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Ageing as a Risk Factor for Disease

Review

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Age is the main risk factor for the prevalent diseases of developed countries: cancer, cardiovascular disease and neurodegeneration. The ageing process is deleterious for fitness, but can nonetheless evolve as a consequence of the declining force of natural selection at later ages, attributable to extrinsic hazards to survival: ageing can then occur as a side-effect of accumulation of mutations that lower fitness at later ages, or of natural selection in favour of mutations that increase fitness of the young but at the cost of a higher subsequent rate of ageing. Once thought of as an inexorable, complex and lineage-specific process of accumulation of damage, ageing has turned out to be influenced by mechanisms that show strong evolutionary conservation. Lowered activity of the nutrient-sensing insulin/insulin-like growth factor/Target of Rapamycin signalling network can extend healthy lifespan in yeast, multicellular invertebrates, mice and, possibly, humans. Mitochondrial activity can also promote ageing, while genome maintenance and autophagy can protect against it. We discuss the relationship between evolutionarily conserved mechanisms of ageing and disease, and the associated scientific challenges and opportunities.

Introduction

Better medical care and living conditions in developed countries have increased both health and life expectancy, from around 50 years in the early 1900s to over 80 at the present time. However, age is the main risk factor for major debilitating and life-threatening conditions, including cancer, cardiovascular disease and neurodegeneration (Figure 1), all of which are therefore increasing in prevalence. Understanding exactly how ageing increases risk of disease is needed to help to tackle this growing problem.

Not long ago, ageing was assumed to be an intractably complex process, resulting from accumulation of multiple forms of damage and pathology in different tissues as a result of failure of cellular maintenance pathways. Evolutionary analysis also tended to confirm the intractability of ageing for experimental analysis or medical intervention. Natural selection acts against ageing, because an organism that does not age would leave more offspring. However, the force of natural selection weakens with age [1–3] because extrinsic hazards such as disease and accidents means that most individuals do not survive to be old: deleterious mutations with an advanced age of onset, such as those causing Huntington's disease (HD), can therefore accumulate [1,2], and natural selection can favour mutants with beneficial effects in youth but at the cost of a subsequently higher rate of ageing (pleiotropy) [4]. Both routes lead to the evolution of ageing as a side effect, rather than a selected trait, and both suggest a complex genetic basis for ageing [3,5].

Surprisingly, however, mutations in single genes were found to extend healthy lifespan in the nematode worm *Caenorhabditis elegans* [6–8]. Subsequently, mutations in components of the nutrient-sensing insulin/insulin-like growth factor (IIS)/Target of Rapamycin (TOR) signalling network proved to extend healthy lifespan in the budding yeast *Saccharomyces cerevisiae*, *C. elegans*, the fruit fly *Drosophila* and mice [9,10]. Recent genetic association studies suggest that this network may also play a role in human ageing [11–13], implying strong evolutionary conservation. Drugs targeting nutrient-sensing networks, like rapamycin and metformin, can also extend lifespan (see Box 1 for details). These are licensed for human use, raising the possibility of modulating ageing in humans pharmacologically; however, both have side effects, which will need to be minimised when developing long-term treatment regimes to improve health during ageing.

Importantly, interventions that prolong lifespan can also decrease morbidity and improve health during ageing [14,15]. For example, nutrient-sensing mutants in *C. elegans* are resistant to tumours [16] and IIS mutant mice are resistant to Alzheimer disease (AD) pathology [15]. Rapamycin treatment of AD mouse models can also improve pathology [17] and dietary restriction (DR), the best-studied longevity-promoting intervention [14,18], provides a broad spectrum of health benefits (see Box 2 for details). Interestingly, lifespan extension and improvement in pathology don't always correlate [15,19], suggesting that amelioration of pathology may require particular modulations of pathway activity, or alterations within specific cell types.

As well as nutrient-sensing pathways, several other conserved traits, including mitochondrial activity, DNA damage response and telomeres, and autophagy are associated with ageing, and also play a surprisingly prominent role in disease development (Table 1). Deleterious mutations affecting predominantly later ages may play a role in disease aetiology. In addition, processes that are beneficial to the young, for instance because they increase fecundity, may contribute to later disease development, either because the activities that they promote in the young generate damage [20], or because the same activities that were beneficial in youth are harmful to the old; for instance, pathways that promote cell growth and proliferation potentially contribute to cancer [21]. Components of ageing pathways could therefore provide both novel, disease-relevant therapeutic targets, and also candidates for a broad-spectrum, protective effect.

Several conserved mechanisms are implicated in ageing. Some, such as nutrient-sensing pathways and mitochondria, maintain metabolic and energy homeostasis; others, such as DNA repair and autophagy, repair damage. We will focus on a few key examples and consider their role in aetiology of disease, exemplified by cardiovascular disease, neurodegeneration and cancer (Box 3, Table 2). Some relationships have been examined in great detail, such as DNA repair and cancer, while others have barely been touched on, like autophagy and cardiovascular disease.

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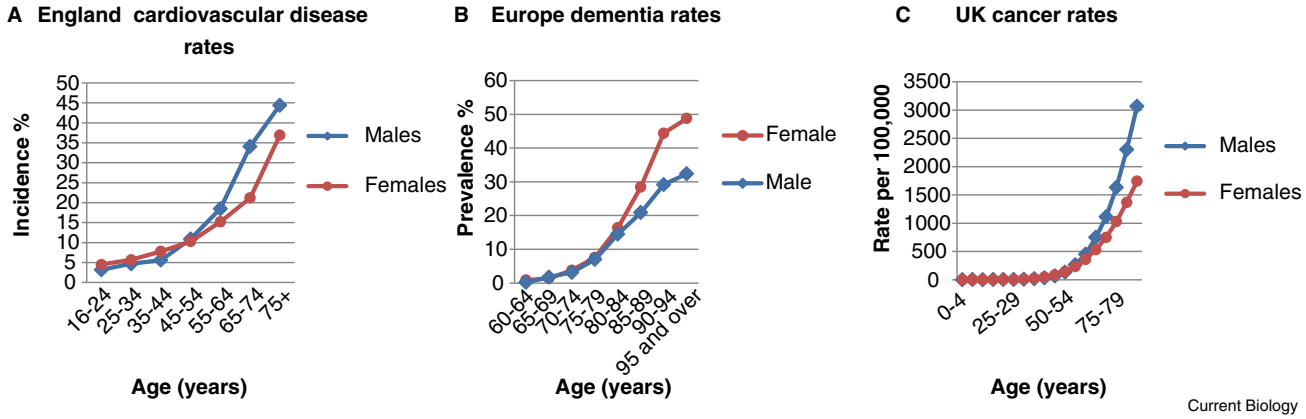

Figure 1. Disease or total death rates for the most common diseases of old age.

