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Editorial

Spelunking the biology of frailty

The word spelunking comes from speleology, the study of caves. Using information from various disciplines including geology, biology, chemistry and physics, speleologists enter dark caves to discover hidden treasures within. This desire to explore unseen new territory with a multidisciplinary lens has motivated early investigators in the emerging field of the biology of frailty. Scientists from several disciplines have promoted the idea that chronological age alone cannot account for the heterogeneity in ageing apparent both in humans and in animal models. They have proposed that individuals with accelerated ageing are frail and that frailty itself can be measured with various instruments that count the accumulation of health deficits in ageing (Banga et al., 2019; Rockwood and Howlett, 2019). In this special issue of Mechanisms of Ageing and Development, we shed light on the biological basis of frailty with this series of original research and review articles by prominent international scientists who have made important contributions to the field.

The biology of frailty is inherently multidisciplinary, with contributions from geriatric medicine, gerontology, pharmacology, physiology and mathematics all contributing to our current understanding of frailty. Here we asked a variety of clinical and biomedical research experts to either contribute new studies on the biology of frailty or to review prior work in the area. We focus on new developments in the field including animal models of frailty, novel biomarkers, and interventions that modify frailty including exercise, geroprotectors, mesenchymal stem cells and diet. We have also asked these researchers to identify unresolved research questions in the field. This collection of articles provides an up-to-date perspective that should help guide future research into the biology of frailty.

The concept of *"frailty"* was first introduced by Vaupel et al. (1979) as an actuarial concept that describes the unmeasured variability in the risk of death in individuals of the same age. Exploration of the biology of frailty began in 2001 when two groups developed novel tools designed to quantify frailty in people; these are the frailty index (Mitnitski et al., 2001) and the frailty phenotype (Fried et al., 2001). In this special issue, the paper by Rockwood and Howlett (2019) focuses on the frailty index approach. They review evidence that frailty can be measured with a frailty index achieved by counting the accumulation of health deficits in an individual. They argue that age-related health deficits confer risk as a group, such that high frailty scores predict the risk of many diseases of old age better than individual, traditional risk factors for these diseases. Interestingly, work with frailty assessment tools has shown that there are marked differences in frailty between the sexes. Gordon and Hubbard (2019) discuss the phenomenon that although females are frailer than males at all ages, they have lower mortality risk. Here, they review possible biological, social and behavioural mechanisms behind this 'morbidity-mortality paradox' and discuss the importance of considering frailty in understanding this paradox. These authors conclude that, while females tolerate frailty better than males, there is little evidence that this paradox arises from sex differences in the severity of chronic diseases, as hypothesized previously.

Another major advance in the field came about a decade later, when the frailty index concept was adapted for use in naturally ageing mice (Parks et al., 2012; Whitehead et al., 2014). This was followed by the development of a frailty phenotype assessment tool for use in pre-clinical models (Liu et al., 2014). In this special issue, Banga et al. (2019) highlight new rodent models that quantify frailty as the accumulation of age-associated deficits. They emphasise that the ability to model frailty in rodent models is a key development that provides powerful new tools to investigate frailty in the context of aging. For example, Kane and Sinclair (2019), in their contribution to this issue, point out that although there are no currently accepted biomarkers of frailty, cross-sectional studies in humans have identified several promising candidates. These can now be explored in longitudinal studies across the life-course using these frailty assessment tools in animal models.

Several papers in this special issue examine the use of both clinical and pre-clinical frailty assessment tools to explore links between age, frailty and chronic diseases. O'Brien and McDougall (2019) consider the complex relationship between age, frailty and osteoarthritis specifically in the context of inflammation and senescence. They argue that frailty is a risk factor for the development of osteoarthritis with increasing age, and that conversely osteoarthritis can contribute to the promotion of frailty. The study by Canevelli et al. (2019) investigates the relationship between frailty and assessment of cognitive function. They measured cognitive function with a battery of neuropsychological tests and quantified frailty with a frailty index. High frailty scores were associated with poor performance on at least one measure of cognitive function. Fielder et al. (2019) show, for the first time, that sub-lethal irradiation causes premature frailty in young adult mice and that this is associated with cognitive decline and increased mortality risk. They propose these mice as a model for long-term tumour survivors who have premature frailty as a result of radiation therapy; interventions to attenuate frailty in these patients also could be tested in this model.

