.

[55] Hetz C, Mollereau B. Disturbance of endoplasmic reticulum proteostasis in neurodegenerative diseases. Nat Rev Neurosci 2014;15 (4):233–49.

[56] Jin H, Mimura N, Kashio M, Koseki H, Aoe T. Late-onset of spinal neurodegeneration in knock-in mice expressing a mutant BiP. PLoS One 2014;9(11):e112837.

[57] Broughton S, Partridge L. Insulin/IGF-like signalling, the central nervous system and aging. Biochem J 2009;418(1):1–12.

[58] Svensson J, Diez M, Engel J, Wass C, Tivesten A, Jansson JO, et al. Endocrine, liver-derived IGF-I is of importance for spatial learning and memory in old mice. J Endocrinol 2006;189(3):617–27.

[59] Logan S, Pharaoh GA, Marlin MC, Masser DR, Matsuzaki S, Wronowski B, et al. Insulin-like growth factor receptor signaling regulates working memory, mitochondrial metabolism, and amyloid-beta uptake in astrocytes. Mol Metab 2018;9:141–55.

[60] Tia N, Singh AK, Pandey P, Azad CS, Chaudhary P, Gambhir IS. Role of Forkhead Box O (FOXO) transcription factor in aging and diseases. Gene 2018;648:97–105.

[61] Hwang I, Oh H, Santo E, Kim DY, Chen JW, Bronson RT, et al. FOXO protects against age-progressive axonal degeneration. Aging Cell 2018;17(1).

[62] Takeda T, Hosokawa M, Higuchi K. Senescence-accelerated mouse (SAM): a novel murine model of accelerated senescence. J Am Geriatr Soc 1991;39(9):911–9.

[63] Akiguchi I, Pallas M, Budka H, Akiyama H, Ueno M, Han J, et al. SAMP8 mice as a neuropathological model of accelerated brain aging and dementia: Toshio Takeda's legacy and future directions. Neuropathology 2017;37(4):293–305.

[64] Virgili J, Lebbadi M, Tremblay C, St-Amour I, Pierrisnard C, Faucher-Genest A, et al. Characterization of a 3xTg-AD mouse model of Alzheimer's disease with the senescence accelerated mouse prone 8 (SAMP8) background. Synapse 2018;72(4):e22025.

[65] Cosin-Tomas M, Alvarez-Lopez MJ, Sanchez-Roige S, Lalanza JF, Bayod S, Sanfeliu C, et al. Epigenetic alterations in hippocampus of SAMP8 senescent mice and modulation by voluntary physical exercise. Front Aging Neurosci 2014;6:51.

[66] Wang CM, Tsai SN, Yew TW, Kwan YW, Ngai SM. Identification of histone methylation multiplicities patterns in the brain of senescence-accelerated prone mouse 8. Biogerontology 2010;11(1):87–102.

[67] Pal S, Tyler JK. Epigenetics and aging. Sci Adv 2016;2(7)e1600584.

[68] Jesko H, Wencel P, Strosznajder RP, Strosznajder JB. Sirtuins and their roles in brain aging and neurodegenerative disorders. Neurochem Res 2017;42(3):876–90.

[69] Karagiannis TC, Ververis K. Potential of chromatin modifying compounds for the treatment of Alzheimer's disease. Pathobiol Aging Age Relat Dis 2012;2.

[70] Baker DJ, Wijshake T, Tchkonia T, LeBrasseur NK, Childs BG, van de Sluis B, et al. Clearance of p16Ink4a-positive senescent cells delays ageing-associated disorders. Nature 2011;479(7372):232–6.

[71] Fuhrmann-Stroissnigg H, Ling YY, Zhao J, McGowan SJ, Zhu Y, Brooks RW, et al. Identification of HSP90 inhibitors as a novel class of senolytics. Nat Commun 2017;8(1):422.

[72] Spittau B. Aging microglia-phenotypes, functions and implications for age-related neurodegenerative diseases. Front Aging Neurosci 2017;9:194.

[73] Rawji KS, Mishra MK, Michaels NJ, Rivest S, Stys PK, Yong VW. Immunosenescence of microglia and macrophages: impact on the ageing central nervous system. Brain 2016;139(Pt 3):653–61.

[74] Fontana L, Partridge L, Longo VD. Extending healthy life span-from yeast to humans. Science 2010;328(5976):321–6.

[75] Vidal RL, Matus S, Bargsted L, Hetz C. Targeting autophagy in neurodegenerative diseases. Trends Pharmacol Sci 2014;35(11):583–91.

[76] Bartke A. Minireview: role of the growth hormone/insulin-like growth factor system in mammalian aging. Endocrinology 2005;146(9):3718–23.

