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EDITORIAL COMMENT

Circulating Progenitor Cells Predict Clinical Outcomes in Patients With Coronary Artery Disease and Renal Insufficiency*

Nikolaos I. Vlachogiannis, MD,[a,b] Konstantinos Stellos, MD[a,b]

Bone marrow-derived $CD34^+$ cells have been used extensively to reconstitute the hematopoietic system after radiation or chemotherapy; however, their regenerative potential has attracted research interest in their broader therapeutic capacity for tissue healing post-injury. Increasing experimental and human evidence shows that $CD34^+$ circulating progenitor cells (CPCs) are integral for cardiovascular resilience through recruitment to sites of injury and in vivo differentiation into endothelial cells. Recent experimental evidence supports that $CD34^+$ cells may induce angiogenesis in animal models of myocardial or peripheral ischemia. Injection of human $CD34^+$ cells in the ischemic limb of diabetic mice has been shown to accelerate healing of ischemic tissue and vessel growth, whereas systematic administration of human $CD34^+$ cells led to more efficient tissue repair in a mouse model of renal ischemia/reperfusion injury through synthesis of proangiogenic cytokines. Interestingly, we have previously shown that human $CD34^+$ cell adhesion onto vascular wall is integral for the reduction of neointima formation in a mouse model of vascular injury (1). Although how $CD34^+$ CPCs exert so many beneficial effects remains a matter of debate, the consensus is that their number in blood is associated with tissue-healing processes.

In this issue of *JACC: Basic to Translational Science*, Mehta et al. (2) address the prognostic value of CPCs in patients with coronary artery disease (CAD) and renal insufficiency. In a large cohort, consisting of 1,253 patients undergoing cardiac catheterization for evaluation of CAD (including 436 patients with renal insufficiency) followed up for a median of 3.5 years, the authors elegantly quantitated CPCs using flow cytometry and examined their prognostic value for cardiovascular (CV) death or nonfatal myocardial infarction (MI) as well as all-cause mortality. CPCs were defined as $CD45^{med+}$ cells expressing $CD34^+$ and 1 of the following CPC markers: CD133, CXCR4, or VEGF2R. The authors confirmed the significance of renal insufficiency (estimated glomerular filtration rate [eGFR] $<$ 60 ml/min/1.73 m^2) as an adverse predictor of cardiovascular outcomes, as it was associated with 48% increase in CV death/nonfatal MI and 39% increase in all-cause mortality. Of interest, the authors provide sufficient evidence that renal insufficiency was associated with an approximately 10% lower number of CPCs, a relationship that was independent of the presence of other cardiovascular risk factors in patients aged 70 years or older. Lower CPCs were associated with CV mortality in the whole study cohort as well as among patients with renal

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From the [a]Biosciences Institute, Vascular Biology and Medicine Theme, Faculty of Medical Sciences, Newcastle University, Newcastle Upon Tyne, United Kingdom; and the [b]Department of Cardiology, Freeman Hospital, Newcastle Upon Tyne Hospitals NHS Foundation Trust, Newcastle Upon Tyne, United Kingdom. Dr. Stellos is supported by grants from the European Research Council (ERC) under the European Union's Horizon 2020 research and innovation program (grant agreement number 759248) and the DFG (SFB834 project number 75732319). Both authors have reported that they have no relationships relevant to the contents of this paper to disclose.

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insufficiency independent of eGFR, age, sex, race, traditional cardiovascular risk factors, hemoglobin, white blood cell count, or therapeutic regimen. Most importantly, the authors robustly demonstrated that addition of CPC number into a model including age, eGFR, current smoking, heart failure history, and hemoglobin level substantially improves the discriminative ability of the model for an adverse cardiovascular event (integrated discrimination index = 15% to 20%). Finally, the authors convincingly showed that patients with renal insufficiency and high CPC numbers had similar risks for CV death/MI with patients with normal renal function, whereas those with both renal insufficiency and low CPCs had 60% to 80% higher risks for CV death/MI and all-cause mortality. These results further confirm the importance of the interplay between chronic kidney disease (CKD) and CPC-mediated tissue repair in cardiovascular outcomes. Further research is warranted to delineate how CKD affects the number and function of CPCs and how CPCs support the maintenance of vascular health in patients with CKD.

This interesting study by Mehta et al. (2) sheds more light on the role of CPCs in renal insufficiency, confirming previous reports showing that low CPCs are associated with adverse cardiovascular events or cardiac remodeling post-MI (3). Endothelial progenitor cells have been previously associated with reduced risk of CV death, major cardiovascular events, or need for revascularization among patients with CAD after adjustment for age, sex, and traditional cardiovascular risk factors. In a recent meta-analysis encompassing 21 longitudinal studies on the prognostic role of CPCs for cardiovascular events, reduced CPC levels were associated with approximately 2-fold increased risk for future cardiovascular events or CV death as well as with increased risk of stent restenosis (4).