(A) Cardiovascular disease incidence in England in 2006 (source: British Heart Foundation 'Coronary heart disease statistics' 2010). (B) Dementia prevalence in EU countries in 2006 (source: Alzheimer Europe, 2009). (C) Age-specific mortality rates per 100,000 population, UK (source: Cancer Research UK).

Nutrient-Sensing Pathways

The IIS [22], TOR and AMP kinase (AMPK) signalling cascades sense the nutritional state of the organism and relay this information to cells, which modulate their metabolism accordingly (Figure 2). Nutrient-sensing pathways promote growth during development and contribute to fecundity [23]; however, their down-regulation can increase lifespan in yeast, *C. elegans, Drosophila* and mice [5,9,10,15]. Genetic variants in a key IIS transcriptional effector, FOXO3A, are also consistently associated with human longevity [12]. Candidate mediators of this effect are reduced cell growth and proliferation at later ages, altered mitochondrial activity and increased cellular detoxification and/or autophagy.

Autophagy is regulated both by AMPK and TOR, and is required for lifespan-extension by rapamycin in flies, worms and yeast [24,25]. Mitochondrial homeostasis and respiration are enhanced by activation of AMPK [26] and inhibition of TOR [27]. Detox pathway components are up-regulated in IIS mutants in flies, worms and mice, and can extend lifespan in worms and flies [5]. However, the relative contribution of each component is unknown. The mechanisms by which the network contributes to ageing-related disease may be the same as those that cause ageing, or may be to some extent disease-specific.

Cardiovascular

IIS/TOR signalling plays a systemic role in cardiovascular disease, by regulating metabolism, and a cell-autonomous one in cardiac function itself. Insulin regulates sugar and fat metabolism, and facilitates uptake of glucose by insulin-responsive tissues to be stored as fat. The nutritional conditions prevailing in nature and during the early evolution of humans would have led to strong selection for the ability to store calories during periods of food abundance for use during food scarcity. However, the ready availability of food for many modern humans combined with reduced energy expenditure on activities, including exercise, immune response and thermoregulation, can cause excessive food intake and insulin secretion and hence accumulation of visceral fat and insulin resistance, major risk factors for cardiovascular disease [28,29]. Inhibition of IIS in the fat body of a *Drosophila* model of high-fat-diet-induced obesity prevents lipid accumulation and protects the heart from pathology [30], underscoring the role of IIS in obesity and disease development.

Obesity triggers insulin resistance through several mechanisms. Adipocytes secrete free fatty acids and adipokines, which can inhibit IIS in peripheral tissues, leading to insulin resistance, hyperglycaemia (because sugar is no longer cleared from the blood) and type II diabetes [29]. Insulin resistance and hyperglycaemia can contribute directly to the formation and progression of atherosclerotic lesions (for details see [31]), a major cause of cardiovascular disease (Box 3). Accordingly, individuals who maintain high insulin sensitivity are less at risk of cardiovascular disease [28]. Strikingly, centenarians maintain high insulin sensitivity [28], whereas genetic variants associated with decreased insulin signalling are associated with insulin resistance and diabetes [31], suggesting systemic IIS pathway activation itself confers protection from cardiovascular disease in the absence of obesity.

TOR also links obesity and heart disease, through several mechanisms [29]. IIS can activate mTORC1, which, via S6K1, phosphorylates and down-regulates Insulin Receptor Substrate 1 (IRS1). Mice null for S6K1 lack this negative feedback and do not develop diet-induced insulin resistance [29]. In a *Drosophila* model of diet-induced cardiac dysfunction, inhibition of TOR signalling, especially in the heart and fat body, rescues cardiac pathology and increases insulin sensitivity [27,32].

Nutrient-sensing pathways also act directly on the heart to influence its function. The heart is insulin-responsive and can develop obesity-induced insulin resistance [33], associated with cardiac remodelling and systolic dysfunction [29]. Both IIS and AMPK activation improve outcome following infarction [33,34–36]. IIS promotes vascular reperfusion and increases glucose availability [33], whereas AMPK stimulates glycolysis and maintains energy homeostasis when oxygen supply decreases [35,36], thus protecting the heart from ischaemic damage. However, long-term IIS activation can lead to pathological hypertrophy and heart failure [37] and in *Drosophila* reducing IIS signalling systemically or specifically in the heart rescues age-related cardiac functional decline [38].

Box 1

Drugs extending lifespan.

Rapamycin
Rapamycin inhibits mTOR, and can increase lifespan in worms, flies and mice [49,118]. By inhibiting mTOR, rapamycin induces autophagy, which is required for lifespan extension in flies, worms and yeast [104]. Other mechanisms of action include inhibition of S6 kinase, essential for its lifespan effect in flies [25], and inhibition of growth and proliferation [45].

Metformin
Metformin is an AMPK activator that can extend lifespan in mice and *C. elegans* [119]. Multiple mechanisms could be at work. Metformin reduces hyperglycaemia in several ways and boosts insulin sensitivity, which has been associated with mammalian, including human, longevity [28]. For metformin to extend lifespan in *C. elegans*, AMPK activity and SKN-1/Nrf2 (nuclear factor, erythroid derived 2), an oxidative stress-responsive transcription factor that has itself been linked to ageing [119], are both required. Metformin also inhibits mTOR and boosts mitochondrial function, which could also contribute to its effect on lifespan [120].

TOR function also seems beneficial: cardiac-specific overexpression of TOR protects against dysfunction following overload [29] and loss of TOR is detrimental. TOR also induces cardiac hypertrophy, which is important in young fit adults in order to increase cardiac output in response to exercise, but in later life TOR-mediated pathological cardiac hypertrophy can lead to heart failure, which can be ameliorated by rapamycin [29], suggesting that quantitative and context-specific modulation of TOR is important.

Nutrient-sensing pathways therefore act in multiple, sometimes opposing, manners to modulate cardiovascular disease development and their effects are context-specific.

