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Review

Endothelial progenitor cells and rheumatic disease modifying therapy

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ABSTRACT

Rheumatic diseases are associated with accelerated atherosclerosis and with increased risk of cardiovascular morbidity and mortality. The mechanisms underlying the higher prevalence of cardiovascular disease are not completely clarified, but it is likely that a pivotal role is played by vascular inflammation and consequently to altered vascular endothelium homeostasis. Also, high prevalence of traditional risk factors, proatherogenic activation and endothelial dysfunction further contribute to vascular damage.

Circulating endothelial progenitor cells (EPCs) can restore dysfunctional endothelium and protect against atherosclerotic vascular disease. However, abnormalities in number and function of these cells in patients with rheumatic condition have been extensively reported.

During the last years, growing interest in the mechanisms of endothelial renewal and its potential as a therapy for CVD has been shown; in addition, pioneering studies show that EPC dysfunction might be improved with pharmacological strategies. However, how to restore EPC function, and whether achieving this aim may be effective in preventing cardiovascular complications in rheumatic disease, remain to be established.

In this review we report an overview on the current stand of knowledge on the effect of pharmaceutical and lifestyle intervention in improving EPCs number and function in rheumatic disease.

1. Introduction

Cardiovascular disease (CVD), including acute coronary syndromes, stable coronary heart disease, stroke, or peripheral arterial disease, represents the main cause of death worldwide [1]. Several rheumatic diseases are associated with increased incidence of CVD [2]. This association is partly attributable to the increased prevalence of traditional cardiovascular risk factors for atherosclerosis, such as diabetes, hypertension and dyslipidaemia, but also disease activity and inflammation seem to play a role in increasing the risk of CVD in patients with rheumatic disease, especially in patients with lower burden of traditional CV risk factors [2,3]. Together, these players cause a proinflammatory status and endothelial dysfunction, leading to premature atherosclerosis.

Impaired endothelial function represents the earliest and likely reversible stage of atherosclerotic plaque formation [4]; the integrity of vascular endothelium is essential for arterial wall functions and homeostasis, and its dysfunction represents the key event which subsequently leads to vascular wall disorders.

Therapeutic attempts may also be aimed at restoring the endothelial dysfunction, improving tissue perfusion and inducing tissue repair [5]. Current studies are focusing on these challenges; however, since mature endothelial cells (ECs) have limited proliferative and repair abilities, much interest in recent years has been directed toward less differentiated cell subsets, including the progenitors of ECs, that are capable of differentiating into mature ECs and of contributing to the recovery and repair of ischemic tissues [5]. In 1997 Asahara et al. isolated for the first time a cell subset likely able to contribute to post-natal angiogenesis, and defined them “putative progenitor endothelial cells” [6]; thereafter, many authors have tried to characterize these cells, and to better identify the immunophenotype(s) eventually committed to differentiate in mature ECs. A number of experimental studies have been performed ex vivo, in order to track the putative profile of the “true” endothelial progenitor cell (EPC). Thus, many different surface antigen, often co-expressed by endothelial and hematopoietic cells, have been already proposed, although the question of which cell phenotype better identifies this putative “true” circulating EPC remains unsolved [7–10]. Moreover, the frequencies of progenitor cells are really low in peripheral blood, and EPCs represent a rare population; so, many other authors developed cell cultures to expand them. Hence, many different

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characteristics have been observed, including the ability to form colonies in cell plates, differentiate, proliferate, tubulize, mobilize, adhere, migrate, and home the vascular endothelium [10–13]. Consistently, different cell culture methods have been developed, including the so-called "CFU-Hill colony counting method" [11], and another one also known as "early-outgrowth EPCs", described by VASA and coll. [13]; both of these methods allow to identify the so-defined "early EPCs". Another method has been developed to identify the late-outgrowth colonies or ECFCs, in which a cell population emerging late in culture shows clear endothelial characteristics. The mechanisms leading to endothelium proliferation in plates is further complicated by the evidence that different cell types seem to be required, including CD14+ mononuclear cells (derived from angiogenic macrophages), and CD31+ T cells (so-called Tang) promoting angiogenesis essentially in a paracrine manner releasing chemokines and other factors [14–16]. Also, CD45+ proangiogenic cells ("early EPC") may be considered of hematopoietic nature and to stimulate angiogenesis indirectly [16]. On the contrary, circulating endothelial cells ("late EPC") may reflect both angiogenesis and vascular properties [17].

All together, the cells appraised in the different studies represent a heterogeneous population of cells in different states of maturation with the ability to differentiate into a broad range of cell types of different organs and systems, including cardiomyocytes, smooth muscle cells, and endothelial progenitor cells (EPC), as well as hematopoietic, stromal, and epithelial cells [7,18–20] EPCs have been shown to home the sites of endothelial injury and also to contribute to angiogenesis; low EPC numbers have been shown to correlate with a higher incidence of cardiovascular events; therefore, EPCs were suggested as biomarkers of disease and predictors of cardiovascular outcomes [18].