A major area of exploration in the biology of frailty field is the identification of lifestyle interventions that modify frailty in humans and animals. In this issue, Seldeen et al. (2019) present new preclinical data investigating the impact of eight weeks of high intensity interval training exercise in aged female mice. This training regimen had beneficial effects on frailty outcomes evaluated with different frailty tools and on mortality. Kehler and Theou (2019) contribute complementary work in humans, showing that physical activity can reduce frailty in older people, while a sedentary lifestyle contributes to frailty. Mitchell et al. (2019) review the preclinical evidence that frailty, or aspects of

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frailty, can be modulated with dietary interventions. They show promising evidence that calorie restriction can delay frailty in animal models. On the other hand, their work highlights many unanswered questions including the effect of other dietary interventions on frailty, the influence of sex on outcomes, and the optimal timing/duration of dietary interventions.

Other papers in this special issue review the evidence and potential for pharmacological interventions to delay or treat frailty in both preclinical and clinical studies. Palliyaguru et al. (2019) focus on interventional studies in mice, and comprehensively summarise preclinical studies that have explored the effect of anti-ageing interventions on frailty or frailty-related outcomes. They discuss promising data showing that small molecule treatments delay aspects of frailty and suggest that standardisation of assessments and further use of the mouse frailty index in interventional studies will increase translation. Trendelenburg et al. (2019) supplement this discussion of preclinical studies with a thorough review of clinical trials that have included frailty as either a selection criteria or an endpoint. They highlight some of the complications associated with testing frailty interventions in older adults. As concluded by Palliyaguru et al. (2019) for preclinical studies, large-scale clinical studies with standardised inclusion criteria and outcome measures are needed to increase the speed of translation of interventions to delay or treat frailty into the clinic. Florea et al. (2019) review an exciting new approach to the modulation of frailty, treatment with mesenchymal stem cells. They consider both preclinical and clinical evidence on the benefits of this approach and discuss the ongoing clinical trials in this area.

It is now clear that frailty itself can affect responses to the pharmacological treatment of chronic diseases. Further in this special issue, Hilmer et al. (2019) explore the effect of frailty on clinical pharmacology and drug therapy. They focus on biological changes in frail older individuals (*e.g.* body composition, organ function, etc) that can affect drug pharmacokinetics and pharmacodynamics. These authors emphasize the importance of polypharmacy and drug-induced adverse effects in frail older people and also highlight the importance of considering frailty in clinical trials of new medications.

We have learned much about frailty after almost two decades of research, but there is still much more to know. Some pressing, unanswered questions are: what are the underlying biological mechanisms of frailty and how distinct are these from mechanisms of ageing and age-related chronic disease? Increased focus on research in preclinical frailty models, models of age-related diseases and studies of interventions to target frailty will expand our understanding, as will our growing knowledge of the biological mechanisms of ageing itself. Another key unanswered question is how to target the underlying mechanisms of frailty to delay or treat this state in older people. The authors of many of the papers in this issue highlight the fact that, despite promising preclinical evidence, there is a lack of well-designed clinical studies testing interventions in frail older people. They suggest that more evidence is needed to understand the biology of frailty and optimise the use of interventions to delay or treat frailty in the older population.

The articles included in this special issue of *Mechanisms of Ageing and Development* highlight much of what is now known about frailty and the biological underpinnings of the frail state. They also draw to attention that there is still a great deal more to learn about the biology of frailty. We are near the mouth of the cave and have yet to explore its depths - there is much spelunking to be done.

References

Banga, S., Heinze-Milne, S.D., Howlett, S.E., 2019. Rodent models of frailty and their application in preclinical research. Mech. Ageing Dev. 179, 1–10. https://doi.org/10.1016/j.mad.2019.01.008.

Canevelli, M., Cesari, M., Raganato, R., Trentin, F., Valletta, M., Salati, E., Bruno, G., 2019. Role of frailty in the assessment of cognitive functioning. Mech. Ageing Dev. in press. https://doi.org/10.1016/j.mad.2019.111122.

Fielder, E., Weigand, M., Agneessens, J., Griffin, B., Parker, C., Miwa, S., von Zglinicki, T., 2019. Sublethal whole-body irradiation causes progressive premature frailty in mice. Mech. Ageing Dev. 180, 63–69. https://doi.org/10.1016/j.mad.2019.03.006.

Florea, V., Bagno, L., Rieger, A.C., Hare, J., 2019. Attenuation of frailty in older adults with mesenchymal stem cells. Mech. Ageing Dev in press.