Neurodegeneration

Nutrient-sensing pathways act indirectly via cardiovascular disease to affect AD because the risk of AD is related to cardiovascular disease risk profile, and AD may indeed have a strong vascular component [39]. IIS signalling also plays a direct role in neuronal development, maintenance and pathology [40], albeit not a simple one. Reduced IIS specifically in neurons extends lifespan in *C. elegans*, *Drosophila* and mice [41], and also ameliorates proteotoxicity and neurodegenerative disease in animal models [42]. However, insulin can also be neuroprotective: insulin resistance impairs memory, is a risk factor for AD and exacerbates Aß deposition in mice [43], and AD patients show reduced insulin signalling, associated with increased tau phosphorylation, a hallmark of AD [43]. Knock-out of the *Irs2* gene in mice also leads to increased phosphorylation of Tau but, surprisingly, it ameliorates Aß pathology [15], suggesting that insulin signalling might have opposing effects on different aspects of AD aetiology. Acute insulin administration can promote memory in rodents, humans [43] and, possibly, in patients with early AD [44], although the effects on disease development are unknown. Hence, IIS can have both positive and negative effects on neuronal decline, possibly depending on the level or mechanism of pathway alteration.

TOR also plays a complex role in neurodegenerative disease. TOR signalling is enhanced in AD neurons, where it may promote tau-mediated neurodegeneration, but it is reduced in cultured cells exposed to Aß, while the TOR inhibitor RTP801 is elevated in the brains of Parkinson's disease (PD) patients [45]. Inhibition of TOR with rapamycin ameliorates toxicity in fly and mouse models of PD, HD, AD and amyotrophic lateral sclerosis (ALS) [45], mostly by activating autophagy, but also by decreasing translation and inhibiting apoptosis [45]. Pharmacological inhibition of TOR is hence a possible therapeutic avenue for neurodegenerative disorders.

Cancer

Cancer, unlike cardiovascular disease and neurodegeneration, is characterised by unwanted cell replication rather

Box 2

Dietary restriction.

Dietary restriction (DR), the best-studied longevity-promoting intervention [18], can increase lifespan in diverse species from yeast to primates [14]. It also provides a broad spectrum of health benefits. DR mice are protected against multiple age-associated diseases, including cancer, diabetes, atherosclerosis, cardiomyopathy, respiratory diseases and neurodegeneration [14]. These health benefits of DR extend to primates: DR rhesus monkeys have reduced incidence of diabetes, cancer, cardiovascular disease, and brain atrophy [14]. Indeed, humans on a DR diet for a limited period of time show a decrease in risk factors associated with coronary heart disease [14], an improvement in glucocorticoid function and increased insulin sensitivity [14]. However, DR does not protect against all disease-related pathology: although it increases lifespan, it does not ameliorate neuronal dysfunction in a *Drosophila* model of AD [19] and in humans DR does not improve muscle and bone function [121]. Moreover, DR has a detrimental effect on some aspects of immunity; DR mice can show increased susceptibility to infection [14] and impaired wound healing that can be restored upon full feeding [14], indicating that its practice in a real-life environment might have drawbacks.

Table 1. Role of ageing pathways in disease.

Pathway	Effects on cardiovascular disease	Effects on neurodegeneration	Effects on cancer
IIS/TOR **AMPK**	Insulin resistance is associated with diabetes and cardiac dysfunction. Insulin, TOR and AMPK have cardio-protective role. TOR and IIS downregulation can sometimes also be protective	Increased signalling might be protective; however, long lived IIS mutants with reduced signalling improve pathology	Negative regulators of IIS and TOR signalling are tumour suppressors
Mitochondrial function	Defective mitochondria lead to cardiomyocyte apoptosis, and cell loss in the heart	Impairment in function and morphology is associated and appears to promote pathology, especially in PD	mtDNA mutations are oncogenic. Mitochondria via ROS production can drive malignancy progression
DNA damage response (DDR) and telomeres	High DNA damage and telomere shortening increase endothelial senescence leading to atherosclerosis; however, telomerase is active in later stages of atherosclerosis. Could also contribute to cell loss in the heart	Attempted re-entry into the cell cycle following DNA damage can lead to neuronal cell death in neurodegenerative diseases Telomere role uncertain	Defects in DDR allow cancer cells to accumulate mutations and grow uncontrollably Telomere shortening leading to replicative senescence is one of the main breaks on tumour progression
Autophagy	Defects in autophagy lead to cardiomyopathy and cardiac hypertrophy. Defects in autophagy also protective for cardiac remodelling following overload	Defects in autophagy lead to accumulation of toxic protein aggregates and defective mitochondria, contributing to pathology	Autophagy is protective to early stages of tumour growth; however, it helps cancer cells spread in later stages

than cell death (Box 3). Nutrient-sensing pathways generally stimulate growth in response to nutrient availability. Accordingly, hyperinsulinaemia stimulates cell division and can induce cancer [46] and positive regulators of IIS signalling are usually oncogenic whereas negative regulators are tumour suppressors [47]. Mutations extending lifespan in *C. elegans, Drosophila* and mice can hence also be tumour suppressors [48]. Drugs targeting nutrient-sensing pathways, such as rapamycin derivatives and metformin, are promising anti-cancer treatments in humans. Rapamycin is already in clinical use as a cancer chemotherapeutic [49] and epidemiological analysis has implicated metformin in protection against cancer [50]. Whether down-regulating IIS/TOR signalling affects tumour progression by inhibiting growth or by other mechanisms remains to be clarified. For example, it may boost immunity [15,51], because cancer development is promoted in immunodeficient mouse models [52]; however, rapamycin is an immunosuppressant, so this is unlikely to be its mechanism of action.

Cancer cells switch from oxidative phosphorylation, active in post-mitotic, differentiated cells, to aerobic glycolysis, usually active in highly proliferating cells, thus diverting glucose into production of biomass to support the high level of cellular proliferation [53]. Glycolysis also allows cells to proliferate in hypoxic conditions, common in tumours [54]. This switch is regulated by components of nutrient signalling pathways, such as phosphoinositide 3-kinase (PI3K)/Akt [53], TOR [55] and oncogenic Ras [54]. Therefore, inhibiting these pathways could also inhibit this metabolic switch and reduce tumour cell proliferation.

