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Cellular and molecular basis of the imbalance between vascular damage and repair in ageing and age-related diseases: As biomarkers and targets for new treatments

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ABSTRACT

Preclinical and clinical studies suggest that specific subsets of cells isolated from the peripheral blood, play an essential role in the imbalance of damage and repair during age-associated diseases, such as metabolic syndrome, diabetes, atherosclerosis, neurodegenerative diseases, osteoporosis and cancer. Endogenous regeneration of the vessel wall involves cells of the vascular wall, inflammatory cells, circulating precursors, and mature endothelial cells, which are capable to restore the endothelium in a concerted interaction. Early detection of such imbalances with specific biomarkers may reduce age-associated diseases and subsequent cardiovascular events. Likewise, new strategies have the potentiality of acting selectively on these cell populations and co-temporally mediate the stimulation of the function and number of those cell populations with regenerative action on the vessel, and inhibit those able to evocate vascular damage. These strategies may be an alternative innovative way with superior and more efficacy biological effects than conventional attempts used for treating actually vascular diseases, characterizing those co-morbidities related to ageing.

1. Introduction: ageing related vascular disease—the problem of ageing population size

According to the World Health Organization (WHO), in 2010 the number of people aged 65 or older has been estimated equal to 524 million in the world. In addition, it has been also assessed that in 2050 the projected old-age dependency ratio will achieve a percentage of 68% particularly in European populations (Balistreri et al., 2014a,b; Ferrucci et al., 2008). This trend implies several medical, economical, social and quality life problems, related principally to increase of non autonomous individuals affected by chronic diseases, such as cardiovascular diseases, diabetes, atherosclerosis, neurodegenerative diseases, osteoporosis and cancer (Yancik et al., 2007; Vasilopoulos et al., 2014). Among these, the major number of aged people have prevalent micro- and macro-vascular diseases, including ischemic heart disease, cerebrovascular disease and peripheral arterial disease, fruit of vascular ageing or as complications of diabetes (Balistreri et al., 2014a,b; Boudina, 2013; Corella and Ordovás, 2014; North and Sinclair, 2012; Ren and Anversa, 2015). Indeed, diabetic patients show a high incidence of cardiovascular diseases (CVDs) (about 40/1000 person/year in Italy), which is 2–4 times higher than that of general aged population (Balistreri et al., 2014a,b; Boudina, 2013; Corella and Ordovás, 2014; Ren and Anversa, 2015). However, onset and clinical manifestations of CVD disorders commonly characterize non-diabetic aged individuals (Balistreri, 2015). Ageing represents the most important determinant of CVDs. Another determining factor related to the population ageing, is the increased number of hypertensive individuals. Hypertension is, indeed, a widely prevalent and important risk factor for CVDs, as established by recent guidelines (Aronow et al., 2011; Ruvolo et al., 2014). Diabetic patients are particularly prone to develop atherosclerotic CVDs and their complications (i.e. metabolic syndrome and neurodegenerative disorders, such as Alzheimer diasease), due to hyperglycemia and associated metabolic abnormalities (Accardi et al., 2012; Balistreri et al., 2014a,b; Boudina, 2013; Corella and Ordovás, 2014; Ren and Anversa, 2015). Atherosclerosis in diabetes is more aggres-

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sive than in the non-diabetic population, since it is premature and rapidly progressive, and involves several arterial districts at the same time. Due to the aggressive nature of macrovascular disease and its pernicious association with micro-vascular disease, diabetic patients with coronary or peripheral complications are often not susceptible to surgical and endovascular revascularization. Thus, a steadily increasing number of no-option patients are doomed to develop disease-related disability and mortality. Based on these observations, novel ways to prevent development or treat macro-vascular/micro-vascular CVDs are particularly sought. In this review, we analyze the current knowledge about the imbalance between damage and vascular repair associated with ageing and its molecular and cellular basis. We also here highlight new cellular targets for innovative preventive and treatment strategies.

