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Review

Interventions to slow cardiovascular aging: Dietary restriction, drugs and novel molecules

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ABSTRACT

Cardiovascular aging is a highly dynamic process. Despite the fact that cardiovascular function and structure change with age, they can still be modulated even in aged humans. The most prominent approaches to improve age-dependent vascular changes include dietary restriction and pharmacologic agents interacting with signaling pathways implicated in this context. These include inhibition of TOR, glycolysis, and GH/IGF-1, activation of sirtuins, and AMPK, as well as modulators of inflammation, epigenetic pathways, and telomeres. Promising nutritional approaches include Mediterranean diet and novel dietary bioactives including flavanols, anthocyanins, and lignins. Many plant bioactives improve cardiovascular parameters implied in vascular healthy aging including endothelial function, arterial stiffness, blood pressure, cholesterol, and glycemic control. However, the mechanism of action of most bioactives is not established and it remains to be elucidated whether they act as dietary restriction mimetics or via other modes of action. Even more importantly, whether these interventions can slow or even reverses components of cardiovascular aging itself and can increase healthspan or longevity in humans needs to be determined.

Contents

1. Introduction

Aging is a major risk factor for the most important age-related diseases including coronary, peripheral, and cerebrovascular artery disease. Atherosclerosis and arteriosclerosis pose the major threats to healthy cardiovascular aging. Subclinical stages of these pathologies can be detected long before cardiovascular disease becomes clinically

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manifest. The mechanisms underlying vascular aging are still not completely understood, but involve all segments of the vascular system. What is known is that increasing age is associated with endothelial dysfunction, vascular stiffening, as well as isolated systolic hypertension, and thus with raised atherogenic risk and a substantial excess of cardiovascular mortality (Kaess et al. 2012). Due to increased arterial stiffness, older humans exhibit an increased pulse wave velocity. In young subjects, the reflected returning pulse wave increases pressure during diastole and therefore contributes to the 'windkessel effect' (i.e. elastic reservoir) of the aorta. In older subjects, the pulse wave will propagate and return faster, coinciding with the systolic forward flow, thus leading to augmentation of systolic blood pressure. Furthermore, stiff arteries are characterized by a decreased absorption of the pulse wave and this results in increasing mechanical stress on the arterioles, which is thought to damage the microvasculature, leading to structural microvascular remodeling and rarefication (Mitchell 2008). There is an age-dependent systemic endothelial dysfunction and intimal hyperplasia, which affects both, the elastic and muscular, conduit arteries (Celermajer et al. 1994; Heiss et al. 2015b; Rossi et al. 2002). These changes rather resemble progressive arteriosclerosis similar to changes that occur with arterial hypertension and can be explained in many regards with mechanical wear and tear of arterial structures. However, it may also be argued that with age daily mechanical wear and tear caused by pulsatile blood flowing through the arteries is not balanced by sufficient maintenance repair. Indeed, with increasing age collagen synthesis and matrix metalloprotease(s) expression as well as activity increase while elastin synthesis decreases and the function of circulating cells (immune cell aging) including "repair cells" (circulating angiogenic cells) decreases (Heiss et al. 2005).

In addition and in many regards distinct from the arteriosclerotic vascular changes described above, localized intimal hyperplasia occurs that progresses towards atherosclerotic plaques, which in turn can result in arterial lumen narrowing and cause decreased perfusion or infarction of dependent tissues. Typically, plaques build up at predisposed areas such as branching points. Mechanistically, local hemodynamic factors such as turbulent flow may favor an increased cell turnover leading to accumulation of senescent cells at these locations with age (Warboys et al. 2014). Consequently, atherosclerotic plaques may be seen as a maladaptive phenotype resulting from insufficient regeneration of ongoing endothelial injury at sites of increased stress. Taken together, these factors appear to converge both in positive, but also in negative ways, on the vascular endothelium with potential profound effects on both healthspan and total lifespan rendering endothelial function one key target of cardiovascular disease prevention and improvements in healthy aging (Heiss et al. 2015a).

