The ill endothelium: how atherosclerosis begins in lupus

The potential value of endothelial biomarkers

This editorial refers to Decreased circulating endothelial progenitor cells as an early risk factor of subclinical atherosclerosis in systemic lupus erythematosus, by Raquel Castejón et al., on pages 631–8.

Cardiovascular disease (CVD) is a significant cause of morbidity and mortality in patients with SLE [1]. The development of atherosclerosis in SLE is premature and accelerated, even in the absence of traditional cardiovascular risk factors, and has been associated with chronic inflammatory activity that might induce endothelial damage leading to atherosclerosis [1]. In this issue, Castejón et al. [2] show that SLE patients with reduced circulating endothelial progenitor cells have pathological arterial stiffness and a higher frequency of cardiovascular risk factors (hypertension, diabetes, smoking) and metabolic syndrome. The study limitations include the limited number of patients (46) and the lack of a control group. However, the results are in line with the main findings on this topic in the last 10 years and highlight the key role that endothelial damage plays in SLE-related atherosclerosis.

The endothelium, a continuous monolayer cell layer that lines the lumen of vessels and acts as a semi-permeable barrier that controls the exchange of oxygen and micronutrients between circulating blood and the tissues, plays an essential role in maintaining cardiovascular homeostasis through control of cellular trafficking, the coagulation system and vascular function (vessel tone and blood flow) [3]. The shift from a healthy to a damaged endothelium alters vascular homeostasis and promotes the emergence of a dysfunctional endothelium with enhanced vasoconstrictive, pro-coagulative and inflammatory responses. Endothelial dysfunction is present in the very early stages of vascular disease, is associated with ageing and cardiovascular risk factors and predicts cardiovascular morbidity and mortality [4]. Therefore, study of the functioning of the human endothelium is useful in investigation of the aetopathogenesis of CVD, using either invasive (i.e. flow-mediated vasodilation studies) or non-invasive (biomarkers) techniques. Several endothelial biomarkers can be detected and measured in the blood, including molecules (cytokines, cellular adhesion molecules) and cells. Fig. 1 summarizes the three main cellular components of the endothelium that can be detected in the bloodstream: circulating endothelial cells (CECs), which are mature cells detached from the endothelium; endothelial microparticles (EMPs), which are anucleate fragments of cellular membrane shed from damaged endothelial cells; and endothelial progenitor cells (EPCs), which are bone marrow-derived circulating progenitors for the endothelial lineage. Increased circulating levels of CECs and EMPs have been associated with endothelial damage, and EPC levels with endothelial repair processes [4, 5].

Human EPCs are mainly identified and characterized by flow cytometric assays for cell surface markers (EPCs are positive for CD34, CD133 and vascular endothelial growth factor receptor 2 (VEGFR-2)) or by cell culture assays (EPCs have the in vitro capacity to form cellular colonies that differentiate into endothelial cells) [6]. Studies have shown reduced levels of circulating EPCs in patients with cardiovascular risk factors, independent of already established CVD [6, 7]. EPC levels inversely correlate with the natural history of atherosclerosis: levels start to decline when cardiovascular risk factors appear, and continue to decline when endothelial damage appears and with the further development and progression of atherosclerotic plaque; when CVD is established, EPC levels may increase due to bone marrow mobilization [7].

Recent studies have found low EPC levels in SLE patients, although the study samples were small, ranging from 15 to 44, in all except two studies [8], and most studies have found no correlation with CVD. Overall, studies using culture techniques have shown more consistent results than those using cytometry [8]. Castejón et al. [2] linked low EPC levels with vascular risk factors and endothelial dysfunction (arterial stiffness), but not with atherosclerosis, suggesting that EPCs could play a role in the very early stages of the atherosclerotic process in SLE. However, it is not only the number of EPCs that may be affected in SLE patients; recent studies have detected dysfunctional EPCs in some SLE patients, who may have a normal number of cells but with reduced migratory and proliferative capacities [8, 9].

In spite of the promising results reported until now, not all studies have demonstrated consistent results with respect to the quantification of EPCs in SLE patients. Discrepant findings in cytometry studies have been associated with various factors [8]. Disease heterogeneity is a key factor: SLE patients may have multiple clinical and immunological phenotypes, a different degree of autoimmune activity and underlying vascular disease and widely varying therapeutic interventions ranging from no treatment to a combination of several drugs (corticosteroids, antimalarials, immunosuppressants and biologics).
whose influence on EPC levels and functions remains unevaluated. Standardization of EPC identification methods is another key point. Improvements in methodological techniques should ensure the accurate and reproducible measurement of the number and functional evaluation of EPCs, although further studies are required to demonstrate that these in vitro changes have a direct in vivo effect on endothelial function in SLE patients [4, 8]. Finally, the clinical significance of reduced levels of EPCs in a patient with SLE is not clear: most reported studies are cross-sectional and often include patients with stable, non-severe disease with no control group of patients with different disease profiles or other autoimmune diseases. Future studies should address these challenges: improving and standardizing methodologies, investigating the possible influence of lupus drugs on endothelial function and including control groups with other clinical profiles or autoimmune diseases with different aetiological mechanisms. Prospective studies evaluating the real clinical consequences of reduced EPC levels and their association with different disease outcomes are necessary.

In the long term, potential therapeutic applications might include the use of EPCs in modelling vascular disease or generating healthy blood vessels in SLE patients with vascular disease [3]. In the shorter term, simultaneous evaluation of the three main endothelial cell circulating components (EMPs, CECs and EPCs) in the same patient could be a more feasible approach to enhancing the potential clinical value of cellular endothelial biomarkers [4] and provide a better, high-definition picture of how the endothelium is functioning and the equilibrium between the mechanisms involved in endothelial lesions and repair. The best way to prevent and treat cardiovascular disease in SLE patients is an in-depth understanding of how it is initiated. The endothelium may be key in achieving this.

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