CORE
Metadata, citation and similar papers at core.ac.uk
Provided by Elsevier - Publisher Connector

CellPress

Intervening in ageing to prevent the diseases of ageing

Linda Partridge[1,2]

[1] Max Planck Institute for Biology of Ageing, Joseph-Stelzmann-Str. 9b, D-50931 Cologne, Germany
[2] Institute of Healthy Ageing, and Department of Genetics, Environment, and Evolution, University College London, Darwin Building, Gower Street, London WC1E 6BT, UK

Increases in human lifespan worldwide have revealed that advancing age is the predominant risk factor for major life-threatening diseases. Recent work has shown that ageing in diverse animals, including humans, is malleable to specific types of genetic mutation, diet, and drugs that can extend lifespan and improve health during ageing. These findings point to the prospect of broad-spectrum preventive medicine for the diseases of ageing based on intervention in relevant aspects of the ageing process itself.

Rising life expectancy

Human populations in developed countries, and in many developing ones, are getting older. Human life expectancy at birth has been increasing by about 2.5 years per decade since the middle of the 19th century, with no demographic hint so far of an intrinsic limit to human lifespan [1]. This sustained trend has been brought about by successive contributions from lifestyle and medical care, including improvements in water and food quality and the prevention of many infectious diseases, which is particularly important for increased survival in children. Recently, improvements in medical care have played an important role, with increasing survival now occurring almost entirely in older age groups, although there is growing evidence that these health benefits are not evenly distributed across different sections of the population [2].

Although increases in health and lifespan are to be celebrated, they come with several downsides. Some of these are economic. In many countries increased lifespan is accompanied by falling birth rates and hence a rapid increase in the proportion of the population that does not participate in the labour force. There is also debate about the extent to which increasing lifespan is also increasing health span [3]. However, the main problem of longer lives is that increasing age is proving to be the major risk factor for all of the common chronic and killer conditions of the developed world: metabolic, cardiovascular, and neurodegenerative disease and cancer [4]. The major burden of ill health is hence now falling on the older section of the population and their carers and there is an urgent need to find ways of keeping people healthy for longer.

Corresponding author: Partridge, L. (linda.partridge@age.mpg.de).
Keywords: ageing; ageing-related disease; insulin/insulin-like growth factor and TOR signalling.

1043-2760/
© 2014 The Authors. Published by Elsevier Ltd. This is an open access article under the CC BY license (http://creativecommons.org/licenses/by/3.0/). http://dx.doi.org/10.1016/j.tem.2014.08.003

Ageing is a malleable process

Because ageing is the major risk factor for all of these diseases, one obvious approach to maintaining the health of older people would be to intervene in the underlying ageing process itself. The intrinsic rate of ageing can be drastically altered by (presumably complex) genetic change, because there is great diversity in the natural lifespans of animals, even when they are brought into environments where they are largely protected from extrinsic hazards. For instance, among mammals, bats, primates, and whales are notably long lived [5]. Scientific discoveries from research into ageing in recent years have also suggested that intervening in human ageing is more plausible than it once seemed. Although ageing is complicated and variable, with diverse kinds of damage and pathology accumulating in a way that varies between both different body tissues and individual organisms, the process has nonetheless proved to be malleable. Both genetic mutations and environmental interventions such as altered diet and drugs can increase lifespan and health during ageing in laboratory organisms (yeast, nematodes, fruit flies, and mice). Furthermore, despite the very different lifespans and lifestyles of these creatures, similar interventions have proved capable of extending health span in all, implying some commonalities in the underlying mechanisms of ageing. Simpler organisms with shorter lifespans can thus contribute to an understanding of the mechanisms of mammalian, including human, ageing, and to the discovery of interventions that could ameliorate it [6–8].

What makes us age?

