Healthy aging

Chapter 8

Impact paragraph

Everyone experiences aging, but we don't know what to expect.

The "2019 Revision of World Population" released by the United Nations reports that the population worldwide is rapidly aging. According to this report, by 2050, one in six people in the world will be over the age of 65, compared to one in eleven registered in 2019. This fraction will possibly be even higher in Europe and North America, where it is predicted that one in four people will surpass the 65 years of age.[1] Population aging is expected to become the trademark of deep societal changes, affecting the job market, economy, healthcare systems and family structures.

This emerging realization has also impacted scientific research, causing a growing urge to better understand the process of senescence and senility in the context of aging. Here, we define the three biological concepts as follows: aging as the passage of time, senescence as the progressive physiologic impairment of organs and organisms that occur with the passing of time and senility as the pathological development of diseases, the incidence of which generally increases with age. Although numerous molecular processes have been detected as crucial contributors to senescence, to this day several unresolved questions persist on the root causes of tissues and organ dysfunction as a result of the unavoidable transition of time. One consideration in particular becomes relevant in the context of the changing demography of our societies; how to define the fine line between senescence, physiological or "healthy" aging of our organs, versus senility, the pathological development of disease accompanying aging, which is of particular interest for medical practice of modern cardiology and our healthcare systems.

The studies reported in this thesis have been designed with the intent of tackling this crucial issue for cardiac aging. One important outcome delivered by these projects is a critical assessment of the currently most used mouse aging models. As thoroughly described in this thesis, we dispute the reliability of mouse models for the study of age-related cardiac diseases, thus

pointing to the need of improved experimental platforms to better mimic the human condition. Our main observation is that in the absence of the typical aging-related pathological disorders, such as hypertension and diabetes, the mouse heart appears generally unaffected by the aging process, in contrast to the human aging heart. As a result, we reason that to study cardiovascular diseases common among the elderly, a suitable animal model should faithfully mimic the overall clinical diagnosis of the subjects, thus preferring a more holistic approach rather than one only centred on the heart. These considerations resonate also in the context of the therapeutic strategies to adopt for the treatment of heart conditions in the elderly. Our findings suggest that, by alleviating the burden on the heart of age-related afflictions, it could be possible to improve the overall cardiovascular condition of the elderly. We even postulate, on the basis of our experimental observations, that the myocardium tolerates oxidative stress, telomere attrition, progerin accumulation and oxidative stress, even at high ages, remarkably well and to such an extent that pathological aging of the heart becomes a questionable concept. Rather, our findings suggest that senescence of the vascular system and concomitant molecular alterations more readily suffer from age-related inflammation, calcification, oxidative stress and atherosclerosis, that indirectly can impact the myocardium by creating disastrous conditions to the heart in the form of hypoxia or even acute ischemic events.

For one of the studies reported in this thesis we have made use of human cardiomyocytes derived from induced pluripotent stem cells as experimental platform. Our findings support the relevance of this model in the cardiovascular research field to perform preliminary studies. Stem cells can recapitulate in a much more stringent fashion the phenomena occurring in human than any other cell system traditionally used for cardiac research. Additionally, stem cell-derived cardiac cells can be used to generate 3D structures, valuable not only as more complex experimental platforms for fundamental research but also as tools for regenerative therapies. Finally, as

a human-derived system, stem cells hold the possibility of future broader applications that could gradually supersede the use of animal models.

The Hutchinson-Gilford progeria syndrome (HGPS) is a congenital disease leading to premature aging in early childhood. It is an extremely rare condition: currently, only 173 diagnosed cases are reported worldwide.[2] However, the production of progerin, the aberrant form of lamin trademark of this disease, is detected also during physiological aging in multiple tissues, suggesting that the molecular mechanisms responsible for the pathophysiology of HGPS are active during normal senescence as well.[3] In this thesis, we hypothesized on the role played by circRNA-ZNF609, an RNA molecule with a circular structure, in the context of this pathology. In fact, we found this molecule to be upregulated in HGPS mice and in human cardiomyocytes carrying the progeria mutation of the *LMNA* gene. Our findings point to the potential effect of circZNF609 on mitochondrial function, cell cycle activity and RNA metabolism. In line with this observation, we foresee the potential of manipulating the levels of circZNF609, or any of the downstream aberrant processes, in aging individuals who are at high risk of developing age-related cardiovascular diseases, as a way to delay or possibly prevent pathological outcomes. As argued before, the individuals who would mostly benefit from such strategy are those affected by hypertension, diabetes, metabolic syndromes and other aging-related comorbidities.

REFERENCES

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