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Fabry Disease: A New Model of Premature Ageing?

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An increase in biological ageing is now commonly recognized in chronic diseases such as chronic kidney disease and chronic obstructive pulmonary disease [1, 2]. In this issue, Vujkovac et al. [3] present data suggesting that Fabry disease may be a disease associated with premature ageing. The authors assessed telomere length (TL) and telomerase activity in a cohort of 33 patients with Fabry disease. Whereas in male patients, the authors observed a reduced TL as compared to age-matched controls, females presented with a higher telomerase activity without a significant difference in TL. The authors did not observe a difference in TL or telomerase between patients with or without enzyme replacement therapy (ERT), nor did they observe a relationship between TL and renal function. Telomere attrition is a feature of ESRD associated with persistent inflammation that predicts poor outcome [4].

Fabry disease is associated with a significantly reduced life expectancy compared to the general population [5], and therefore, the association with a premature ageing process is not unexpected. However, establishing biological age is not straightforward. Both phenotypical criteria and biomarkers are used for this purpose. Whereas phenotypically premature ageing is characterized by frailty, sarcopenia, reduced physical function, and cognitive dysfunction; these are not definite criteria for its diagnosis [6]. Whereas a reduced executive function and information processing speed were observed in patients with Fabry disease, and global cognition appeared to be preserved [7]. We could not identify studies from the literature assessing frailty, body composition, or physical function in adults with Fabry disease.

Regarding ageing biomarkers, telomere attrition, which was measured in this study, has been associated with outcomes at a population level in different disease states, but is generally considered to be an insensitive biomarker [8]. The ageing process is typified by significant interindividual variation and differences in physiological function between individuals of the same chronological age. This holds also for TL. The case for TL as a biomarker of ageing has been made repeatedly [9]. Systematic reviews of the evidence relating TL to outcome have found few actual mortality studies, all of which suffered from survivor bias. Few studies have examined the relationship with age-related decline in physiological function. Data from these were equivocal and all lacked statistical power [10, 11]. TL as a biomarker of age-related health is beset by methodological issues and has proven inferior to the use of CDKN2A [12, 13].

An exciting alternative has been the use of methylation-based epigenetic clocks, which show good correlations with chronological age and acceleration in disease states [14]. Caveats to their use, however, include their degree of fit with physiological function in normative

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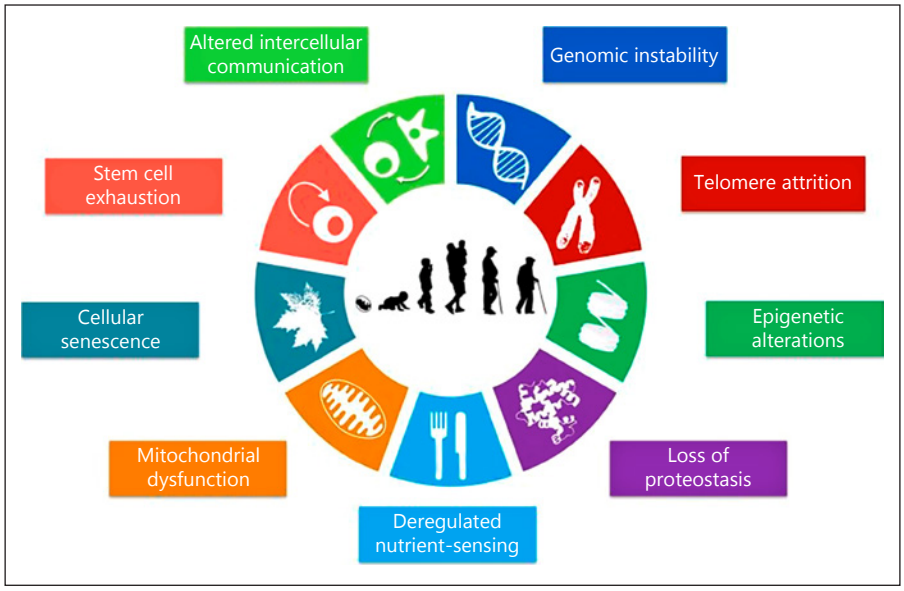

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Fig. 1. Hallmarks of aging. From [17], with permission.

ageing, a limited understanding of the significance of their respective methylation sites and the underlying mechanism. Additionally, the associated methylation sites lack conservation between species.

More recently, a ribosomal DNA-based clock has been described [15], with a proposed mechanism based on DNA methylation counteracting increased nucleolar size and rDNA transcription levels. This is also consistent with the MTR (mitochondrial, telomere nucleo-protein complexes, and control of ribosome synthesis) theory of ageing, as described in [16].

At a molecular and cellular level, 9 hallmarks are associated with the ageing process, namely, genomic instability, telomere attrition, altered intracellular communication (such as due to inflammation), epigenetic alterations, loss of proteostasis, deregulated nutrient sensing, mitochondrial dysfunction, cellular senescence, and stem cell exhaustion [17] (Fig. 1).

In patients with Fabry disease or in experimental models, dysregulation of several of these hallmarks has been identified. Whereas telomere attrition was observed in the study of Vujkovac et al. [3] and Squillaro et al. [18] observed DNA damage in a mesenchymal stem cell line despite the activation of DNA damage.