Fried, L.P., Tangen, C.M., Walston, J., Newman, A.B., Hirsch, C., Gottdiener, J., Seeman, T., Tracy, R., Kop, W.J., Burke, G., McBurnie, M.A., 2001. Cardiovascular Health Study Collaborative Research Group. Frailty in older adults: evidence for a phenotype. J. Gerontol. A Biol. Sci. Med. Sci. 56, M146–M156.

Gordon, E.H., Hubbard, R.E., 2019. Do sex differences in chronic disease underpin the sex-frailty paradox? Mech. Ageing Dev. 179, 44–50. https://doi.org/10.1016/j.mad.2019.02.004.

Hilmer, S.N., Wu, H., Zhang, M., 2019. Biology of frailty: implications for clinical pharmacology and drug therapy in frail older people. Mech. Ageing Dev. https://doi.org/10.1016/j.mad.2019.111119. in press.

Kane, A.E., Sinclair, D.A., 2019. Frailty biomarkers in humans and rodents: current approaches and future advances. Mech. Ageing Dev. 180, 117–128. https://doi.org/10.1016/j.mad.2019.03.007.

Kehler, D.S., Theou, O., 2019. The impact of physical activity and sedentary behaviors on frailty levels. Mech. Ageing Dev. 180, 29–41. https://doi.org/10.1016/j.mad.2019.03.004.

Liu, H., Graber, T.G., Ferguson-Stegall, L., Thompson, L.V., 2014. Clinically relevant frailty index for mice. J. Gerontol. A Biol. Sci. Med. Sci. 69, 1485–1489.

Mitchell, S.J., Mitchell, G.J., Mitchell, J.R., 2019. Modulation of frailty syndrome by diet: a review of evidence from mouse studies. Mech. Ageing Dev. 180, 82–88. https://doi.org/10.1016/j.mad.2019.04.003.

Mitnitski, A.B., Mogilner, A.J., Rockwood, K., 2001. Accumulation of deficits as a proxy measure of aging. Transfus. Apher. Sci. 1, 323–336.

O'Brien, M.S., McDougall, J.J., 2019. Age and frailty as risk factors for the development of osteoarthritis. Mech. Ageing Dev. 180, 21–28. https://doi.org/10.1016/j.mad.2019.03.003.

Palliyaguru, D.L., Moats, J.M., Di Germanio, C., Bernier, M., de Cabo, R., 2019. Frailty index as a biomarker of lifespan and healthspan: focus on pharmacological interventions. Mech. Ageing Dev. 180, 42–48. https://doi.org/10.1016/j.mad.2019.03.005.

Parks, R.J., Fares, E., Macdonald, J.K., Ernst, M.C., Sinal, C.J., Rockwood, K., Howlett, S.E., 2012. A procedure for creating a frailty index based on deficit accumulation in aging mice. J. Gerontol. A Biol. Sci. Med. Sci. 67, 217–227. https://doi.org/10.1093/gerona/glr193.

Rockwood, K., Howlett, S.E., 2019. Age-related deficit accumulation and the diseases of ageing. Mech. Ageing Dev. 180, 107–116. https://doi.org/10.1016/j.mad.2019.04.005.

Seldeen, K.L., Redae, Y.Z., Thiyagarajan, R., Berman, R.N., Leiker, M.M., Troen, B.R., 2019. High intensity interval training improves physical performance in aged female mice: a comparison of mouse frailty assessment tools. Mech. Ageing Dev. 180, 49–62. https://doi.org/10.1016/j.mad.2019.04.001.

Trendelenburg, A.U., Scheuren, A.C., Potter, P., Müller, R., Bellantuono, I., 2019. Geroprotectors: a role in the treatment of frailty. Mech. Ageing Dev. 180, 11–20. https://doi.org/10.1016/j.mad.2019.03.002.

Vaupel, J.W., Manton, K.G., Stallard, E., 1979. The impact of heterogeneity in individual frailty on the dynamics of mortality. Demography. 16, 439–454.

Whitehead, J.C., Hildebrand, B.A., Sun, M., Rockwood, M.R., Rose, R.A., Rockwood, K., Howlett, S.E., 2014. A clinical frailty index in aging mice: comparisons with frailty index data in humans. J. Gerontol. A Biol. Sci. Med. Sci. 69, 621–632. https://doi.org/10.1093/gerona/glt136.

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