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A novel hypothesis of atherosclerosis: EPCs-mediated repair-to-injury

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Summary Recent findings demonstrate the vital role of endothelial progenitor cells in the homeostasis of the vessel wall and the development of atherosclerosis. Endothelial progenitor cells (EPCs) play important roles in repair-to-injury of arteries. Many evidences have shown Cardiovascular risk factors closely correlated with EPCs numbers and function. Levels of circulating EPCs represented a better predictor of endothelial function than conventional risk factors. Depletion of bone marrow and Cardiovascular risk factors are the two prerequisits of atherosclerosis. All conditions of manifest atherosclerotic disease are accompanied by reduced EPC numbers and migratory capacity. Therefore, based on response-to-injury hypothesis and these findings, we build up EPCs-mediated repair-to-injury hypothesis, which may have important therapeutic implications in the prevention and therapy of atherosclerosis. The use of EPCs for vascular repair may be important therapy strategies with a maximized benefit for the patient in the future.
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Introduction

Atherosclerosis is the leading cause of death in the world and is an inflammatory process that selectively affects arteries and is highly prevalent in both women and men. Thrombo-occlusive complications of atherosclerosis, including stroke and myocardial infarction, are major causes of morbidity and mortality. Despite intense research efforts, the underlying molecular mechanisms of atherosclerosis are still incompletely understood, however, many findings have demonstrated the vital role of progenitor cells in the homeostasis of the vessel wall and the mitigation of atherosclerosis. Therefore, based on response-to-injury hypothesis of atherosclerosis, we set up EPC-mediated repair-to-injury hypothesis.

The risk factors of atherosclerosis closely correlated with EPCs numbers and function

A growing body of evidence suggests that circulating EPCs play an important role in endothelial cell

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regeneration. Small clinical studies have shown that the number of circulating EPCs inversely correlates with risk factors for atherosclerosis [1,2]. Hill et al. demonstrated a strong correlation between the number of circulating EPCs and the patient's combined Framingham risk factor score [1]. Cardiovascular risk factors have been closely associated with reduced EPCs numbers and function. All conditions of manifest atherosclerotic disease are accompanied by reduced EPC numbers and migratory capacity [2]. Circulating CD34/KDR-positive progenitor cells are reduced in patients with coronary artery disease (CAD). In addition, EPCs isolated from patients with CAD displayed an impaired migratory response, which was inversely correlated with the number of cardiovascular risk factors [3—5]. Vasculoprotective agents increase the number and function of endothelial progenitor cells improving endothelial function and preventing progression of atherosclerosis. Human studies clearly demonstrate that high EPC levels are associated with reduced cardiovascular event rates underlining the vasculoprotective action of EPCs [6,7]. All major known cardiovascular risk factors negatively influence number of EPCs, migratory capacity, as well as the clonogenic potential of progenitor cells.

The crucial roles of progenitor cells in repair-to-injury process

Various studies have underlined the important role of bone marrow—derived endothelial progenitor cells (EPCs) in vasculogenesis and angiogenesis of ischemic tissue. All conditions of manifest atherosclerotic disease are accompanied by reduced EPC numbers and migratory capacity [2].

Most likely, the observed impairment of progenitor cells in these patients is attributable to the accumulation of cardiovascular risk factors resulting in a reduced regenerative potential. According to the response-to-injury hypothesis, cardiovascular risk factors induce a chemical or mechanical injury of the endothelium that triggers and finally results in endothelial dysfunction [8]. The latter is a prerequisite of atherosclerosis [9—11]. The injured arterial wall mounts a profound systemic response that involves a cascade of molecular and cellular events to promote the repair of the vessel wall.The repair and remodeling of the arterial wall are regulated by circulation of progenitor cells by the bone marrow and other organs. Many evidences have shown EPCs plays a crucial roles in this process of repair and remodeling.When remodeling becomes pathological, especially in advanced atherosclerosis, it can lead to reduced flow as a result of narrowing of the lumen and consequent ischemia for downstream tissues. The pathological remodeling usually result in acute coronary syndromes, even acute myocardial infarction these disease frequently go along with elevated numbers of EPCs, which also indicating that EPC-mediated tissue and vessel repair is a ''physiological'' response of the organism after severe ischemia, simultaneously, the mobilized EPCs are functionally impaired [12—14].

Local injury of the arterial wall also triggers a powerful recruitment of vascular cells, either through in situ proliferation or by engraftment of bone marrow — derived progenitor cells [15,16]. This process of repair can be misguided and contribute to vascular lesion progression [17,18]. As a general rule, the repair is rapid and successful and the inflammatory reaction are self-limited [19], however, Failure to repair the arterial wall in response to inflammatory signals will further promote atherogenesis and hence create a positive feedback loop that propagates vessel injury.

Prerequisites of atherosclerosis: Cardiovascular risk factors and depletion of bone marrow

In the presence of competent bone marrow, the repair to injury of arterial always can be successful or self-limited.The inflammatory reaction is self-contained because the repair of the arterial wall results in the discontinuation of the stimulus that had triggered the inflammatory reaction.

In contrast, in the absence of competent marrow, an arterial lesion has no opportunity to become repaired, and this lack of repair contributes to perpetuating and even intensifying of the atherosclerotic inflammation, with progressive senescence and dysfunctional remodeling of the arterial wall.

Most likely, the observed impairment of progenitor cells in these patients is attributable to the accumulation of cardiovascular risk factors resulting in a reduced regenerative potential [2]. Cardiovascular risk factors, especially Aging, can lead to depletion of bone marrow cells capable of repair of the arterial wall [20—22]. Indeed, the depletion of bone marrow—derived progenitor cells may account for a large fraction of the aging risk in the development of vascular disorders [22]. Such depletion of competent cells may involve the loss of production of progenitors by a dysfunctional marrow or the marrow production of dysfunctional progenitor cells that are therefore incapable of

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