2. Focus on self-repair as strategy for reducing and/or retarding CVD onset and progression

Ageing related-CVDs (secondary or not to diabetes) are characterized by a complex patho-physiology, orchestrated by

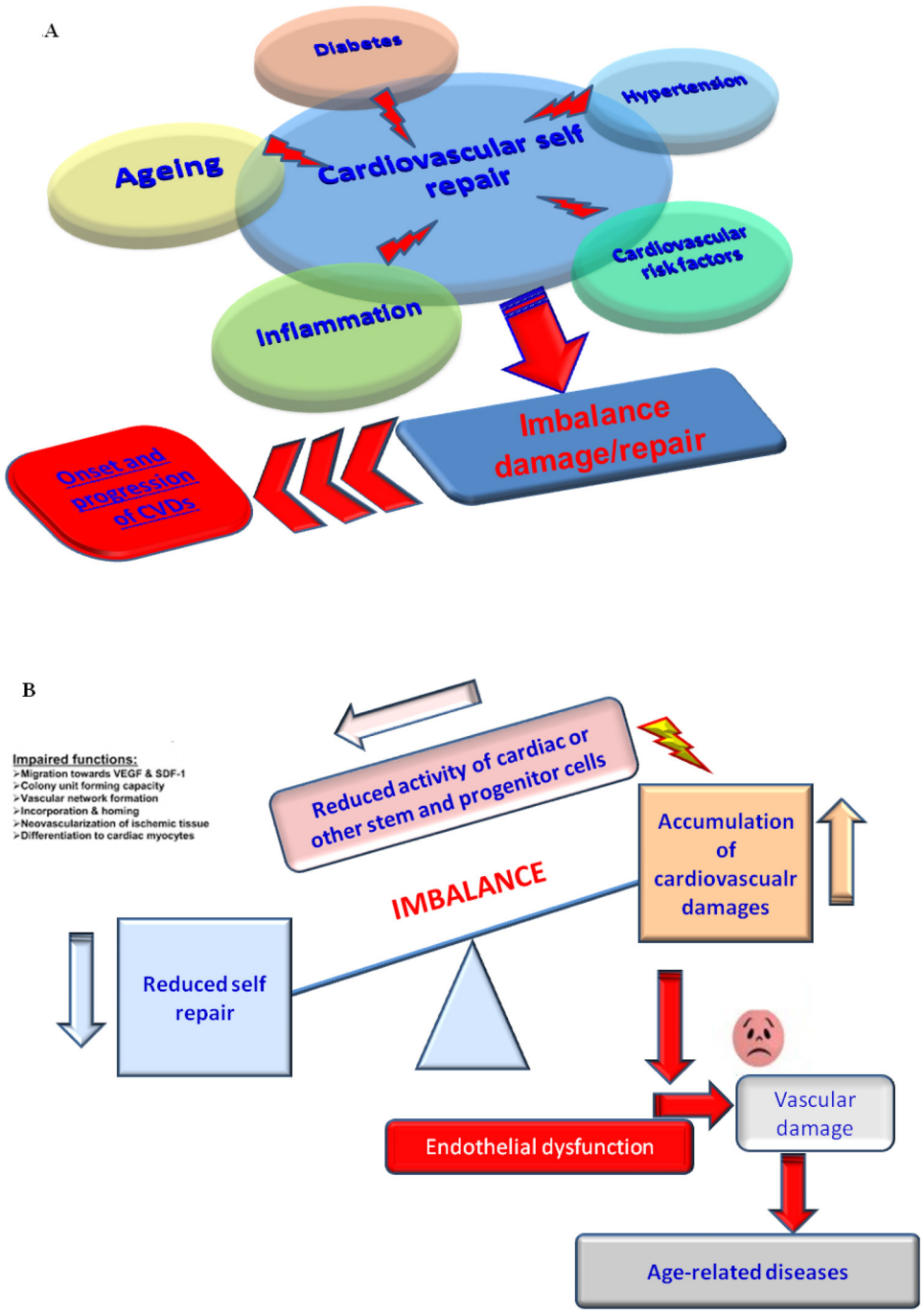

Fig. 1. (A) Impairing of cardiovascular self repair. Firtly ageing, but also other factors related to process, affect cardiovascular repair by evocating the development of an imbalance of damage and self repair, responsible with advancing age of onset and progression of CVDs. (B) Onset of imbalance between damage and self reapir. Cardiac or other stem and progenitors cells (i.e. EPC cells) show impaired functions with age. This determines incapacity of counteracting damages evocated by age-related risk factors (showed in A). Accumulation of damages consequently is inevitable. Thus, endothelial dysfunction occurs responsible of onset of vascular damage and its complications, including CVDs.

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