Could Circulating Progenitor Cell Count Be a Barometer for Coronary Artery Disease Progression?

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The endothelium forms a continuous lining of blood vessels, which provide nutrients and oxygen in response to tissue requirements. As such, the endothelium is exposed to a variety of noxious stimuli that can cause dysfunction. Endothelial dysfunction can induce inflammation, thrombosis, abnormal proliferation of vascular smooth muscle, and narrowing or destruction of vessels. Repair and replacement of the injured endothelium are required to avoid these disasters, implying that endothelial function is a predictor of the risk of vascular diseases. Since the report on the presence of circulating progenitor cells (CPCs) in patients with coronary artery disease (CAD), the role of CPCs in repairing the denuded part of vessels has been studied in experimental and clinical models, including acute myocardial infarction, cardiomyopathy, atherosclerosis, and peripheral vascular disease.

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CPCs, derived from the bone marrow, are heterogeneous cells that express a variety of surface markers found on different progenitors, including hematopoietic, endothelial, monocytic, and poorly defined lineages. Overlapping surface markers and lack of distinct identifying markers make it difficult to isolate CPCs and their identity is debated. Nevertheless, many studies have identified CPCs by CD34+, CD133+, VEGFR2+ or their combinations and by functional capabilities as evaluated by endothelial colony-forming unit formation (CFU-EC). The number and functionality of CPCs are considered to vary with coronary risk factors. Moreover, CPC numbers correlate somewhat with endothelial dysfunction and disease severity in patients with CAD. Indeed, CPCs are transiently increased in acute cardiovascular diseases, whereas they are maintained at low levels in healthy subjects. Following tissue or vessel injury, CPCs mobilize from the bone marrow, proliferate, and promote new vessel formation, which leads to recovery at the site of injury. Thus the number of CPCs has been taken as a diagnostic marker for latent, and a prognostic marker for overt, cardiovascular diseases.

In this issue of the Journal, Arao et al identified CPCs as CD34+CD133+ cells and showed that the baseline number of CPCs was low in patients with AP compared with controls, although conventional coronary risk factors were similar between the 2 groups. This result is in accordance with the report that the basal level of CPCs is decreased in patients with chronic cardiovascular diseases, perhaps because of a decreased reservoir of CPCs caused by the chronic nature of the condition.

Arao et al also investigated whether CPC number was affected by coronary risk factors and vascular intervention (eg, PCI) in patients with stable AP. Some reports suggest that the number of CPCs determined by CFU-EC inversely correlates with the Framingham risk score, and a decrease in CPCs is used as a biological marker of vascular damage. It has also been suggested that CPCs characterized by CD34+VEGFR2+ or CD133+ contribute to restoration of denuded endothelial cells and are a useful tool for predicting cardiovascular outcome in CAD patients. In contrast, several reports suggest that CPCs defined as Dil-Ac-LDL/lectin-positive cells increase with the Framingham risk score. Arao et al found no association between baseline CPC numbers and risk factors such as diabetes mellitus, hypertension, or dyslipidemia. Furthermore, they showed that daily exercise, current smoking, or statin administration had no effect on baseline CPC numbers either. Secondly, Arao et al evaluated whether an acute increase in CPCs would occur after PCI in patients with stable AP. Vascular interventions such as PCI are often considered as a coronary risk factor for endothelial-cell injury. Endothelial denuding during PCI in CAD patients acts as a trigger for CPC mobilization into the circulation, activation, and homing to the damaged region requiring repair. Thus monitoring CPC numbers induced by PCI may be helpful for identifying high-risk patients for secondary prevention. However, Arao et al noted no significant change in CPC numbers within the 24h following elective catheter coronary revascularization with balloon angioplasty or stent placement (bare metal or sirolimus-eluting). Overall, Arao et al demonstrate that the decrease in CPCs in patients with stable AP is complex and not caused by coronary risk factors. CPC count may not be an appropriate prognostic marker of endothelial dysfunction and repair, at least in patients with stable AP.

The apparently conflicting results between several studies complicate the role of CPC count as a biomarker of vascular disease status and progression. The conflict may arise because of the following: low numbers of CPCs in the periph-
eral blood, which makes it difficult to isolate them; poor methodology in flow cytometry and cell culture techniques used to isolate CPCs; CPC levels identified by different surface markers because of CPC heterogeneity; and severity and type of vascular disease in individual patients. Therefore, the usefulness of the CPC count as a prognostic marker depends on identification of CPC identity and distinct markers, and optimizing the experimental conditions and clinical models in a larger population.

Acknowledgments
This work was supported by the Ministry of Health Welfare & Family Affairs (A085136) and the National Research Laboratory grant (20100018854) from the Korea Science and Engineering Foundation (KOSEF) funded by the Korea government (MEST).

References