ORIGINAL ARTICLE

Inflammation and hemostasis in older octogenarians: implication in 5-year survival

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Social changes and medical advances have increased longevity, but the conditions governing healthy vs unhealthy cardiovascular (CV) aging are not fully known. Factors beyond classical CV risk factors may have an important unrecognized value. We sought to identify proteins differentially expressed in healthy octogenarians (HOs) without a history of cardiovascular disease (CVD) and preserved functional and cognitive state compared with octogenarians with a history of CVD and cognitive decline (UHOs) using a systems biology approach, and investigated how these proteins relate to CV mortality at 5-year follow-up. Plasmas obtained from older octogenarians (87 ± 0 years) were analyzed by 2-DE + MS and bioinformatic pathway analysis in HOs (N = 38) and UHOs with cognitive (MEC<25) and functional (Barthel<90) decline and a previous ischemic event (acute myocardial infarction and/or stroke; N = 27). Results were validated by ELISA in HOs and UHOs and in an additional group of older octogenarians without cognitive impairment but with a previous CVD manifestation (HO-CVD; N = 35). UHOs showed a coordinated change in several inflammation-related proteins (AMBP, RBP4, and ITIH4; $P < 0.05$), together with a significant increase in the major inducer of the acute-phase reaction, interleukin-6 ($P = 0.03$). UHOs also showed a coordinated increase in hemostatic proteins that was associated with an impairment of fibrinolysis and an increased 5-year CV mortality ($P = 0.003$). The combination of inflammation (ITIH4 and interleukin-6) and hemostatic markers (D-dimer, A2AP, and coagulation factor XIII) was able to discriminate the presence of an unhealthy phenotype in the elderly (AUC = 0.750; $P = 0.001$). Unhealthy older octogenarians show increased levels of several plasma proteins of inflammation and coagulation. In older octogenarians, the increase in hemostatic markers indicated an increase in 5-year CV mortality at follow-up. (Translational Research 2017;■:1–13)

Abbreviations: 2-DE = bidimensional electrophoresis; ACEI = angiotensin-converting enzyme inhibitors; ALT = alanine aminotransferase; AMBP = alfa-1-microglobulin/bikunin precursor; AUC = area under the curve; A2RA = angiotensin-2-receptor antagonists; BMI = body mass index; CVD = cardiovascular disease; CRP = C-reactive protein; ELISA = enzyme-linked immunosorbent

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assay; FXIII = coagulation factor XIII; HO = healthy octogenarians; HDL-C = high-density lipoprotein cholesterol; ITIH4 = inter-alfa-trypsin inhibitor heavy chain H4; LDL-C = low-density lipoprotein cholesterol; MALDI-TOF/TOF = matrix-assisted laser desorption/ionization time-of-flight; MEC = Spanish version of the Mini-Mental State Examination; MNA = Mini Nutritional Assessment; MS = mass spectrometry; OAD = oral antidiabetic drugs; RBP4 = retinol-binding protein; TG = triglycerides; tPA = tissue plasminogen activator; UHO = unhealthy octogenarians

AT A GLANCE COMMENTARY

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Background

We are facing a progressive aging of the population with an increasing need to more accurately qualify what is called ''healthy aging''. But there is little understanding on the molecular pathways that associate with healthy old age as opposed to an unhealthy phenotype in the elderly, and whether a specific coordinated proteomic signature, reflecting impairment of discrete biological pathways, is associated with unhealthy aging predisposing to mortality. Indeed, until now, there are no accepted biomarkers for the assessment of the global health status in the elderly in order to identify those patients at higher risk.

Translational Significance

Our study has shown a coordinated change in the distribution profile of several plasma proteins related to inflammation and hemostasis in unhealthy octogenarians with a previous episode of vascular disease, suggesting a potential implication of this protein-network in the development of CVD and cognitive impairment in the elderly. These findings, if validated in larger cohorts, could establish the basis for the development of novel therapeutic strategies in the elderly to target the hemostatic imbalance and the increased formation of fibrin microthrombi, without increasing the bleeding risk, in order to favor healthy aging and longevity.

INTRODUCTION

Advanced age is associated with increased risk for cardiovascular (CV) event presentation. Indeed, the risk for CV atherothrombotic disease starts in the second decade of life and accrues over the years.[1] The increase in cardiovascular disease (CVD) prevalence with aging has been attributed to several age-related alterations such as changes in the vascular wall elasticity, hemostatic system, platelet activity, endothelial dysfunction, and an impaired regenerative capacity.[2-4]

Importantly, mounting evidence highlights the impact of vascular disease in cognitive decline in the elderly leading to a "vascular hypothesis" in the development of Alzheimer's disease.[5] In fact, previous studies have reported the relation between the presence of vascular risk factors, such as diabetes or hypercholesterolemia, in midlife and the development of Alzheimer's disease.[6] However, there seems to be a discrepancy between the chronological and the "biological age" that results in a differential impact of the aging process and thus a differential distribution of the risk among elderly patients.[7] During the last years, several studies have focused on the analysis of coagulation and inflammation pathways among older adults.[8,9] Indeed, increased plasma concentrations of several clotting factors have been found in elderly individuals such as fibrinogen,[10] high-molecular-weight kininogen, and prekallikrein.[11] Furthermore, a link between an abnormal clotting system and cognitive deficits has been suggested in part due to the association between elevated fibrinogen levels with cognitive decline[12] and increased risk of Alzheimer's disease.[13]

On the other hand, the increase in PAI-1 expression, together with a chronic inflammatory state, has been considered the major contributor to the age-related thrombotic disorders in the elderly.[14] Furthermore, the presence of higher C-reactive protein (CRP) levels in the elderly has been associated not only to a higher risk of suffering CV events but also to a worse prognosis after suffering an acute event.[15]

In the last years, frailty assessment has emerged as a potential measure of "biological age" aiding in the identification of high-risk elderly patients and representing a risk factor for falls, disability, institutionalization, and death.[16] The most important clinical markers of frailty are: nutritional status, mobility, functional activity, strength, cognitive status, and mood. But there is little understanding on the molecular pathways that associate with healthy old age as opposed to an unhealthy phenotype in the elderly, and whether a specific coordinated proteomic signature, reflecting the impairment of discrete biological pathways, is associated with unhealthy aging predisposing to mortality. Indeed, until now, there are no accepted biomarkers for the assessment of the global health status in the elderly to identify those patients at higher risk.