Evidence regarding the scientific understanding of the ageing process, how research might lead to treatments for delaying ageing and the current and future status of the microbiome research field in relation to ageing

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How complete is the scientific understanding of the biological processes of ageing and their epidemiologies (including the relative roles of genetics, epigenetics, lifestyle, environment, etc.)?

Genetics

Over the last couple of decades we have gained significant understanding of biological processes underlying. Only 30 years ago, most researchers believed ageing is a passive process that occurs on its own, like an old car wearing out, becoming rusty and eventually breaking down. We now know that ageing is caused by our own genes, and many of these genes have been identified. Work initially using model organisms in the laboratory identified signalling pathways such as insulin/insulin-like signalling and target of rapamycin (mTOR) and many other. Genetic studies in humans have subsequently confirmed that some of these genes are overrepresented in long-lived human populations and longevity studies in monozygotic twins have shown that genetic factors explain 20 to 30% of the differences observed in life spans of monozygotic twins. Together these findings provide strong evidence that genetic variants of specific genes can be protective or make us more vulnerable to ageing.

Lifestyle

In addition, lifestyle is a very strong factor in determining the development of age-related diseases such as cancer, cardiovascular disease and Alzheimer's disease and many others. Exercise stands out as the strongest single factor with most beneficial effects. Thousands of scientific studies report on the protective effects of exercise on multiple aspects of late life health, and recently studies have started to pinpoint the underlying mechanisms such as improved immunity, decreased cellular senescence and maintained mitochondrial function.

The question if and how our environment plays in ageing remains to be answered. There are a few small studies indicating that pollution plays a role in the development of Alzheimer's disease. E.g. a study conducted in London showed that old people living in more polluted neighbourhoods are more likely to develop Alzheimer's compared to controls in less polluted areas. Studies in wild and domesticated animals have also shown that living in polluted areas increases the risk of neurodegeneration. This is a research field that is becoming more active, and we will learn more about pollution and other environmental factors over the coming years.

Diet

Diet and nutrition play a major role in the development of age-related diseases and frailty. There is compelling evidence for diet being a major driver for many age-related diseases such as type 2 diabetes and cardiovascular diseases and there is also evidence for nutrition being important for the development of frailty. The effect of dietary interventions on ageing is a major research field with many ongoing studies focused on different diets such as the Mediterranean, vegetarian and ketogenic diets. Even though at this point it is difficult to conclude which exact diet is most efficient, it is clear that highly processed and sugary foods are detrimental to health and accelerate some aspects of ageing. In addition, studies in model organisms very convincingly show that dietary restriction currently is the single strongest intervention to promote healthy ageing. This has been shown again and again in multiple species, and the effect of dietary restriction, fasting and fast-mimicking diets on human health and ageing is a very active research field. The human gene with strongest association to decreased lifespan is ApoE, a lipoprotein involved in fat metabolism and that also is strongly associated to Alzheimer's and cardiovascular disease. The strong effect of ApoE illustrates how interactions between genetics, diet and lifestyle may be involved in in ageing.

Epigenetics

One way that lifestyle and environmental factors affect ageing is through epigenetics. Epigenetics represents the reversible heritable mechanisms that occur without any mutations of the underlying DNA sequence and involves changes regulation of the transcriptional machinery, resulting in changes expression of genes. With age there are clear epigenetic effects resulting in global changes in gene expression. This is a very active research field and we are only starting to learn about what the effects on health and ageing are, but it is becoming clear that the lifestyle and age of both mothers and fathers affect lifespan and development of age-related diseases in their offspring through epigenetics.

