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Geroscience: reframing ageing research

Summary

- Ageing is a major challenge for health systems, particularly because of frequent multimorbidity.
- Geroscience is a systems biology approach to study ageing and common biology between age-related diseases.
- Geroscience has identified hallmarks of ageing that describe common biological features contributing to and driving the ageing process.
- All hallmarks are interrelated and geroscience could identify interventions to either delay or slow onset of disease. This may reduce risk or progression of other age-related diseases.

Background

Advancements in living standards, public health policies and innovation in medicine have increased life expectancy across the globe. However, ageing is strongly associated with the onset of common, complex diseases and syndromes (e.g. hearing loss, diabetes and dementia). Living longer often means living more years in poor health with consequences for patients and health systems. As individuals age, they experience greater multimorbidity (occurrence of two or more chronic conditions), resulting in complex health needs, that a highly specialised model of health service delivery is not necessarily equipped to address.

Ageing can be considered through different lenses: 'longevity' refers to a long life, whereas 'healthspan' refers to the number of years someone can expect to live in (general) good health. This briefing will address how 'geroscience' aims to reframe ageing and how this may translate into improved healthspan.

What is geroscience?

Geroscience is an interdisciplinary field that aims to understand the biology of ageing by identifying common biological mechanisms and their role in age-related disease (ARD). This science takes a systems biology approach, considering information from cells, tissues, organs and whole-body measurements, and has described to date fourteen hallmarks of ageing.

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Three main categories have been identified [1]:

- Primary hallmarks reflect damage to all components of the cell (from the genome to organelles) that accumulate with time and have consequences for fundamental cell biology, e.g. genome instability and telomere shortening.
- Antagonistic hallmarks reflect how the cells respond to damage with harmful consequences to cell and tissue function, e.g. mitochondrial dysfunction and cellular senescence.
- Integrative hallmarks arise when the cell or tissue is no longer able to compensate for accumulated damage resulting in altered tissue function, e.g. chronic inflammation and stem cell exhaustion.

These hallmarks should not be thought of independently, because all hallmarks are strongly related to each other. For example, DNA damage can impact genes, leading to changes in how the cell responds to external pressures, which may alter their function. The observation of shared hallmarks in chronic disease and the occurrence of multimorbidity, suggests that there may be common underlying causes. Targeting these pathways could delay or slow onset of one or more diseases.

Geroscience is a broad field which seeks to establish a unifying theory to enable a more holistic and integrated approach to researching age-related disease. It is an emerging science with pockets of activity where researchers seek to take these insights forward in novel treatments. This briefing explores chronic obstructive pulmonary disease (COPD) geroscience research and how researchers have approached translational research to identify novel treatments.

Geroscience in COPD research

Chronic obstructive pulmonary disease is a progressive respiratory condition characterised by chronic inflammation, loss of alveoli (the part of the lung where gas exchange takes place) and progressive decline in lung function. The ageing lung shares characteristics of COPD (i.e. inflammation of the lung and enlarged alveoli) exacerbated by known risk factors such as smoking, air pollution and history of childhood respiratory infections. Different geroscience hallmarks have been described for COPD, for example:

Telomere shortening (primary) is a natural process where telomeres of replicating cells become progressively shorter through cell division. Telomeres protect the ends of chromosomes and function as quality control for cell division. COPD severity is correlated with telomere length, and this natural process is accelerated by smoking. Shorter telomeres cause genomic instability, driving DNA damage, epigenomic changes (chemical modifications to DNA that affect gene expression without altering the sequence) and altered protein expression, that fundamentally change cell function.

Cell senescence (antagonistic) is when cells stop dividing and is a key hallmark in COPD. Both lung and immune cells are affected. Increased cell senescence fundamentally changes tissue function, exacerbating cell damage and reducing tissue repair. Senescent cells behave differently to other cells, due to changes to the cell and cell processes (e.g. metabolism and oxidative stress), and cell behaviour.

Inflammaging (integrative) or chronic low-grade inflammation happens when balance is lost between inflammatory and anti-inflammatory signals. This causes the accumulation of tissue damage, an increasingly dysregulated immune system and senescent cells, further driving inflammation by secreting proinflammatory cytokines. Inflammaging impacts neighbouring tissue continuing a cycle of progressive damage, cell senescence and inflammation.

Patients with COPD have been found to have accelerated ageing and to die younger with more comorbidities. Several age-related diseases frequently occur alongside COPD (e.g. diabetes or hypertension). These diseases share hallmarks of ageing, particularly systemic inflammation, and common risk factors.

Opportunities for treating COPD

Current options for COPD treatment are quite limited. Most interventions work by alleviating symptoms (bronchodilators) and manage complications of disease (e.g. smoking cessation or antibiotics for infection), rather than offering a cure.

