EBioMedicine xxx (2016) xxx–xxx

Contents lists available at ScienceDirect

EBioMedicine

journal homepage: www.ebiomedicine.com

Review

Therapeutic Manipulation of Ageing: Repurposing Old Dogs and Discovering New Tricks

Venkatesh Mallikarjun *, Joe Swift

Wellcome Trust Centre for Cell-Matrix Research, Division of Cell Matrix Biology and Regenerative Medicine, Faculty of Biology, Medicine and Health, University of Manchester, Manchester M13 9PT, United Kingdom.

ARTICLE INFO

Article history:
Received 1 September 2016
Received in revised form 14 November 2016
Accepted 14 November 2016
Available online xxxx

Keywords:
Ageing
Biomarkers
Drug repurposing
Clinical trials

ABSTRACT

Ageing is a leading risk factor for many debilitating diseases. While age-related diseases have been the subject of over a century of intense investigation, until recently, physiological ageing was considered unavoidable. Pharmacological and genetic studies have since shown that ageing is a malleable process and that its abrogation can prevent its associated diseases. This review summarises a sample of the most promising efforts to deliver the products of ageing research to the clinic. Current efforts include the use of clinically approved drugs that have since been repurposed, as well as the development of novel therapeutics, to target ageing. Furthermore, ongoing research has sought reliable biomarkers of ageing that will accelerate the development of such therapeutics. Development of these technologies will improve quality of late-life and help relieve the enormous stress placed on state healthcare systems by a rapidly ageing global population. Thus, for both medical and socioeconomic reasons, it is imperative that ageing is made to yield to intervention.

Contents

1. Introduction

The ageing global population represents one of the greatest challenges to modern society. Ageing is the biggest risk factor for some of the most debilitating and distressing diseases known, including neurodegenerative diseases such as Parkinson's and Alzheimer's, as well as

* Corresponding author.
E-mail addresses: venkatesh.mallikarjun@postgrad.manchester.ac.uk (V. Mallikarjun), joe.swift@manchester.ac.uk (J. Swift).

http://dx.doi.org/10.1016/j.ebiom.2016.11.020

cardiovascular, inflammatory and metabolic disease, as well as cancer. Collectively, the diseases of ageing represent the biggest causes of morbidity and mortality in the developed world (Kennedy and Pennypacker, 2014). While the study and treatment of these diseases in isolation has yielded a great deal of knowledge and a significant improvement in patient quality of life, it is important to acknowledge that these diseases do not exist in isolation. An aged individual may possess any number of co-morbidities, each of which can exponentially complicate any required therapeutic interventions. Given the complexity of treating age-related co-morbidities separately, the idea of targeting ageing itself as a means of reversing the pathogenesis of several diseases at once is appealing (Faragher et al., 2009).

This review will evaluate current developments in translating basic ageing research into useful therapeutics. Particular attention will be paid to ongoing attempts to repurpose already available drugs, before touching on promising drugs that, based on recent evidence in pre-clinical models, could also be repurposed. Additionally, new therapeutics being developed specifically to target ageing are discussed. Finally, since any appraisal of anti-ageing function will only be possible with robust biomarkers of ageing (Kenessary et al., 2013), we present a brief review of the search for powerful predictors of physiological age. To highlight strategies with greatest potential to manipulate human ageing, only drugs that have demonstrable effects in mammals will be considered. Other reviews have covered longevity-enhancing treatments in non-mammalian models (Vaiserman and Marotta, 2016; Vaiserman et al., 2016).

2. Ageing as a Clinical Indication

Twenty years ago, the eminent epidemiologist Richard Doll argued that ageing as a single unified phenomenon did not exist (Peto and Doll, 1997). Doll proposed that, on the balance of evidence available at the time, it was better to consider each of the apparently independent diseases of ageing as separate in nature and thus separate in possible treatments. Current advances in gerontology have since shown that many age-related diseases do indeed share common causes and thus may be reversed or prevented through common cures. Since then the shift in scientific consensus from regarding ageing as an inexorable, entropic process to one that is mediated by well-defined - and importantly, malleable - biochemical pathways has been dramatic. Initial studies in nematodes demonstrated genetic manipulation of longevity was possible (Kenyon et al., 1993). Subsequent studies are just beginning to tease out the many genetic determinants of human longevity (Zhang et al., 2016). Briefly, ageing is thought to be caused by developmental processes that evolved to ensure successful reproductive maturation but carry on long after reproductive maturity is reached (antagonistic pleiotropy; Williams, 1957), resulting in molecular and physiological defects that render organisms frail and less able to respond to stress. These molecular and physiological defects manifest in many forms over several hierarchical layers of molecular, cellular and tissue biology. Cells within old individuals may possess aggregated proteins, dysfunctional mitochondria, (*epi*)genetic lesions and eroded telomeres. This can lead to senescence and subsequent depletion of active stem cell populations, impairing regenerative capacity and further promoting tissue ageing. Systemically, age-related immunodegeneration, disrupted circadian rhythms, impaired nutrient sensing and improper autocrine and paracrine signalling processes combine to promote an "aged" extracellular environment, causing or exacerbating organ failure and leading to the exponential increase in morbidity and mortality that characterises an ageing population (reviewed by López-Otín et al., 2013; Kirkwood, 2005; summarised in Fig. 1).