Mitochondria

Mitochondria produce most of the cell's energy, in the form of ATP, through respiration. As a by-product, reactive oxygen species (ROS) are generated. Until recently, ROS were considered a leading cause of ageing. However, direct experimental evidence for this hypothesis is lacking [56,57], because reduced activity of antioxidant enzymes can increase susceptibility to oxidative stress without affecting lifespan [58], while increased protection by over-expression of antioxidant enzymes does not generally increase lifespan [58,59], or does so by means other than reduced production of ROS [60].

Mitochondria, however, probably do play an important role in ageing. Transcription of genes encoding mitochondrial proteins declines with age [42], and impaired mitochondrial fission leads to disorganized mitochondrial morphology [61]. Whether these changes are purely a result of age-specific genetic effects or are a consequence of events beneficial earlier in life remains to be seen. Moderately reduced mitochondrial activity can increase lifespan in yeast, worms, flies and mice [10], although the exact mechanisms at work await discovery.

The role of mitochondria in disease development is not well explored, with notable exceptions such as PD. However, evidence is emerging that they have an important role in cardiovascular disease and as a driver for cancer progression.

Cardiovascular

Cardiomyocytes contract constantly, and hence require highly efficient mitochondria to meet their energy demands. Dysfunctional mitochondria accumulate in ageing cardiomyocytes [62], leading to reduced energy production and impaired contractility. Excessive accumulation of defective mitochondria triggers apoptosis, and the resulting cell loss can contribute to heart failure [63]. ROS production from mitochondria can stimulate cellular events, leading to pathological myocardial remodelling and consequent heart failure [64]. A mouse model with increased mitochondrial (mt)DNA mutation rate shows traits characteristic of premature ageing and an enlarged heart [65], suggesting that normal mitochondrial function is important for heart function.

Neurodegeneration

Neurons also have a high oxygen consumption and rely on efficient mitochondria. Indeed, genetic disorders of mitochondria predominantly impair neuronal and muscle function, and occur in many neurodegenerative diseases [66].

Box 3

Diseases of old age.

Cardiovascular disease

Cardiovascular disorders are the leading cause of death in the western world [122]. The term encompasses any disease affecting the heart or the circulatory system, the two most prominent forms being coronary heart disease and stroke. The main common cause of cardiovascular disease is atherosclerosis, caused by the localised accumulation of cholesterol within the walls of arteries, leading to the formation of hard plaques and the narrowing of the arterial lumen and, occasionally, the break-off of a clot. Both can lead to a blockage, cutting-off vital oxygen supply and causing downstream tissue death. In the heart this leads to an acute myocardial infarction (AMI) and in the brain to a stroke.

The other main risk factors for cardiovascular disease are obesity, HDL/LDL ratio, type II diabetes, high blood pressure [62] and, mostly, age (Figure 1). In fact, older people are not only more likely to develop AMI, but also more likely to die from it [62]. This is possibly because even healthy heart function declines with age due to cardiomyocyte loss, decrease in contractility, decrease in stress resistance, cardiac hypertrophy and fibrosis [35].

Neurodegeneration

Neurodegenerative diseases are characterised by the progressive death of neurons and loss of brain structures. There are a number of these disorders, with AD and PD being the most common. Although these conditions can affect different parts of the brain and present with different symptoms (Table 2), age is the main common risk factor. Also in common is the abnormal deposition and mis-localisation of insoluble protein aggregates, associated with progressive, age-related decline in neuronal function.

Exactly how age acts as the chief risk factor for these diseases is not clear. Insoluble, toxic proteins may accumulate with time, and older neurons may be more vulnerable to toxic effects. Abnormalities in protein turnover and processing might also make older neurons less able to degrade toxic proteins.

Cancer

Unlike cardiovascular and neurodegenerative diseases, which are characterized by cellular senescence, apoptosis and decreased mitosis, cancer is characterized by uncontrolled cellular proliferation, where cells become unresponsive to the usual check-points, leading to tumour growth and metastasis.

Age, a family history of disease and an unhealthy lifestyle increase the risk of developing cancer. However, environmental exposure to specific factors, such as tobacco, sunlight, viruses and certain hormones, seems to play a much greater role, which varies with different types of cancer: tobacco for lung cancer, sunlight for melanoma and papillomavirus for cervical cancer, to give some examples.

Why older people are more susceptible to cancer is not totally understood: cells might need time to accumulate enough mutations to become cancerous or older individuals might be more susceptible to oncogenic mutations [123].

Several mutations causing autosomal recessive PD are directly or indirectly involved in mitochondrial metabolism [67]. In particular, PINK1 and Parkin affect mitochondrial morphology and turnover in *Drosophila* and mouse models [68]. In PD brains, the activity of the mitochondrial electron transport chain (ETC) complex I is often reduced, and exposure to an ETC complex I inhibitor causes PD-like symptoms in both animals and humans [67]. Mitochondria may thus be important in the aetiology of sporadic PD, although the precise mechanisms are an area of current research focus.

In AD, Aß accumulation in mitochondria is associated with reduced activity of ETC complexes III and IV and of COX [67]. Human AD brains and animal and cellular models of AD display defects in mitochondrial transport and morphology, possibly mediated by Drp1, a dynamin-related protein important for mitochondrial fission [67]. Whether these mitochondrial defects are a cause or consequence of AD aetiology remains controversial.

Impairment of mitochondrial function in AD and PD could be caused by mtDNA ROS damage; in both AD and PD, deletions, mutations and fragmentation of mtDNA are observed [67]. This could trigger apoptosis, thus contributing to neurodegeneration [66]. The mitochondria-targeted antioxidant MitoQ prevents loss of spatial memory and early neuropathology in a transgenic AD mouse model [69], indicating a possible causal link between ROS-induced mtDNA damage and neurodegeneration.

Mitochondrial defects also occur in HD, and modulating mitochondrial function can ameliorate the pathological phenotypes of fly [70], and mouse [71] models, suggesting that targeting mitochondrial function could be a viable therapeutic approach, at least in some neurodegenerative disorders.

Cancer

In cancer cells, mtDNA can be highly mutated, and numerous polymorphisms and mtDNA mutations have been linked to increased cancer susceptibility [72], suggesting that mtDNA alterations, like nuclear genomic alterations, play an important role in cancer development.