Recruitment of CPCs from bone marrow or peripheral niches to sites of tissue injury is a multistep process requiring the mobilization, chemoattraction, rolling, and adhesion of CPCs onto vascular wall and migration into areas of tissue injury. We, and others, have previously shown that platelets have a central role in domiciliation and subsequent differentiation of CPCs. Platelets form aggregates with $CD34^+$ CPCs, which adhere firmly to ischemic endothelium. The adhesion of platelet-$CD34^+$ cell coaggregates onto the extracellular matrix and to endothelial monolayer is enhanced compared with $CD34^+$ cells alone under high shear rates in vitro and within the microcirculation of mice after ischemia-reperfusion injury, as assessed by intravital microscopy (3). This CPC-platelet interaction is further enhanced by the platelet-derived chemokine stromal cell-derived factor-1 (SDF-1), which chemoattracts circulating $CD34^+$ cells and enhances their adhesion to arterial endothelium (5). Adhesion of human $CD34^+$ progenitor cells over platelets immobilized on the endothelium is further enhanced by JAM-A-JAM-A homophilic bonds and JAM-A-LFA-1 heterophilic bonds, which, along with binding of SDF-1 to its counter-receptor CXCR4, also drive the differentiation of $CD34^+$ cells into endothelial progenitor cells (1,3,5). Circulating platelet-$CD34^+$ cell coaggregates are significantly increased in acute MI, and their number was associated with a lower myocardial infarct size and better left-ventricular function 3 months post-MI (3). Whether CKD affects the formation of platelet-$CD34^+$ cell coaggregates remains to be shown in future studies.

Multiple efforts have been made to capitalize on the regenerative capacity of endothelial progenitor cells in acute ischemic settings. Stents that capture endothelial progenitor cells have led to significant reduction of neointimal area and percent area stenosis in preclinical MI models, showing excellent safety and efficacy profiles, also in clinical trials. Moreover, administration of $CD34^+$ cells reduced the risk for amputation in patients with critical limb ischemia, with the number of applied $CD34^+$ cells being an independent predictor of limb salvage and wound healing. Similarly, administration of $CD34^+$ cells was shown to improve pulmonary hemodynamics in pulmonary arterial hypertension. Despite promising early results, several issues regarding $CD34^+$ availability and differentiation potential remain to be addressed; based on the number of cells used in animal models, several liters of blood would be required to isolate sufficient endothelial progenitor cells to treat critical limb ischemia in an average adult patient, which—in combination with the lower number of CPCs in patients with CAD and especially in those with renal insufficiency as shown in the current study—precludes the use of $CD34^+$ cells in everyday clinical practice. Moreover, the differentiation potential and function of endothelial progenitor cells may be severely compromised in patients with CAD, and especially in those with renal insufficiency, because of increased senescence. Therefore, there is an imperative need for further basic and translational science studies addressing the

"rejuvenation" of $CD34^+$ cells in ischemic and chronic kidney disease. Understanding how CKD affects $CD34^+$ cells will pave the way toward the development of novel therapies, as this is a mechanism that, according to the convincing data provided in the current report by Mehta et al. (2), warrants further investigation.

ADDRESS FOR CORRESPONDENCE: Dr. Konstantinos Stellos, Faculty of Medical Sciences, Newcastle University and Newcastle Hospitals NHS Foundation Trust, International Center for Life, Central Parkway, Newcastle Upon Tyne NE1 3BZ, United Kingdom. E-mail: konstantinos.stellos@ncl.ac.uk.

REFERENCES

1. Stellos K, Langer H, Gnerlich S, et al. Junctional adhesion molecule A expressed on human CD34+ cells promotes adhesion on vascular wall and differentiation into endothelial progenitor cells. Arterioscler Thromb Vasc Biol 2010;30:1127–36.

2. Mehta A, Tahhan AS, Liu C, et al. Circulating progenitor cells in patients with coronary artery disease and renal insufficiency. J Am Coll Cardiol Basic Trans Science 2020;5:770–82.

3. Stellos K, Bigalke B, Borst O, et al. Circulating platelet-progenitor cell coaggregate formation is increased in patients with acute coronary syndromes and augments recruitment of CD34+ cells in the ischaemic microcirculation. Eur Heart J 2013;34:2548–56.

4. Rigato M, Avogaro A, Fadini GP. Levels of circulating progenitor cells, cardiovascular outcomes and death: a meta-analysis of prospective observational studies. Circ Res 2016;118:1930–9.

5. Stellos K, Langer H, Daub K, et al. Platelet-derived stromal cell-derived factor-1 regulates adhesion and promotes differentiation of human CD34+ cells to endothelial progenitor cells. Circulation 2008;117:206–15.

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