Regarding altered intracellular commination, Fabry disease is characterized by chronic low-grade systemic inflammation [19], resulting from an interaction between Gb3 and toll-like receptors, which likely contributes to tissue damage [20]. In the study of Vujkovac et al. [3], no relation between levels of proinflammatory biomarkers and TL was observed. However, given the small sample size, this does not necessarily suggest that systemic inflammation is not involved in the ageing process given the cross-sectional nature of the study. With respect to loss of proteostasis, dysregulated autophagy, which serves for the removal of cellular waste products, has been identified in cellular cultures with α-Gal A depletion [21]. Furthermore, nutrient sensing did seem to be in a podocyte cell culture model in Fabry disease, given the lower expression of mechanistic target of rapamycin. Nutrient sensing in the ageing process is a complicated phenomenon. Whereas activation of the anabolic pathways such as mechanistic target of rapamycin leads to accelerated ageing in experimental models, a downregulation of this pathway can be a defense mechanism under cell stress, preserving energy for cellular survival [17, 22].

With respect to mitochondrial dysfunction, a recent study has shown higher plasma markers reflecting oxidative stress in patients with Fabry disease on ERT [23], which is possibly in part related to superoxide dismutase 2 downregulation [24]. Squillaro et al. [18] showed that α-Gal A deficiency induced cell cycle arrest and senescence in cultures of amniotic and bone-marrow derived mesenchymal stem cells. In conclusion, there are several arguments for a disturbance in the "hallmarks" of ageing in patients and models of Fabry disease, although definitely more research is needed.

ERT did not appear to affect telomere attrition. Indeed, it has been shown that ERT can delay disease manifestation, and it is not able to completely prevent

the progression of organ damage in Fabry disease [25]. Inflammatory markers were even higher on patients receiving ERT, which might be a consequence of confounding by indication. An important characteristic of α-Gal A-depleted cell lines is an impairment of autophagy and protein turnover, leading to an increase in oxidative stress, which does not seem to be fully reversible by ERT [21, 23, 26]. The role of defective autophagy in the ageing process is increasingly recognized [27].

In a recent study, ERT cleared Gb3 from podocytes in cell cultures but was not able to normalize dysregulated autophagy, TGF-β expression, or oxidative stress, suggesting that other as yet incompletely identified mechanisms beyond Gb3 accumulation also are involved in the organ damage of FD [21, 23]. Also, ERT did not appear to be able to normalize the decreased energy metabolism in pluripotent stem cell-derived cardiomyocytes that were reprogrammed with a mutated GLA gene of a patient with Fabry disease [28].

Despite existing controversy around this subject [29], it has been suggested that skewing of X chromosome inactivation affects the phenotype of female patients with FD [29]. Whereas patients with random inactivation showed a progressive course with advancing age, Echevarria et al. [30] have observed that those with skewed inactivation displayed either a mild course or a rapidly progressive course of the disease depending on the expression of the mutant *GLA* allele. Ageing has been shown to induce skewing of lead X chromosome expression, which has been implicated in the pathogenesis of several auto-immune disorders [31]. It might be hypothesized that biological ageing, by inducing skewing of X chromosome inactivation, may also play a role in the progression of FD and its phenotypic expression in females in a mutually reinforcing way. However, this assumption needs to be addressed in future studies.

The finding that females, who usually have a milder form of disease, had telomere levels comparable to controls, but higher telomerase levels are intriguing. It was suggested that a higher telomerase level serves as a temporary compensatory mechanism under stressful conditions in order to preserve TL, whereas data from dialysis patients showing both reduced TL and telomerase activity suggest that this process is exhausted with more progressive disease [32]. This assumption is also supported by the fact that telomerase was decreased in male patients with eGFR levels <60 mL/min/1.73 m^2. Interestingly, whereas it might be logically argued that a decrease in renal function would be primarily responsible for the telomere attrition in FD patients given the fact that chronic kidney disease is considered a model of premature ageing [2, 4], TL was not related to an impairment in renal function, nor to cardiac biomarkers. In future studies, it would be interesting to study the relation between more specific aging biomarkers and specific organ dysfunction in more detail.

The findings of Vujkovac et al. [3] are intriguing and stimulate larger studies to assess the relation between aging biomarkers, markers of metabolic load such as Gb3, as well as detailed phenotypical alterations. Whether the present results have therapeutic implications is yet uncertain. Generalized strategies to delay premature aging include generic factors, such as exercise [33], whereas at the horizon, senolytic drugs, such as quercetin, fisetin, and dasatinab, are emerging as potential treatments for conditions associated with premature ageing [34]. Another promising target appears to be the transcription factor NRF2-KEAP1 and increased oxidative stress [35], which may be involved in both specific organ damage as well as a generalized aging process [36].

At present, the study of Vujkovac et al. [3] presents preliminary evidence that Fabry disease may represent another model of premature aging. Future research could shed more light on the systemic nature of the disease, which possibly extends even beyond the multiorgan involvement directly related to G3b accumulation. This study should be followed by larger and more detailed studies looking into mechanisms and potential targets to prevent premature ageing in Fabry disease beyond the conventional treatment strategies.

Disclosure Statement

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