When cancerous cells up-regulate aerobic glycolysis, mitochondrial activity is reduced. For example, the catalytic subunit of mitochondrial ATP synthase is down-regulated in human carcinomas [73]. The shift to glycolysis also makes the mitochondria more stable and less able to activate apoptosis, thus helping cancer cells to proliferate [73]. Recently, mitochondria have also emerged as a driver of malignant transformation, through ROS production. In early tumours, as mitochondrial activity is impaired, ROS production increases, leading to further mtDNA damage, and decreased mitochondrial function. This vicious circle of

Table 2. Characteristics of neurodegenerative disorders.

Disease	Initial brain area affected	Presentation	Histological hallmarks	Genetic factors
Alzheimer's disease	Entorhinal cortex, spreading to temporal lobe and frontal cortex	Memory loss and behavioural disturbances	Extracellular plaques composed of Aß protein and intracellular neurofibrillary tangles composed of Tau protein	APP, PS1 PS2, ApoE4, PICALM, BIN1, PICALM, CLU, CR1
Parkinson's disease	Dopaminergic neurons of the substantia nigra	Resting tremor, postural instability, gait disturbances, bradykinesia and rigidity	Cytoplasmic inclusion called Lewy bodies containing aggregated alpha synuclein protein	α-synuclein, LRRK2, PINK1, parkin and DJ-1
Huntington's disease	GABAergic neurons in striatum and cortex	Chorea, psychiatric disturbances and cognitive impairment	Mutant Htt protein aggregates	Htt
Amyotrophic lateral sclerosis	Lower motor neurons in the spinal cord and in the brain stem; corticospinal upper motor neurons in the precentral gyrus; and, frequently, prefrontal motor neurons	Progressive muscle weakness, muscular atrophy, spasticity and eventual paralysis	Cytoplasmic aggregates of SOD1, FUS or TDP-43	SOD1, ALS2, FUS/TLS, ALS10, TDP-43

increased ROS, mitochondrial and nuclear DNA damage eventually leads to the accumulation of enough oncogenic mutations to allow the tumour to metastasize [54]. Transferring mtDNA from a highly metastatic cell line can make a poorly metastatic cell line highly metastatic, and inhibition of ROS blocks this metastatic potential [74], implicating it in driving cancer progression. Defects in mitochondrial function therefore not only impair tissue function (for example, in neurons and cardiomyocytes) but also, through ROS production, can act as a driver of disease development.

Pathways involved in metabolism and energy homeostasis can clearly have substantial effects on disease development; however, the relationship is not a straightforward one, where interventions that increase lifespan improve pathology across the board. On the contrary, a complex picture emerges, where the activity of these pathways has to be modified in particular ways, to particular extents and in specific tissues to confer protection against disease.

DNA Damage Response Pathway and Telomeres

Both environmental factors, such as UV irradiation and the cell's own metabolic processes (generating ROS) can lead to DNA damage, which tends to accumulate with time [75]. The DNA damage response (DDR) pathway plays a crucial role in maintaining the integrity of an organism's DNA, by monitoring and repairing any damage and, if the damage is too extensive, by triggering cellular senescence and apoptosis.

The integrity of chromosome ends is ensured by specific structures called telomeres, replicated by the telomerase complex. In adult cells telomerase is only partially active, and as the organism ages and cells divide, telomeres shorten. Once telomeres become critically short, the DNA damage checkpoint is activated, triggering replicative senescence [76]. This system limits the number of times a cell can divide and is one of the main brakes on tumour development. Mutations in DDR components, such as p53 or Rb (retinoblastoma), lead to cancers in early life [77]. In later life, however, telomere shortening and accumulation of senescent cells may contribute to ageing; an example of ageing occurring as a result of an activity that helps to prevent cancer at younger ages. Telomere shortening reduces the regenerative potential of stem cells [76] and clearance of senescent cells in a mouse model of premature ageing delays ageing-associated pathologies [78]. Moreover, some p53 alleles that confer cancer resistance induce early ageing in both humans and mice [79], suggesting that the earlier cancer-resistance function does indeed, as a side effect, induce ageing.

Defects in the DNA repair and telomerase pathway components in humans and mice can result in premature ageing [80], underscoring their importance in early life. Whether this equates to a causal role in ageing is more controversial [81]. Manipulation of DNA repair and telomere pathways can extend lifespan under certain conditions. Polymorphisms in telomerase reverse transcriptase (hTERT) [12] have been associated with longevity in humans, while increased telomerase activity can increase lifespan in cancer-resistant mice [15]. However, mice have much longer telomeres than humans, and any connection between telomere length and rate of ageing across species is highly complex and does not suggest any simple causal relationship [82].

Over-expression of p53, a powerful tumour suppressor involved in DNA repair, can extend lifespan in *Drosophila* and mice. However, a reduction of p53 activity is also associated with lifespan extension in *C. elegans*, *Drosophila* and humans [83]. Moreover, it is unclear whether p53's role in longevity is due to its interaction with the IIS and TOR pathways [83], or its roles in cellular senescence [75] or DNA repair [83]. Given the varied evidence, more work is needed to clarify the importance of genomic maintenance in ageing. Better established is its role in cancer, and recent evidence points to a role in cardiovascular disease and neurodegeneration (Figure 3).

Cardiovascular

Increased DNA damage and decreased telomere length are associated with atherosclerosis, coronary artery disease and heart failure [84,85]. The high levels of DNA damage and shortened telomeres in the vascular endothelium are thought to promote cellular senescence, which feeds the inflammatory cycle, leading to plaque deposition [85,86]. The internal mammary artery, which is protected from atherosclerosis, has longer telomeres than other arteries [87] and increasing telomerase activity can protect from endothelial senescence [87], whereas reducing DDR by mutation of the ataxia