[77] Mitchell SJ, Scheibye-Knudsen M, Longo DL, de Cabo R. Animal models of aging research: implications for human aging and age-related diseases. Annu Rev Anim Biosci 2015;3:283–303.

[78] Kirkland JL. Translating the Science of Aging into Therapeutic Interventions. Cold Spring Harb Perspect Med 2016;6(3)a025908.

[79] Shineman DW, Basi GS, Bizon JL, Colton CA, Greenberg BD, Hollister BA, et al. Accelerating drug discovery for Alzheimer's disease: best practices for preclinical animal studies. Alzheimers Res Ther 2011;3(5):28.

[80] Mattison JA, Vaughan KL. An overview of nonhuman primates in aging research. Exp Gerontol 2017;94:41–5.

[81] Barlow C, Hirotsune S, Paylor R, Liyanage M, Eckhaus M, Collins F, et al. Atm-deficient mice: a paradigm of ataxia telangiectasia. Cell 1996;86(1):159–71.

[82] Eilam R, Peter Y, Elson A, Rotman G, Shiloh Y, Groner Y, et al. Selective loss of dopaminergic nigro-striatal neurons in brains of Atm-deficient mice. Proc Natl Acad Sci U S A 1998;95(21):12653–56.

[83] Meshulam L, Galron R, Kanner S, De Pitta M, Bonifazi P, Goldin M, et al. The role of the neuro-astro-vascular unit in the etiology of ataxia telangiectasia. Front Pharmacol 2012;3:157.

[84] Liu N, Stoica G, Yan M, Scofield VL, Qiang W, Lynn WS, et al. ATM deficiency induces oxidative stress and endoplasmic reticulum stress in astrocytes. Lab Invest 2005;85(12):1471–80.

[85] Nevedomskaya E, Meissner A, Goraler S, de Waard M, Ridwan Y, Zondag G, et al. Metabolic profiling of accelerated aging ERCC1 d/- mice. J Proteome Res 2010;9(7):3680–7.

[86] Sun XZ, Harada YN, Zhang R, Cui C, Takahashi S, Fukui Y. A genetic mouse model carrying the nonfunctional xeroderma pigmentosum group G gene. Congenit Anom (Kyoto) 2003;43(2):133–9.

[87] van der Horst GT, van Steeg H, Berg RJ, van Gool AJ, de Wit J, Weeda G, et al. Defective transcription-coupled repair in Cockayne syndrome B mice is associated with skin cancer predisposition. Cell 1997;89(3):425–35.

[88] Andressoo JO, Mitchell JR, de Wit J, Hoogstraten D, Volker M, Toussaint W, et al. An Xpd mouse model for the combined xeroderma pigmentosum/cockayne syndrome exhibiting both cancer predisposition and segmental progeria. Cancer Cell 2006;10(2):121–32.

[89] Song L, Shan Y, Lloyd KC, Cortopassi GA. Mutant Twinkle increases dopaminergic neurodegeneration, mtDNA deletions and modulates Parkin expression. Hum Mol Genet 2012;21(23):5147–58.

[90] Dufour E, Terzioglu M, Sterky FH, Sorensen L, Galter D, Olson L, et al. Age-associated mosaic respiratory chain deficiency causes trans-neuronal degeneration. Hum Mol Genet 2008;17(10):1418–26.

[91] Sorensen L, Ekstrand M, Silva JP, Lindqvist E, Xu B, Rustin P, et al. Late-onset corticohippocampal neurodepletion attributable to catastrophic failure of oxidative phosphorylation in MILON mice. J Neurosci 2001;21(20):8082–90.

[92] Maltecca F, Magnoni R, Cerri F, Cox GA, Quattrini A, Casari G. Haploinsufficiency of AFG3L2, the gene responsible for spinocerebellar ataxia type 28, causes mitochondria-mediated Purkinje cell dark degeneration. J Neurosci 2009;29(29):9244–54.

[93] Almajan ER, Richter R, Paeger L, Martinelli P, Barth E, Decker T, et al. AFG3L2 supports mitochondrial protein synthesis and Purkinje cell survival. J Clin Invest 2012;122(11):4048–58.

[94] Kondadi AK, Wang S, Montagner S, Kladt N, Korwitz A, Martinelli P, et al. Loss of the m-AAA protease subunit AFG(3)L(2) causes mitochondrial transport defects and tau hyperphosphorylation. Embo j 2014;33(9):1011–26.

[95] Wang S, Jacquemyn J, Murru S. The mitochondrial m-AAA protease prevents demyelination and hair greying. PLoS Genet 2016;12(12):e1006463.