Research on interventions in the context of cardiovascular aging stems from basic science research and to a smaller degree clinical studies. Basic science has focused on experimental models with a focus on the identification of signaling pathways related to aging or single gene mutations associated with longevity in model organisms. On the other hand, many clinical studies rather phenomenologically show that clinical endpoints, which are associated with vascular aging (and cardiovascular risk), can be positively affected by pharmacological, nutritional, and life style intervention approaches. However, most studies are performed in humans at cardiovascular risk or manifest disease. Due to the lack of specific biomarkers of 'aging' it is very difficult to dissect whether 'aging' per se or a disease process distinct from 'aging' is affected by the intervention (and secondarily affects 'aging'). Longevity is not a feasible endpoint in humans and very few longterm studies were performed in 'healthy' humans. By definition, these trials are often termed primary prevention trials and the endpoints are mostly established as disease risk markers and not health markers, as the latter have not been clearly defined. Most studies are cross-sectional or short-term intervention trials that are not able to investigate aging as a dynamic process, healthspan, or longevity. This dilemma results in a large disconnect between basic and clinical science and underscores that translational studies aiming at bridging this gap are necessary (Fig. 1). One of the difficulties in translation between basic science and clinical studies in order to mechanistically tie changes in clinical outcomes to effects on molecular aging pathways is the fact that different endpoints are used and the biology of aging shows subtle differences between species and in proliferative and non-proliferative tissue within species. One way that promises to overcome some of the difficulties maybe to facilitate animal model with almost identical methodologies as used in human studies such as flow-mediated dilation for endothelial functional testing and pulse wave velocity to monitor arterial stiffness in living animals (Heiss et al. 2006; Schuler et al. 2014). This would allow the evaluation of several pharmacological and nutritional interventions that promise to affect cardiovascular aging together with the molecular mechanisms side by side in humans and animal models.

In a recent workshop entitled 'Interventions to Slow Aging in Humans: Are We Ready?' held in Erice, Italy, leading experts in the biology and genetics of aging were brought together in order to obtain a consensus related to the discovery and development of safe interventions to slow aging and increase healthy lifespan in humans (Longo et al. 2015). There was consensus that there is sufficient evidence that aging interventions will delay and prevent disease onset for many chronic conditions of adult and old age. Essential pathways have been identified, and behavioral, dietary, and pharmacologic approaches have emerged. Although many gene targets and drugs were discussed and there was not complete consensus about all interventions, the participating experts selected a subset of the most promising strategies that could be tested or are currently tested in humans for their effects on healthspan. These were: (i) dietary restriction and dietary interventions mimicking chronic dietary restriction; (ii) drugs that inhibit the growth hormone/IGF-I axis; (iii) drugs that inhibit the mTOR pathway; (iv) drugs that activate AMPK and activators of specific sirtuins. These choices were based in part on consistent evidence for the pro-longevity effects and ability of these interventions to prevent or delay multiple age-related diseases and improve healthspan in simple model organisms and rodents and their potential to be safe and effective in extending human healthspan. However, there are several less well explored strategies or targets including epigenetic mechanisms, inflammation, and a number of promising novel drugs and molecules that may act via one or several of the above mechanisms.

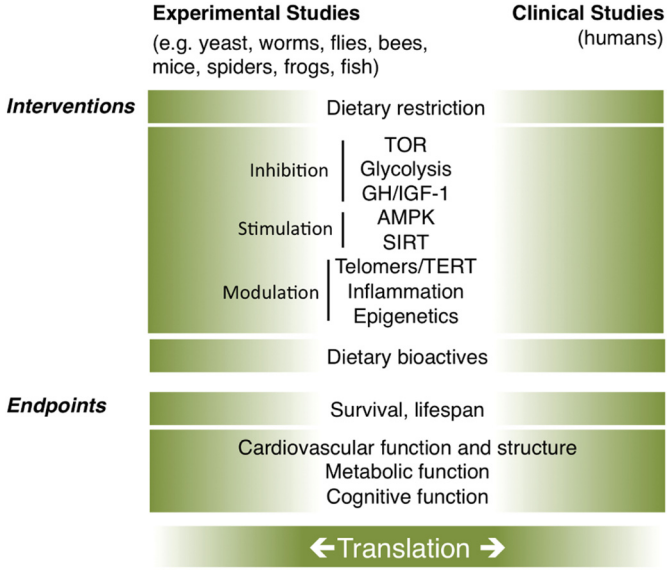

Fig. 1. Summarizing scheme.

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