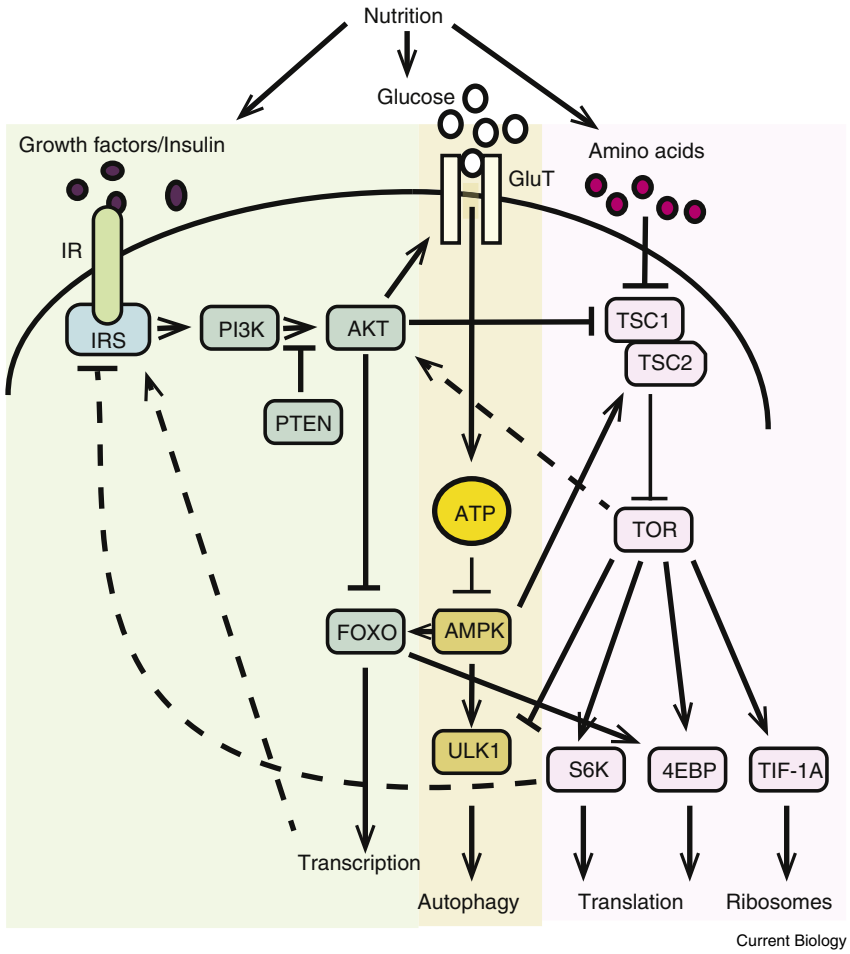

Figure 2. Nutrient-sensing pathways.

Illustration of nutrient-sensing pathways' responses to nutritional signals and how they interact with each other. Dotted arrows represent negative feedback interactions between the pathways. Upon insulin/IGF binding, insulin-like receptors signal via the Insulin Receptor Substrate (IRS) to Akt to inhibit FOXO and stimulate the glucose transporter (GluT) to allow glucose import. Amino acids stimulate TOR via TSC1/TSC2 inhibition to down-regulate autophagy and promote translation via S6K and 4EBP. ATP levels modulate AMPK, which can promote autophagy and also interacts both with the IIS and TOR pathways. In a number of organisms there are multiple paralogue copies of insulin-like receptors, IRS, FOXO and GluT, but for simplicity only one is depicted.

telangiectasia mutated (ATM) protein worsens the vascular phenotype of a mouse model of atherosclerosis [84], suggesting that DDR and telomeres play a protective role in atherosclerosis. However, late atherosclerotic lesions induce proliferation of vascular smooth muscle cells, which requires telomerase activity, and mice with shortened telomeres are protected from aortic atherosclerosis [87], suggesting a complex relationship.

DNA damage and short telomeres in ageing cardiomyocytes may lead to cell loss by increasing cellular senescence and apoptosis, and limiting the proliferative potential of cardiac progenitor cells, thus contributing to heart failure [62,87]. Mutations in DDR genes, including *ATM* and *BRAP2*, increase the risk of developing ischaemic heart disease in humans [84]. In mice, short telomeres halve cardiomyocyte numbers and increase heart dysfunction, whereas increased telomerase activity reduces apoptosis and improves function following ischemic injury [87], indicating a protective role for telomeres and DDR in cardiac function.

Neurodegeneration

Post-mitotic neurons are both metabolically active and long-lived, and over the course of a lifetime gradually accumulate DNA damage. This initially compromises the expression of subsets of genes important for neuronal function [88] and eventually triggers cell cycle re-entry, which in neurons leads to apoptosis and neurodegeneration [11]. DNA damage and markers of cell cycle re-entry accumulate in brains of patients with AD or PD and in disease models [11,89] and inhibiting cell cycle re-entry blocks apoptosis in these models [90]. Cdk5, p53 and ATM have all been implicated in cell cycle re-entry in both AD and PD, and blocking Cdk5 activation inhibits tau hyperphosphorylation, cell-cycle re-entry, synaptic loss and neuronal death triggered by Aß in mice [90]. Recently, two DNA damage biomarkers, chitinase (chitotriosidase activity) and stathmin protein, were found to be significantly increased in AD and non-AD dementia, although any causal link between these biomarkers, DNA damage and AD development is yet to be demonstrated [91].

Telomerase expression is high in neuronal stem cells and is important for brain development [92]; it decreases in differentiated neurons, but can be reactivated in response to stress, where it may play a protective role, because inhibiting telomerase increases neurons' susceptibility to apoptosis [93]. The role of telomeres in neurodegeneration is much less clear. Telomere shortening seems to play no role in PD development [94] and, surprisingly, seems to be protective in AD [95]. Further work will be required to clarify mechanisms.

Cancer

The main hallmark of cancer is genomic instability leading to uncontrolled cell proliferation, and most cancer risk factors cause DNA damage. Many DDR components were first identified as tumour suppressors and patients harbouring DDR mutants are highly susceptible to cancer [96]. In cancer cells, DDR pathway components, such as ATM and BRCA1, have to be impaired for a tumour to develop [97], allowing cells to proliferate regardless of their damaged DNA, and without repairing it, which leads to further DNA damage and, eventually, to a highly proliferating and mutagenized cellular population that can escape its local environment and metastasise.