The ageing process remains a considerable biological mystery. Virtual immortality of cell lines is clearly possible because all current life on earth originated from a common ancestor, as evidenced by the use of a common genetic code. Germlines, therefore, do not have to die. Also, some multicellular organisms, such as *Hydra* and some sea anemones, do not become less able to reproduce or more likely to die over time [9]. Organisms are generally maintained in a youthful state during their development and it is only with the onset of reproduction that the effects of ageing start to become apparent [8]. However, it is not clear in any organism how the ageing process starts and which of the many phenotypes of ageing are causal in the different aspects of functional decline and risk of ageing-related diseases. Many features may be bystander effects with little functional significance, such as the greying of hair. Homeostatic responses of the organism to ageing-related damage and loss of function also occur. Some hallmarks of

CrossMark

ageing across different organisms have recently been assembled [10]. Common features of ageing include genomic instability, telomere attrition, epigenetic alterations, loss of proteostasis, deregulated nutrient-sensing, mitochondrial dysfunction, cellular senescence, stem cell exhaustion, and altered intercellular communication. These hallmarks vary in prominence between different tissues and are present to differing degrees in different organisms. Their functional significance and the causal nexus between them are the subject of intense study. In multicellular organisms the picture is further complicated by systemic effects, with one tissue affecting the ageing of others.

Slowing down ageing

Interventions that improve health during ageing and increase lifespan across multiple organisms, including mammals, are of particular interest. They indicate that the normal ageing process has been targeted and can therefore reveal both fundamental mechanisms of ageing and potential drug targets for the prevention of ageing-related disease. Dietary restriction (DR), a reduction of food intake short of malnutrition, increases health during ageing in nearly all organisms so far investigated, including primates and possibly humans [8]. DR is not a practical intervention for most humans because compliance with this rigorous dietary regimen is low. However, recent work in both animals and humans has suggested that reduced intake of certain nutrients, particularly specific amino acids, may be more important than reduced calorie intake in conferring the health benefits of DR [11]. Furthermore, altered activity of the key metabolic and endocrine signalling networks that sense nutrients can also improve health during ageing. Mutations that reduce the activity of insulin/insulin-like growth factor signalling (IIS) and the connected target of rapamycin (TOR) network can extend lifespan in organisms ranging from yeast to mammals. There is also a broad-spectrum improvement in the health of these animals during ageing [7–9]. For instance, mutant-IIS mice show improvements in glucose handling, immune profile, and motor performance and are protected against osteoporosis, cataract, and skin problems. Importantly, there are many potential drug targets in this signalling network, including several kinases, and rapamycin, a specific inhibitor of TOR, can extend lifespan in mice [12].

The IIS/TOR network senses the status of nutrients, growth factors, and various forms of stress and adjusts growth, metabolism, and reproduction accordingly. Extreme alterations of its activity can therefore be harmful. For instance, reduced insulin signalling can cause diabetes. However, it is clear that specific reductions in IIS and TOR activity (which one being determined possibly by the magnitude of the reduction or the exact part of the network affected) can improve overall health during ageing. For these and other interventions, such as diet and drugs, the key challenge is to understand exactly how they do it, to triage away beneficial effects on health from undesirable side effects. The hallmarks of ageing provide candidate processes for further detailed analysis [10]. For instance, experimental work has addressed the potential role of cellular quality-control processes including autophagy and proteasomal degradation of damaged proteins and the maintenance of telomeres in maintaining the health of the whole organism during ageing.

Mechanistic connections between ageing and ageing-related disease

The improvements in health during ageing seen in animal models of slowed ageing provide an excellent context in which to understand the mechanistic connections between ageing and ageing-related disease. For instance, in the fruit fly *Drosophila*, rapamycin administered to old flies was recently shown to lower dopamine activity and hence reverse their natural, age-related fragmentation of night sleep, a common problem in older humans [13]. The interaction between interventions that slow ageing and genetic models of disease has also proved informative. For instance, in the nematode *Caenorhabditis elegans*, genetically reduced IIS protected against the pathology associated with a worm model of cancer by altering the expression of genes that were highly enriched with the worm equivalents of human oncogenes and tumour suppressors, including a worm orthologue of lysosome-associated transmembrane protein 4B (LAPTM4B), which stimulates cell proliferation and inhibits cell death in mammalian cancer [14]. Dementia in humans is proving a particularly intractable feature of ageing, with the incidence projected to increase to unmanageable levels in many countries. Mouse genetic models of this condition have shown that reduced IIS and rapamycin can ameliorate the associated pathology, and understanding the detailed mechanisms at work may help to solve this major medical problem.