The microbiome

Another way that genetic, lifestyle and environmental factors might affect ageing is through the microbiome, the community of microbes inhabiting our guts. Recent development of whole genome sequencing techniques has resulted in an explosion of studies demonstrating association between the composition of our microbiome and many disease and health states, including age-related diseases. Exciting findings indicate that gut microbes can affect ageing of e.g. the brain, impacting cognitive function, neurodegenerative diseases and mental health. This is an emerging research field, and the main challenge currently is to demonstrate causation (in contrast to association) and to identify the underlying mechanisms. The human microbiome is massively complex and difficult to study, and studying it in mouse models is also very challenging due to the costs associated with keeping animals germ-free, making it particularly difficult to study in the context of ageing. However, there are some studies in mice and also in other animals such as nematodes, flies and fish, showing that the microbiome is a direct cause of ageing and that e.g. faecal transplants from young to old animals can improve ageing. There are also studies showing that the microbiome secretes metabolites with beneficial effects on ageing, opening up for the possibility to bypass bacteria and utilise these metabolites to improve ageing. Continued research over the coming years, and an increased use of simple and inexpensive model organisms (nematodes, flies and fish), will show the extent to which we can manipulate and utilise our microbiome, and there is already significant activity both in the academic and industrial sectors.

How firm is the scientific basis for public health advice about healthy lifestyles to increase health span, including physical health and mental health?

Implementation of existing health care advice

The advice for public health provided by the government and charities is somewhat basic and centred on recommendations on smoking, alcohol intake, diet and activity patterns. These kind of recommendations are certainly based on rigorous scientific research, and implementation of these recommendations by the public would benefit quality of life and health of many individuals, as well as take a large load of an already strained health and social care system. The challenge here is not the recommendations per se, it is the implementation. In many ways society is setting us up for *not* following the public health care advice, as having a sedentary lifestyle and unhealthy diet is easier and cheaper than choosing an active and healthy lifestyle, regardless of age. Government needs to focus on finding ways to achieve lifelong health in the general population, and reduce the influence that the food and alcohol industries have over policy making. Implementation of public health advice needs to start early, in infancy, continue throughout life and be a natural part of life.

A rich and varied microbiome for lifelong health

When it comes to the microbiome, evidence mostly based on metagenomic studies are suggesting that having a rich and diverse microbiome is associated with health and youth, but currently it is too early to give public health advice on how to maintain a healthy microbiome. Work over the coming years will clarify the dietary and lifestyle measures that are needed. It is likely that this advice will be in the same lines of what is already in place, as the evidence is pointing towards that having a varied plant-based diet free of processed and sugary foods is the basis for a microbiome that promotes health. There is also evidence that specific dietary components such as sugar and highly processed meats boost microbial species that are detrimental to us, causing infection and chronic inflammation, and that many diseases are associated with a less diverse microbiome.

Our microbiome becomes less diverse with age and it has been proposed that a negative cycle of decreased gut function, suppressed immune function and imbalance of the microbiome plays an important role in ageing. Thus diet but also the ageing process itself contributes to changes in the microbiome, and that in turn is likely to further affect overall health. Relevant to health advice, studies of elderly in Ireland showed that old people living in health care homes have a poorer diet and less diverse microbiome compared to old people living in the community, and also that they are more frail and in poorer health. This means that in the future we might have to take the nutritional value of foods served at long term health care institutions into closer consideration.

Which developments in biomedical science are anticipated in the coming years, in time to contribute to the Government's aim of five more years of healthy and independent life by 2035?

A giant leap in our understanding of the biology and genetics of ageing

The last 30 years have seen a giant leap in our understanding of the biological processes governing ageing, and in genes and pathways that could be utilised to develop pharmaceutical interventions. In response to the medical, social and economic needs of our ageing societies, the research community has moved away from solely studying longevity to also study healthy ageing, that ageing free of disease and disability, further acquiring knowledge that can be utilised to increase health in late life. Insight into the molecular pathways activated by e.g. exercise and dietary restriction has opened up for developing drugs that utilise these pathways to achieve benefits on health.

This progress has resulted in significant investment in the development of drugs that act to improve the ageing process as a whole and prevent or delay the development of age-related diseases. This approach is different from the traditional approach designed and used by the pharmaceutical industry and health care providers, where each age-related disease is treated individually (e.g. cancer, cardiovascular disease, osteoporosis, etc). A growing cohort of small companies is working on preclinical candidates and advancing candidates that could slow or prevent ageing-related diseases. In addition, some big pharmaceutical companies are exploring their options.

