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EDITORIAL

Vasculogenesis in rheumatoid arthritis

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Abstract

Decreased number and impaired functions of endothelial progenitor cells (EPCs) leading to impaired vasculogenesis have been associated with rheumatoid arthritis (RA). Defective vasculogenesis has also been implicated in premature atherosclerosis in RA. Recently, early-outgrowth monocytic and late-outgrowth hemangioblastic EPC subsets have been characterized. Hemangioblastic EPCs may exert increased numbers in active RA and may play a role in vascular repair underlying RA.

Endothelial progenitor cells (EPCs) are hematopoietic stem cells expressing CD34, CD133, type 2 vascular endothelial growth factor (VEGF) receptor (VEGFR-2 or Flk-1), and the CXCR4 chemokine receptor [1-4]. During vasculogenesis, EPCs are mobilized from the bone marrow and they differentiate into mature endothelial cells [3]. Under normal conditions, vasculogenesis is involved in both prenatal and postnatal tissue development, vascular repair, and atherosclerosis [2,3].

In rheumatoid arthritis (RA), several groups have described defective vasculogenesis related to impaired EPC numbers and functions in RA [4-6]. Impaired vasculogenesis has been associated with increased cardiovascular morbidity and mortality in RA [7,8]. Effective antirheumatic therapy, such as corticosteroids and tumor necrosis factor-alpha (TNF-α) blockers, may stimulate the outgrowth and function of EPCs and thus may restore defective vasculogenesis in arthritis [5]. In addition, as the induction of vasculogenesis may be beneficial for patients with cardiovascular disease [8], the stimulation of EPCs and vasculogenesis may also suppress premature atherosclerosis underlying RA [7].

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In the previous issue of *Arthritis Research & Therapy*, Jodon de Villeroché and colleagues [1] assessed late-outgrowth EPCs in RA and found increased colony-formation capacity of these cells in RA. Furthermore, higher or lower EPC numbers correlated with active disease and disease in remission, respectively. These results seem to be somewhat controversial as a number of other investigators reported defective EPC function in RA and lower EPC numbers in active RA [5,6]. There has been only one report by the same group, Allanore and colleagues [9], suggesting that circulating EPC numbers may be higher in RA. Nevertheless, Jodon de Villeroché and colleagues [1] conducted an approach that was significantly different from that of others. Instead of analyzing all EPCs, they differentiated two EPC subpopulations, namely EPCs of monocytic versus hemangioblastic origin. These two EPC subsets have recently been described and characterized as early-outgrowth and late-outgrowth EPCs, respectively [1,10]. There is no clear consensus on the accurate definition of EPCs after all [10]. In their study, Jodon de Villeroché and colleagues [1] characterized late-outgrowth EPCs of hemangioblastic origin as Lin^-/7-aminoactinomycin D $(7AAD)^-$/$CD34^+$/$CD133^+$/$VEGFR\text{-}2^+$ cells and the number of these cells was indeed higher in RA patients compared with controls. In addition, the colony-forming capacity of these late-outgrowth EPCs was significantly higher in RA.

Jodon de Villeroché and colleagues [1] claim that, in all previous studies, EPCs also consisted of the early-outgrowth monocyte-derived cells characterized by only three surface markers (CD34/CD133/VEGF-R2) [5,6]. According to Jodon de Villeroché and colleagues [1], the use of Lin and 7AAD markers may enable investigators to select only late-outgrowth EPCs.

Thus, while there may be a general impairment of EPC function and vasculogenesis in RA and low EPC numbers may be associated with RA activity and increased cardiovascular risk, late-outgrowth EPCs of solely hemangioblastic origin may be involved in vascular repair. As this EPC subset may be preferentially involved in the active stage of the disease, it is likely that hemangioblastic EPC-dependent vasculogenesis is more prominent in active RA associated with high-grade systemic inflammation and accelerated atherosclerosis.

Regarding potential relevance for therapy, corticosteroids and anti-TNF agents may, in general, stimulate EPC number and function [5,11] but the possible effects of these agents on the function of late-outgrowth EPCs need further characterization.

Abbreviations

7AAD, 7-aminoactinomycin D; EPC, endothelial progenitor cell; RA, rheumatoid arthritis; TNF, tumor necrosis factor; VEGF, vascular endothelial growth factor; VEGFR-2, type 2 vascular endothelial growth factor receptor.

Competing interests

The authors declare that they have no competing interests.

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