No COPD treatment targets the underlying disease process or slows progression of disease without risk of harm (e.g. infection). Treatments targeted against the underlying disease pathology could reduce the chronic effects of disease and improve response to protective interventions (e.g. vaccines). Geroscience research has identified senescent cells as a primary driver of COPD. Senescent cells underly the chronic inflammation that characterises this disease.

Several treatments have been trialled which demonstrate the activity, opportunities and challenges of a geroscience approach to COPD treatment:

- **Resveratrol** is a molecule with anti-inflammatory and antioxidant properties that extends the lifespan of some organisms. This may be mediated by direct or indirect effect on sirtuin-1, a protein that regulates gene expression and cell metabolism, and is a focus of geroscience study as a target for anti-ageing. In tissue models, resveratrol reduces inflammation of senescent alveolar immune cells. However, a small clinical trial in COPD patients found no clinical benefits and participants experienced surprising weight loss of predominantly lean muscle mass [2]. Resveratrol has poor bioavailability (aka absorption into the body), and similar compounds are now being explored with greater bioavailability and more potent anti-inflammatory properties.
- **Metformin,** widely used as a first line treatment for type 2 diabetes, is a known ‘geroprotector’ with anti-ageing properties observed in animal models and human epidemiology studies. Metformin activates the AMPK signalling pathway, which reduces cell senescence, chronic inflammation and enhances cell responses to oxidative stress. COPD and type 2 diabetes frequently occur together, and in retrospective studies metformin seems to reduce hospitalisation and mortality. A short trial did not find any clinical benefit (NCT03651895), however, and larger, longer duration studies may be needed to see if Metformin delays the progression of COPD.
- **Rapamycin** is an immunosuppressant, which is known to reduce oxidative stress and cell senescence and has been found to be protective against COPD in mouse models. In small studies, rapamycin had adverse effects (e.g. mouth ulcers). Preventative treatments in elderly populations by necessity need to have a high tolerability, particularly if intended to be taken at low doses for long durations.

Geroscience is a broad concept and the confines of standard clinical trials may not be the most appropriate methodology. Studies have been small and short in duration, and therefore insufficiently powered to assess treatment effectiveness. They are also often focused on outcomes that may take time to realise, such as hospitalisation.

While clinical trials are typically centred on one disease, geroscience trials aim to target mechanisms of ageing in order to prevent the onset or reduce the progression of age-related diseases [3]. 'Gerotherapeutic' drugs may target fundamental ageing processes, rather than specific diseases (like COPD).

This approach is being explored in the Targeting Ageing with Metformin (TAME) trial. The study will take place over six years in 3,000 participants aged 65-85 in the USA, and aims to understand if metformin modulates ageing, i.e. going beyond observed benefit for diabetes [4]. Results from the study are highly anticipated. Proponents want to redefine the regulatory and market approval approach to consider ageing, rather than specific diseases related to ageing. This in turn could incentivise pharmaceutical companies to invest in geroscience research.

The controversy of geroscience

Ageing is multifaceted, particularly in relation to chronic disease. Risk of chronic disease varies and the role of ageing in disease progression is yet to be determined [5]. There is open debate on fundamental questions, such as 'what is ageing and when does it start' [6]. Moreover, geroscience trials face methodological challenges in both study design and measuring outcomes.

What is not controversial is the need for holistic approaches when managing multimorbidity in elderly populations. The fragmented nature of current health models compounds challenges, and this makes treatment of ageing itself an attractive idea. Health systems globally would benefit from interventions that treat or prevent multiple diseases. Yet, current approaches to build evidence for interventions will not address the questions geroscience propose.

Trials need to be able to answer questions about the effectiveness of interventions in relation to the mechanisms underlying ageing, rather than clinical outcomes. Biomarkers of ageing identify individuals who are biologically 'older' or 'younger' and could be used to predict 'age trajectory' [7]. These biomarkers could function as a proxy for the efficacy of geroscience interventions. Populations, where there is demonstrable need, are highly likely to benefit from a geroscience approach and the high incidence of comorbidities provides an opportunity to capture evidence related to these wider health outcomes.

One consideration, essential to this debate, is that the burden of age-related diseases is not felt equally. Individuals from lower socioeconomic or ethnic backgrounds are disproportionately affected by the incidence of disease, earlier in life and for a greater proportion of their life with shorter overall life expectancy. It is not yet clear whether or how these health inequalities are informing geroscience. If we are to realise the benefits of geroscience, this research must prioritise populations most affected by age-related diseases.

Conclusion

Globally, the average age of populations is increasing and the increase in chronic disease is a challenge for health systems. Geroscience research is an emerging field with the potential to pull together what has been a fragmented, disease-centred landscape to build a more holistic understanding with broad health implications.

Undoubtedly, collective action is required from governments, funders, industry and health systems to address the health needs of ageing populations. Geroscience is in the early days and builds on wider research into prevention of age-related diseases. While promising, there are fundamental and practical questions to address. Joined up thinking around health data, clinical trial design and preventative medicine will be critical to evaluating the success of geroscience and any related interventions.

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