In the recent past, there was the misconception that CD34 identifies a cell of hematopoietic origin, only, so CD34+ cells were often regarded as hematopoietic contamination in the sampled pool and subsequently disregarded [20]. Indeed, although the mechanisms on how CD34+ cells exert their role in angiogenesis are uncertain, CD34 appears to identify a cluster of cell types with progenitor and stem activity, and in many cases, the CD34+ population showed a more potent or pronounced differentiation capacity, and also transdifferentiation ability [20]. Fadini and coll. Evaluated the impact of different immunophenotypes of CPCs on the ability to predict or associate with CV risk factors and outcomes [21–24]. They suggested that CD34+ cell count is closely linked to CV risk, better than CD133+ cell number and multiple positive phenotypes (CD34+/CD133+, CD34+/KDR+, CD133+/KDR+, and triple positive CD34+/CD133+/KDR+); so, an extensive antigenic characterization of circulating CD34+ cells may not be useful to stratify the CV risk, and there are already a number of evidence in this way, candidating CD34+ cells as a valuable marker of CV disease presence, progression, and outcome [21–24].

In rheumatic diseases, several factors could be involved in modulating the number and the activity of progenitor cells, including increased oxidative stress, systemic inflammation, and also local angiogenesis of inflamed synovia [25–28]. Over time, EPC mobilization from the bone marrow may be impaired, owing to the bone marrow dysfunction, in which impaired stromal cell function occurs, thereby hampering their supportive function for the progenitor cells; it has been suggested that chronic inflammation may progressively exhaust progenitor cell reserve and/or mobilization capacity [5,18,19]. In addition EPCs could be recruited from the bloodstream to the affected joints and might therefore contribute to tissue remodelling and formation of pannus [25–28].

Strategies for increasing EPC numbers and function have been tested in different trials, also in rheumatic diseases. Furthermore, therapeutic intervention aimed at suppressing the inflammatory process, or addressed to comorbidities, could improve EPCs number and function and therefore contribute in maintaining endothelium homeostasis.

However, after more than twenty years, a definite consensus about the definition of "EPC" is to date lacking; in this review we maintained the definition reported originally in each paper considered.

This literature review aims to give an overview on the current stand of knowledge on the effect of pharmaceutical and lifestyle interventions that have been proven to improve EPCs number and function.

2. Corticosteroids

Corticosteroids (CS) have rapid anti-inflammatory effects as seen by a fast improvement of clinical signs and symptoms, decrease of acute phase reactants, and reduction of proinflammatory cytokines, including TNFα, a pivotal cytokine in Rheumatoid Arthritis (RA) pathogenesis. Grisar et al. treated 29 RA patients with 25–50 mg prednisolone daily for 7 days, after which the proportion of hemangioblastic EPCs within the lymphocyte population had increased by 104% and the CFU-capacity of monocytic EPCs by 125% [29].

In antineutrophil cytoplasmic autoantibody-associated vasculitis (AAV), De Groot measured EPC levels in 26 patients at 1, 3 and 6 months after commencing high-dose CS therapy; this treatment was combined with cyclophosphamide in most patients, or with methotrexate or azathioprine in a few. An increase in the levels of HPCs and EPCs was observed, reaching a peak at 3 months of 75% and 87% higher, respectively, with respect to baseline levels. The effect was largely sustained after 6 months [30].

In polymyalgia rheumatic (PMR), the administration of steroids for one month led to a decreased number of EMPs, an increased number of EPCs, and also the EMP/EPC ratio was consistently reduced. These results confirmed that systemic inflammation disturbs the balance between endothelial injury and repair and suggest that short-term anti-inflammatory treatment with a corticosteroid may be helpful in controlling the deleterious effects of inflammation on the vascular system; in addition, the authors suggested that the long term adverse effect on endothelium homeostasis could not be ruled out [31].

Indeed, in 25 pts with juvenile idiopathic arthritis (JIA), EPC numbers were found normal when compared to controls, but the levels decreased after treatment with glucocorticoids [32]. However, it remains unclear if the levels found in this subset may be really normal, or the result of an increased but balanced turnover.

Patschan [33] showed that systemic lupus erythematosus (SLE) patients did not show differences in percentages of total circulating EPCs, but SLE patients displayed significantly lower colony numbers as compared with healthy controls (HC), indicating impaired EPC regeneration and mobilization. Furthermore, low and high disease activities were associated with decreased EPC regeneration, while moderate disease activity was not. Patients not receiving hydroxychloroquine treatment and those undergoing glucocorticoid therapy showed impaired EPC regeneration as well.

Steroids reduce inflammation, as well as stimulate myelopoiesis and therefore doubly contribute to the increase in EPCs number (Table 1).

3. Methotrexate

Methotrexate (MTX) is an antimetabolite of the antifolate type. MTX has been used for RA treatment since 1980. It is the most common effective disease-modifying antirheumatic drug (DMARD) for RA, and it is considered to be the anchor drug, to which other DMARDs or biological agents are added to, in order to achieve an optimal therapeutic effect [34].

In 17 patients with RA, after six month of therapy with MTX, there were no differences as regards the number of EPCs colonies [35].

In patient with JIA, Rusak and coll observed that a treatment with MTX did not affect EPC levels [32]. The authors found few significant correlations between EPC and CVD risk factors (e.g. endogenous insulin, HOMA IR and TNF-alpha). This finding may suggest that the increase of pro-inflammatory mediators in JIA patients may not to be as strongly related to changes in EPC levels as in adult RA patients, or that