Ongoing development of treatments for healthy ageing

Most advanced is the work with *metformin*, an FDA approved drug used for treatment of type 2 diabetes that has been shown to have beneficial effects on ageing in multiple models and is currently undergoing clinical trials. Another strategy that has gained large interest in recent year is *senolytics*, the inhibition and removal of senescent cells through pharmaceutical interventions. Senescent cells are cells that have stopped dividing and that secrete damaging inflammatory compounds. Senescent cells are central to the ageing process and contribute to dysfunction to multiple tissues. Current trials involve drugs that target knee joint, eye- and pulmonary disorders individually and locally, with the hope that in the future senolytics can be delivered systemically and safely. Additional treatments under development are mTOR inhibitors acting to suppress immunosenescence and "young blood", in which blood plasma from young individuals is transferred to old people.

The microbiome – a potential route to healthy ageing

The microbiome is becoming an increasingly attractive target for potential therapeutics and has a huge potential to improve health of the elderly. It is possible to manipulate the microbiome through diet, prebiotics, probiotics and faecal transplants. One of the biggest challenges in microbiome research is to determine cause-effect relationships and to design microbiome-based therapies that are able to achieve predictable outcomes on the microbial community and host health.

- *Probiotics* aims at altering the microbial composition of the gut through exogenous administration of live microbes. Probiotics are becoming increasingly popular but there is little consistent evidence for their efficacy.
- *Prebiotics* are compounds that are consumed with the intention of affecting microbiome composition or function in a beneficial way. Prebiotics, like probiotics, are a relatively unspecific approach to microbiome-based interventions, and further study is needed to fully characterize the effects of prebiotics on different bacterial species.
- *Faecal transplants* involve transplanting faeces containing microbes from healthy individuals to ill or old people to restore balance of the microbiome and is also gaining momentum. Grotesque as it might sound, there is increasing evidence in both animals and humans supporting this avenue to improve health.

Bypassing the microbiome through secreted microbial metabolites

Alternatively, completely bypassing the microbiome and instead utilising microbial compounds and metabolites as pharmaceuticals offers a more controlled approach. Research over the past few years has revealed that the intestinal microbial community exerts much of its impact on host physiology through the secretion of small molecules that modulate cellular and organismal functions of the host, targeting host genes and proteins. These small molecules serve as an effective means of communication in host-microbe interactions. Rather than targeting the aberrant microbial composition, exogenous administration or inhibition of metabolites has the potential to counteract and correct the negative effects of imbalances of the microbiome.

Metabolite-based interventions are therapeutically attractive for several reasons. Metabolites are physiologically abundant at high concentrations, and thus the potential for toxicity is low. In contrast to the administration of live organisms, their dosage and routes of administration follow the principles of pharmacokinetics. Moreover, metabolites are present at most body sides and thus suitable for different routes of administration. Additionally, metabolites are generally stable in the systemic circulation and thus amenable for scalable modulation of their concentration.

The future of ageing treatments

Research on treatments based on the microbiome is only in its infancy, and the coming 20 years might yield completely novel approaches to ageing. Interestingly, there is strong evidence that metformin, mentioned above as an ageing treatment undergoing clinical trials, acts through the microbiome. This illustrates the potential of microbiome as a means for healthy ageing and opens up for the possibility that also other existing drugs might be acting through the microbiome without our knowledge.

Even though it is likely that most of the ageing treatments that are under development will not pass clinical trials, development of one or a few successful treatments could have a massive impact on the health of our ageing population, and might well contribute to the Government's target of adding 5 years of health by 2035. Further studies, and importantly increased funding to academic and industrial research in the ageing field will increase the likelihood of this being successful.

What technologies will be needed to facilitate treatments for ageing and ageing related diseases, and what is their current state of readiness?

Concerning the microbiome, there are very exciting studies showing association between the microbiome and age-related diseases and frailty, but there is a lack understanding of underlying mechanisms and treatments. If the field is to make significant progress, systematic approaches using simple and inexpensive models are needed. There is a massive need for high-throughput platforms allowing and unbiased screening approaches of microbial strains and microbial metabolites. In addition, using multiple model systems, such as cell lines, nematodes, flies, and short-lived vertebrates such as killifish, combined with rodents would be highly beneficial to establish evolutionary conservation and identify interventions that are likely to be translatable to humans.

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