[96] Ferreirinha F, Quattrini A, Pirozzi M, Valsecchi V, Dina G, Broccoli V, et al. Axonal degeneration in paraplegin-deficient mice is associated with abnormal mitochondria and impairment of axonal transport. J Clin Invest 2004;113(2):231–42.

[97] Martinelli P, La Mattina V, Bernacchia A, Magnoni R, Cerri F, Cox G, et al. Genetic interaction between the m-AAA protease isoenzymes reveals novel roles in cerebellar degeneration. Hum Mol Genet 2009;18(11):2001–13.

[98] Merkwirth C, Martinelli P, Korwitz A, Morbin M, Bronneke HS, Jordan SD, et al. Loss of prohibitin membrane scaffolds impairs mitochondrial architecture and leads to tau hyperphosphorylation and neurodegeneration. PLoS Genet 2012;8(11):e1003021.

[99] Preisig DF, Kulic L, Kruger M, Wirth F, McAfoose J, Spani C, et al. High-speed video gait analysis reveals early and characteristic locomotor phenotypes in mouse models of neurodegenerative movement disorders. Behav Brain Res 2016;311:340–53.

[100] Klein JA, Longo-Guess CM, Rossmann MP, Seburn KL, Hurd RE, Frankel WN, et al. The harlequin mouse mutation downregulates apoptosis-inducing factor. Nature 2002;419(6905):367–74.

[101] El Ghouzzi V, Csaba Z, Olivier P, Lelouvier B, Schwendimann L, Dournaud P, et al. Apoptosis-inducing factor deficiency induces early mitochondrial degeneration in brain followed by progressive multifocal neuropathology. J Neuropathol Exp Neurol 2007;66(9):838–47.

[102] Pickrell AM, Pinto M, Hida A, Moraes CT. Striatal dysfunctions associated with mitochondrial DNA damage in dopaminergic neurons in a mouse model of Parkinson's disease. J Neurosci 2011;31(48):17649–58.

[103] Pickrell AM, Fukui H, Wang X, Pinto M, Moraes CT. The striatum is highly susceptible to mitochondrial oxidative phosphorylation dysfunctions. J Neurosci 2011;31(27):9895–904.

[104] Madsen PM, Pinto M. Mitochondrial DNA Double-strand breaks in oligodendrocytes cause demyelination, axonal injury, and CNS inflammation. J Neurosci 2017;37(42):10185–99.

[105] Pickford F, Masliah E, Britschgi M, Lucin K, Narasimhan R, Jaeger PA, et al. The autophagy-related protein beclin 1 shows reduced expression in early Alzheimer disease and regulates amyloid beta accumulation in mice. J Clin Invest 2008;118(6):2190–9.

[106] McKnight NC, Zhong Y, Wold MS, Gong S, Phillips GR, Dou Z, et al. Beclin 1 is required for neuron viability and regulates endosome pathways via the UVRAG-VPS34 complex. PLoS Genet 2014;10(10):e1004626.

[107] Komatsu M, Waguri S, Chiba T, Murata S, Iwata J, Tanida I, et al. Loss of autophagy in the central nervous system causes neurodegeneration in mice. Nature 2006;441(7095):880–4.

[108] Rudnick ND, Griffey CJ, Guarnieri P, Gerbino V, Wang X, Piersaint JA, et al. Distinct roles for motor neuron autophagy early and late in the SOD1(G93A) mouse model of ALS. Proc Natl Acad Sci U S A 2017;114(39):E8294–303.

[109] Komatsu M, Wang QJ, Holstein GR, Friedrich Jr VL, Iwata J, Kominami E, et al. Essential role for autophagy protein Atg7 in the maintenance of axonal homeostasis and the prevention of axonal degeneration. Proc Natl Acad Sci U S A 2007;104(36):14489–94.

[110] Inoue K, Rispoli J, Kaphzan H, Klann E, Chen EI, Kim J, et al. Macroautophagy deficiency mediates age-dependent neurodegeneration through a phospho-tau pathway. Mol Neurodegener 2012;7:48.

[111] Friedman LG, Lachenmayer ML, Wang J, He L, Poulose SM, Komatsu M, et al. Disrupted autophagy leads to dopaminergic axon and dendrite degeneration and promotes presynaptic accumulation of alpha-synuclein and LRRK2 in the brain. J Neurosci 2012;32(22):7585–93.

[112] Liang CC, Wang C, Peng X, Gan B, Guan JL. Neural-specific deletion of FIP200 leads to cerebellar degeneration caused by increased neuronal death and axon degeneration. J Biol Chem 2010;285(5):3499–509.