The induction of senescence in response to DNA damage is mediated by well known tumour suppressors such as p53

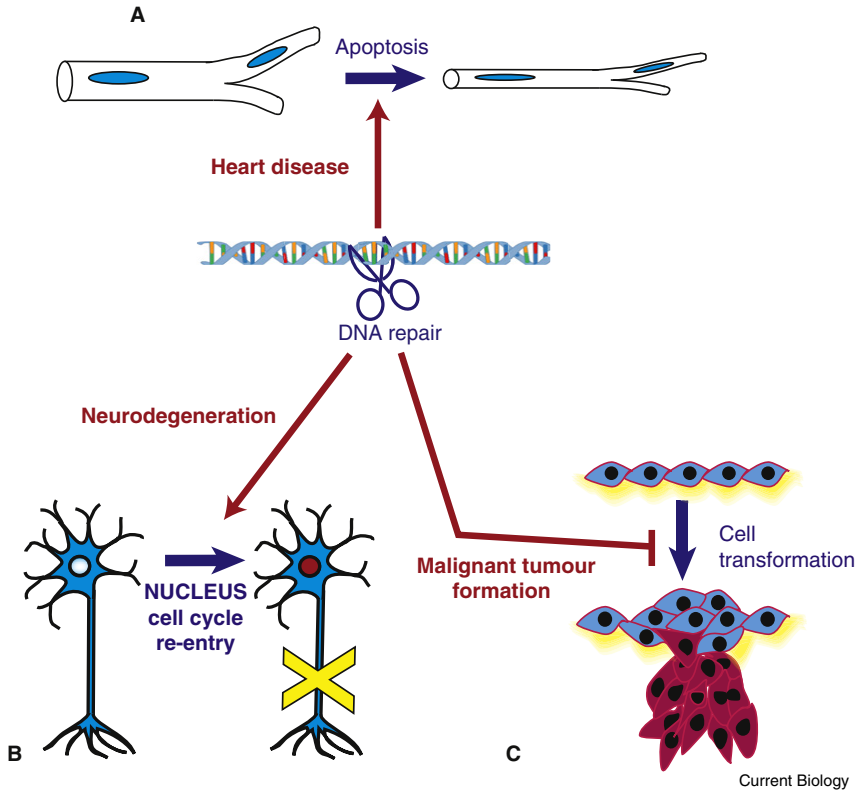

Figure 3. DNA repair in disease development.
Diagram of the contribution of DNA damage repair to the development of disease. (A) By inducing senescence and apoptosis in cardiomyocytes, DNA damage repair contributes to heart disease. (B) Triggering cell cycle re-entry contributes to neurodegeneration; (C) but when working efficiently blocks cancer development.

or Rb1 [98] and limits the proliferative potential of damaged cells, providing the main protection an organism has against cancer. Accordingly, an activated DDR, inducing cellular senescence, has been observed in early, benign lesions with accumulated DNA damage [99,100]. The importance of p53 has been underscored by two studies showing that re-activation of p53 in tumours leads to their clearance; however, this was at least partly due to induction of an innate immune response that targeted the tumour cells *in vivo* [101,102].

Limiting proliferative potential of useful cells (such as stem cells) could, however, contribute to ageing phenotypes. But p53 can also protect against both cancer and ageing; mice with increased expression of p53 and Arf were resistant to both [103], suggesting that cancer resistance and longevity are not mutually exclusive.

Another mechanism that helps to prevent cancer development is replicative senescence induced by telomere shortening. To overcome this barrier cancer cells either activate telomerase or have found a way to replicate their telomeres in the absence of telomerase [98]. Confirming the role of telomeres, mice with short telomeres are resistant to tumours whereas transgenic mice with increased TERT (the catalytic subunit of telomerase) activity are susceptible to cancers [76]. However, activation of telomerase in cancer-resistant mice does increase lifespan [76], again demonstrating that cancer resistance and longevity can co-exist.

DDR and replicative senescence due to telomere shortening therefore provide an efficient barrier to cancer development throughout life, and would probably have come under selective pressure for this role but, in later life, might also induce cell loss in post-mitotic tissues such as the heart and brain, contributing to cardiovascular disease, neurodegeneration and ageing.

Autophagy

Autophagy allows digestion of cytoplasmic material and organelles by lysosomes [104]. This contributes to cellular maintenance by eliminating and recycling damaged components, and provides biofuel for the cell. Its role in aging has gained prominence in recent years. Autophagy plays a crucial role in youth, since both elevation of and defects in autophagic activity can impair fitness [104]. Expression of the proteins required for autophagy declines in ageing tissues and in age-related disorders [104], and correcting this deficiency in mouse liver can ameliorate age-related phenotypes [104]. The exact reasons for the age-related decline in expression of autophagy genes are unknown. Such defects in gene expression are a more general feature of ageing [105], but why the reduced intensity of natural selection should lead to this outcome is not clear.

Many lifespan-extending interventions require autophagy [104]. For example, rapamycin cannot extend lifespan if autophagy is inhibited [104]. Moreover, in *Drosophila*, brain-targeted overexpression of Atg8, a component of the autophagy pathway, is sufficient to extend lifespan [104].

Autophagy could promote longevity by a number of mechanisms. It helps to clear toxic proteins and defective mitochondria, it suppresses oncogenic transformation and could help maintain stem cells, boost immune function and possibly regulate insulin homeostasis [104]. Any of these downstream effectors could mediate its lifespan effect, and the exact mechanisms await further clarification.

Its role in disease development is also gaining increasing attention.

Cardiovascular

Autophagy plays an important role in cellular maintenance in the myocardium. During ageing, autophagic flux is slowed, leading to accumulation of damaged and toxic organelles and proteins, which can lead to cardiac dysfunction and heart failure [106]. Patients with mutations in lysosomal associated membrane protein 2 (LAMP2), which is required for lysosome-autophagosome fusion, have defects in autophagy leading to severe cardiomyopathy [106], strongly implicating autophagy in the maintenance of a healthy heart. Experimental models confirm the importance of autophagy, which is induced in response to cardiac injury in a number

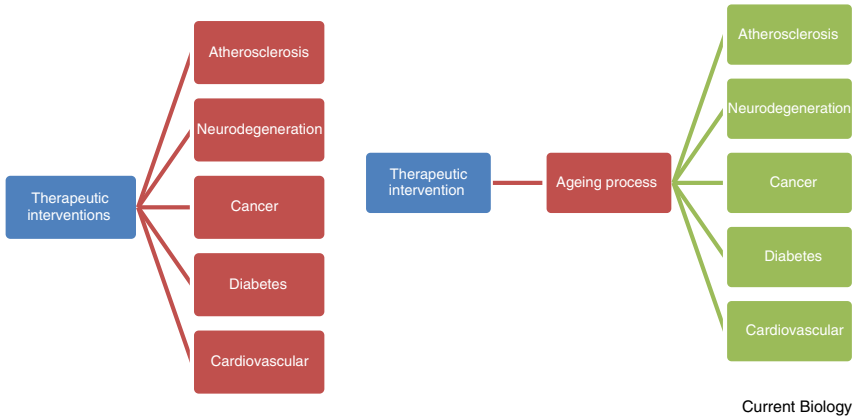

Figure 4. Current therapies target individual diseases in isolation; therapies targeted to the ageing process itself aim to cover many diseases simultaneously.

