

Endothelial progenitor cells and cardiovascular risk: does ageing trump all other factors?

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Discovered nearly 20 years ago, endothelial progenitor cells (EPC) attract both basic and clinical researchers (1). As key regulators of vascular homeostasis in health and disease, circulating progenitor cell levels reflect endogenous regenerative potential. Upon endothelial damage, EPC are mobilized from the bone marrow and follow chemokine gradients to sites of endothelial injury where they assist in endothelial repair mainly via paracrine mechanisms. Next to the production of angiogenic growth factors, novel modes of paracrine regulation are being discovered, such as the release of endothelial cell-derived microparticles or microvesicles that contain pro-angiogenic microRNAs (2). The regenerative capacity of EPC depends on both their number and functionality. Indeed, low EPC number and/or impaired EPC function are predictive for cardiovascular disease in different clinical settings (3-5) including healthy subjects (6). Apart from their usefulness as prognostic biomarker, the promise of EPC as therapy forced the field back to the bench. For example, selective modulation of miRNA expression profiles *ex vivo* before adoptive transfer could improve cell survival (e.g., by targeting senescence) and function of progenitor cells *in vivo* (7). Other approaches to optimize the regenerative capacity of EPC include various pharmacological and lifestyle interventions (8). Indeed, physical exercise influences EPC levels and function, probably by increasing NO bioavailability (9).

Ageing is the main risk factor for clinical cardiovascular

disease (CVD), and this relation is mainly driven by the development of endothelial dysfunction. Indeed, healthy ageing is associated with progressive endothelial dysfunction as the net result of perpetuated stressors to the endothelium (oxidative stress and inflammation in particular) in the absence of adequate protective mechanisms (10-12). Similarly, the prevalence of traditional cardiovascular risk factors such as arterial hypertension, hypercholesterolemia, diabetes mellitus and smoking, all contribute to a phenotype which is characterized by premature vascular ageing.

In the largest study performed up to now, including 2,792 adults, Al Mheid *et al.* explored the effect of both healthy ageing and accelerated ageing on circulating progenitor cell levels, including CD34+/vascular endothelial cell growth factor receptor 2 (VEGFR2)+ EPC (13). By including healthy subjects (n=498), patients with 1-2 traditional cardiovascular risk factors (n=1,036) and patients with ≥ 3 risk factors or established CVD (n=1,253), they were able to demonstrate that age-related differences in circulating progenitor cells are significantly modulated by the burden of cardiovascular risk factors, and this independent of sex, body size, and statin use. Indeed, for younger subjects (<40 years), the presence of risk factors was associated with increased progenitor cell counts, whereas for subjects older than 60 years, the presence of risk factors or established CVD, was accompanied by lower circulating progenitor cell counts. Interestingly, in the absence of cardiovascular

risk factors, there was no significant decline in progenitor cells counts with age, which illustrates their critical role in homeostasis maintenance. In conclusion, the authors suggest that protracted exposure to the deleterious effects of cardiovascular risk factors might result in exhaustion of circulating progenitor cells.

This study adds to the knowledge on the effects of ageing on progenitor cell biology, but prudence must be called when one gives in to the temptation to extrapolate these findings to the field of EPC. Firstly, EPC represent a specific subpopulation of progenitor cells, expressing at least both CD34 (a surface marker common to hematopoietic stem cells and mature endothelial cells) and VEGFR2 at their cell membrane. Apart from the technical challenge inherent to flow cytometric rare event analysis, the term EPC covers an amalgam of different cell types, which also can be distinguished by *in vitro* cell culture assays (14). The term ‘progenitor cell’ in the article by Al Ahmeid and colleagues covered the following subpopulations (all CD45^{med}): CD34⁺ cells, dual-positive CD34⁺/CD133⁺, CD34⁺/CXCR4⁺, and CD34⁺/VEGFR2⁺, and triple-positive CD34⁺/CD133⁺/CXCR4⁺ cell populations. Notably, the above described decline with increasing age and RF burden, held true for all populations but not CD34⁺/VEGFR2⁺, i.e. the cells with the EPC phenotype. However, other groups have provided evidence that ageing affects all aspects of EPC biology: mobilization, migration, proliferation, differentiation and paracrine function (15). Oxidative stress and low-grade inflammation are thought to play a major role (16). The diminished contribution of aged EPC to vascular repair and regeneration leads to an increased propensity towards vascular pathology in normal human ageing (17).

Al Mheid and co-authors looked into the effect of traditional cardiovascular risk factors, which all converge in the phenotype of vascular ageing. It would have been interesting to study the importance of the presence and/or degree of chronic kidney disease (CKD), since this entity can be seen as a ‘novel’ traditional cardiovascular risk factor and represents a model of premature vascular ageing (18). Indeed, the burden of CVD in patients with CKD is tremendously high (19). CKD-related vascular disease is related to functional and structural changes of both intimal and medial layer (atherosclerosis and arteriosclerosis, respectively). Impaired number and function of EPC have been described in CKD (20) and is a valuable target for preventive and even therapeutic strategies. Based on the high number of patients studied,

no report of renal insufficiency as an exclusion criterium, and available epidemiological data that about ten percent of the population worldwide is affected by CKD, one can presume that an important part of the subjects included in the study by Al Mheid *et al.* suffered from CKD. It is a missed opportunity in this large study with a diverse population, that the effect of increased creatinine levels or other estimations/measurements of glomerular filtration rate on progenitor cell biology was not reported.

More and more strategies emerge to rejuvenate the progenitor cell pool and the EPC population in particular. Thorough understanding of EPC biology and the mechanisms underlying its impairment associated with ageing is mandatory, whether it concerns healthy or premature ageing. The study by Al Mheid and colleagues identified older subjects with high cardiovascular risk as the most vulnerable population. By consequence, these patients might be appropriate subjects for novel cell-based therapeutic studies. Indeed, the quest for the fountain of youth commences at the endothelium, since ‘a man is only as old as his arteries’ (Thomas Sydenham, MD, English Physician, 1624–1689).

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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