Targeting ageing to treat diseases of ageing

Economic analysis has shown that amelioration of ageing would have enormous health benefits [15]. Specific

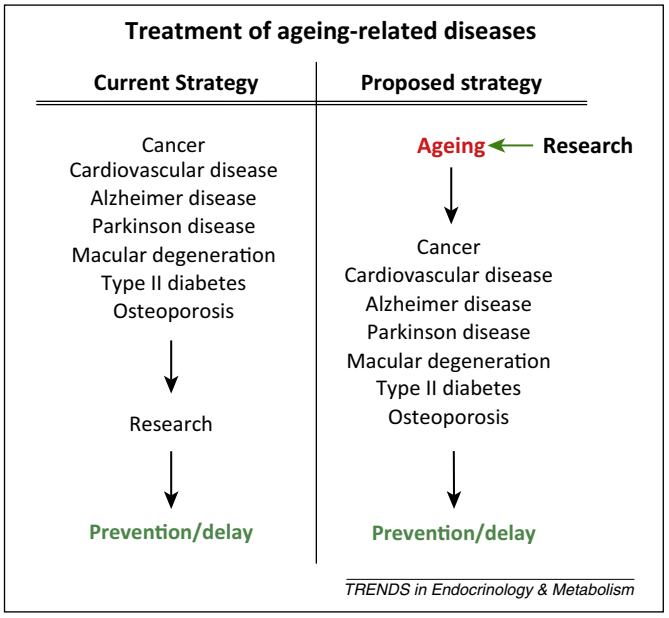

Figure 1. Current and potential future strategies for understanding and preventing ageing-related diseases. Left: Current strategy tends to research and treat individual ageing-related diseases separately. Right: Recent research points to the prospect of research to understand and intervene in the underlying ageing process as a means for simultaneously preventing multiple diseases of ageing.

interventions for specific problems of ageing are important and will continue to be so. What the animal models of slowed ageing have shown us is that there is also the prospect of a broad-spectrum preventive medicine for the diseases of ageing (Figure 1). Rapamycin is an early example of a licensed drug proving to have a wider therapeutic range than previously suspected and others such as metformin and aspirin are starting to show similar features.

Acknowledgements

The author thanks the Max Planck Society and the Wellcome Trust for funding her research.

References

1 Oeppen, J. and Vaupel, J.W. (2002) Demography. Broken limits to life expectancy. *Science* 296, 1029–3101
2 Olshansky, S.J. *et al.* (2012) Differences in life expectancy due to race and educational differences are widening, and many may not catch up. *Health Aff. (Millwood)* 31, 1803–1813
3 Fries, J.F. *et al.* (2011) Compression of morbidity 1980-2011: a focused review of paradigms and progress. *J. Aging Res.* 2011, 261702
4 Niccoli, T. and Partridge, L. (2012) Ageing as a risk factor for disease. *Curr. Biol.* 22, R741–R752
5 Nussey, D.H. *et al.* (2013) Senescence in natural populations of animals: widespread evidence and its implications for bio-gerontology. *Ageing Res. Rev.* 12, 214–225
6 Kenyon, C.J. (2010) The genetics of ageing. *Nature* 464, 504–512 erratum in Nature 467, 622
7 Fontana, L. *et al.* (2010) Extending healthy lifespan – from yeast to humans. *Science* 328, 321–326
8 Partridge, L. (2010) The new biology of ageing. *Philos. Trans. R. Soc. Lond. B: Biol. Sci.* 365, 147–154
9 Martínez, D.E. (1998) Mortality patterns suggest lack of senescence in *Hydra*. *Exp. Gerontol.* 33, 217–225
10 López-Otín, C. *et al.* (2013) The hallmarks of aging. *Cell* 153, 1194–1217
11 Solon-Biet, S.M. *et al.* (2014) The ratio of macronutrients, not caloric intake, dictates cardiometabolic health, aging, and longevity in *ad libitum*-fed mice. *Cell Metab.* 19, 418–430
12 Harrison, D.E. *et al.* (2009) Rapamycin fed late in life extends lifespan in genetically heterogeneous mice. *Nature* 460, 392–395
13 Metaxakis, A. *et al.* (2014) Lowered insulin signaling ameliorates age-related sleep fragmentation in *Drosophila*. *PLoS Biol.* 12, e1001824
14 Pinkston-Gosse, J. and Kenyon, C. (2007) DAF-16/FOXO targets genes that regulate tumor growth in *Caenorhabditis elegans*. *Nat. Genet.* 39, 1403–1409
15 Goldman, D.P. *et al.* (2013) Substantial health and economic returns from delayed aging may warrant a new focus for medical research. *Health Aff. (Millwood)* 32, 1698–1705