of animal models [107]. Decreasing autophagy — for example, by decreasing the level of autophagy protein 5 (atg5) — leads to hypertrophy and heart failure in a mouse model [106]. However, decreasing Beclin-1 function reduces autophagy induction and decreases maladaptive cardiac remodelling following overload [106]. This suggests that whereas autophagy is required for myocardial homeostasis, excessive induction following a cardiac insult might be detrimental.

Neurodegeneration

Because autophagy can remove protein aggregates, which are associated with most neurodegenerative diseases (Table 2), it is perhaps unsurprising that it plays a protective role [104]. In AD, PD and HD brains autophagic and lysosomal vesicles accumulate, suggesting a blockage in the autophagy process [108]. The toxic proteins associated with neurodegeneration might directly inhibit autophagy. For instance, human Aß inhibits autophagy in a *Drosophila* model [109], pathogenic alpha-synuclein can inhibit chaperone-mediated autophagy, and mutation of Htt perturbs ER function leading to an increase in autophagosomes [108]. Genetic or pharmacological enhancement of autophagy can ameliorate phenotypes in a number of neurodegenerative disease models in *Drosophila* [42] and mice [110], whereas inhibition of autophagy by hyperactivation of TOR [111] or mutants in autophagy itself promote protein aggregation and neurodegeneration in various model organisms [104,112].

Autophagy also removes defective mitochondria, especially important in post-mitotic cells such as neurons [104] and PD-associated PINK1 and Parkin selectively target defective mitochondria to autophagic degradation, with defects in these genes resulting in accumulation of defective mitochondria, leading to PD [108,113]. Autophagy's protective role in neurodegeneration could therefore also be due to its role in mitochondrial clearance.

Cancer

Oncogenes tend to inhibit and tumour suppressors activate autophagy, suggesting that autophagy needs to be down-regulated for cancer proliferation [98,114]. However, abrogation of autophagy in mouse models (by *atg5* or *atg7* deletions) leads to an increase only in benign tumours, suggesting that total lack of autophagy promotes the initial stages of cancer development but prevents tumour metastasis [114].

Partial impairment of autophagy, on the other hand, promotes malignancy: human breast and ovarian cancers often show loss of one copy of the *BECN1* gene, which only partly decreases autophagy, and mice heterozygous for *BECN1* show an increase in benign and malignant tumours [114]. This could be because once a tumour is established, autophagy becomes re-activated and promotes cancer survival [114]. ROS, hypoxia and nutrient deprivation, all experienced by cancer cells, stimulate autophagy. Also, the initial conditions promoting mutagenesis and allowing cell transformation, such as DNA instability and ROS, would hinder rapid growth. Autophagy re-activation helps reduce damaged organelles and proteins allowing the tumour cells to thrive while providing amino acids and fatty acids to fuel the growth and the metabolic reactions of these highly proliferating cells. A number of cancers, such as Ras-positive ones, show a high level of basal autophagy and its down-regulation impairs cancer cell metabolism and tumour growth [114]. Chemotherapy drug combinations that include autophagy inhibitors have shown promise in pre-clinical trials and animal models [114,115]. Further studies will be needed to establish the true efficacy of this approach in cancer therapy and whether it is indeed attributable to altered autophagy, rather than some other, as yet unknown, function.

Conclusions

With age, the disease burden increases. Interestingly, the same pathways that modulate longevity affect the development of multiple, age-related pathologies. Ageing as a disease risk factor can be thought of as the accrued effect of a finite number of evolutionarily conserved pathways. These pathways either have been selected for a specific beneficial function in earlier life, for instance DNA repair, and, as a side effect, actively contribute to the ageing process, or come under weakening evolutionary pressure later in life and therefore accumulate mutations with deleterious effects in aged organisms. Interestingly, interventions that extend lifespan in model systems often appear to lead to a broad spectrum improvement in health [9,15]. However, the effect on specific disease models often appears more complex. Conflicting reports in the literature might suggest that the efficacy of a particular intervention is specific to the experimental approach used. The exact molecular component targeted may be important. For example, insulin or IGF1 receptors, usually assumed to be involved in IIS, have a pro-apoptotic function independent of IIS [116], suggesting that some outcomes may be mediated by another, unidentified, role of the particular protein targeted. With these considerations in mind, however, the consistent association between processes involved in ageing and ageing-related disease aetiology suggests that it should be possible to modulate these processes to improve the cellular and systemic environment of older individuals and provide a broad-spectrum health improvement (Figure 4).

Table 3. Lifespan- and disease-specific effects of rapamycin and metformin.

	Rapamycin	Metformin
Lifespan	Extends lifespan in mice, worms and flies	Extends lifespan in mice and worms
Cardiovascular	Decreases pathological cardiac hypertrophy Reduces restenosis following stent procedure	Reduces type II diabetes and its associated complications
Neurodegeneration	Protects flies and mice models of AD, PD, HD and ALS	No effect on male and harmful in female ALS mice model
Cancer	Used therapeutically for renal cell carcinoma	Reduces incidence of some cancers

This approach is not as far-fetched as it may first appear. Drugs often affect more than one disease, metformin and rapamycin being key examples (Table 3). Lifestyle choices affect multiple diseases: smoking and obesity are risk factors for most ageing disorders and a good cardiovascular risk factor profile reduces the overall mortality risk from any disease [117]. Recent research provides a reason: the same conserved signalling pathways are involved in most if not all diseases of old age. These pathways may have been selected to provide an evolutionary advantage to organisms in situations of limited resources and exposure to numerous pathogens, where few individuals reach old age. In laboratory animals or western society these conditions no longer exist, opening the possibility of re-tuning these pathways to fit new circumstances. Direct manipulation of these pathways therefore could offer a more comprehensive, and possibly cost-effective, way of improving health in later life.

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