Given that ageing is the biggest risk factor for many debilitating diseases that render individuals frail and rob them of their independence and dignity, there are strong moral and economic imperatives to tackle it and prevent the associated pathologies. Newly armed with an idea of how humans age, numerous companies and government-funded programmes have sprung up to address human ageing as a problem in and of itself, rather than trying to address the diseases of ageing separately. High profile examples include the (formerly Google) Alphabet-funded ageing research venture, Calico (**Ca**lifornia **Li**fe Sciences **Co**mpany); the interventions testing program (ITP) run by the National Institute on Aging (NIA), designed to test the longevity-enhancing potential of a variety of different drugs; and Human Longevity Inc., co-founded by J. Craig Venter, which aims to elucidate and treat the (*epi*)-genetic causes of age-related diseases. Furthermore, the SENS (**S**trategies for **E**ngineered **N**egligible **S**enescence) Research Foundation performs its own research and helps fund the research of other institutes, and focuses on utilising combinations of regenerative medicine, gene therapy and pharmacology to reverse ageing. More recently, work showing that clearance of senescent cells improves health in old mice (Baker et al., 2016; and discussed later) prompted the creation of Unity Biotechnology. Unity is attempting to develop "senolytics" – therapeutics that recapitulate this effect in humans. Meanwhile in Oxford, UK, Chronos Therapeutics is developing pharmaceuticals to combat age-related diseases. Far from being an inscrutable, purely academic problem, both young start-ups and established companies are now seeing ageing as a tractable and potentially profitable venture.

3. Repurposing Drugs to Combat Ageing

Finding new applications for existing therapeutics (drug repurposing) is a commonly used strategy to allow drugs to reach wider markets and greater numbers of patients (Dudley et al., 2011). Repurposing drugs that have already made it to the market is an attractive strategy for many reasons. Drug development can often cost billions of dollars (Adams and Brantner, 2006) and take 10–17 years to go from early phase clinical trials to market-ready product. Drug repurposing circumvents much of the exploratory work needed to determine mechanisms of action, formulation, manufacture procedure and pharmacokinetics. Importantly, market-tested drugs have already gone through clinical trials and have proven their safety and efficacy in their initially intended application. Consequently, the development time for repurposed drugs can be markedly reduced (3–12 years).

There are two major approaches of drug repurposing: drug-centred and disease-centred (reviewed in greater detail by Dudley et al., 2011). Briefly, drug-centred repurposing relies on the physicochemical properties (e.g. structural similarity to other drugs) or biological effects (e.g. similar transcriptome response between different drugs) of the drug in question. Indirect properties, such as common side-effects between drugs indicated for different diseases can also be used. More recently, computational modelling of drug-protein interactions (molecular docking simulations) can also be used to perform high-throughput screens of possible interaction partners. Disease-centred approaches rely on using similarities between different diseases to suggest potentially repurposable drugs. Generally, if two different diseases possess similar molecular aetiologies, then therapies used to treat one may also work for the other. The two approaches are not mutually exclusive and depending on the knowledge available regarding drug and/or disease of interest, one or both approaches can be utilised.

To facilitate drug-centred repurposing approaches to target ageing, such as the NIA's ITP, geroprotectors.org provides a database of >250 compounds found to extend lifespan in various model organisms (Moskalev et al., 2015). Of the 103 compounds listed by geroprotectors.org that are approved for use in humans, there is already considerable interest in repurposing at least two of them: the immunosuppressant rapamycin and the anti-diabetic drug, metformin.

3.1. Rapamycin and mTOR Inhibition

Within the gerontology literature, few compounds can claim to have received as much attention as rapamycin. Rapamycin has been shown to extend murine lifespan and healthspan (Wilkinson et al., 2012),

Please cite this article as: Mallikarjun, V., Swift, J., Therapeutic Manipulation of Ageing: Repurposing Old Dogs and Discovering New Tricks, EBioMedicine (2016), http://dx.doi.org/10.1016/j.ebiom.2016.11.020