Endothelial progenitor cells (EPCs) are immature cells that have the capacity to proliferate, migrate, and differentiate into endothelial lineage cells. Embryological research has clarified that embryonic hematopoietic stem cells (HSCs) and EPCs are derived from a common precursor (ie, hemangioblast) and share many surface marker antigens such as Flk-1 (VEGFR2), Tie-2, c-Kit, Sca-1, CD133 (CD133), and CD34. In 1997, Asahara et al demonstrated that adult peripheral blood contains progenitors of endothelial cells by showing that CD34 antigen-positive (CD34+) mononuclear cells isolated from adult human peripheral blood could differentiate into an endothelial cell-like phenotype expressing many endothelial cell-specific markers in vitro. In animal models of ischemia, heterologous, homologous, and autologous EPCs were shown to incorporate into sites of active neovascularization. This finding was followed by diverse identifications of EPCs using equivalent or different methodologies by several groups. Because adult EPCs share many markers with HSCs as in the embryonic situation, no simple definition of EPCs by exactly specific marker expression exists. However, many studies have identified circulating EPCs (CPCs) by cell surface markers, such as CD34+, CD133+, VEGFR2+ or their combinations, to quantify the number of circulating EPCs.

Recent studies have found that the number and functionality of CPCs may predict the clinical outcome and prognosis of cardiovascular disease. Vasa et al reported that number and migratory capacity of CPCs appearing as CD34+KDR+ are impaired in patients with coronary artery disease (CAD) compared with age-matched healthy controls. Furthermore, this impairment of CPCs inversely correlated with the number of the risk factors for CAD. Hill et al investigated the relationship between the number of CPCs and cardiovascular risk in subjects with various degrees of cardiovascular risk but no history of cardiovascular disease. The number of CPCs significantly correlated with the subject’s combined Framingham risk factor score. Measurement of flow-mediated brachial-artery reactivity also revealed a significant relation between endothelial function and the number of CPCs. In addition, CPCs from subjects at high risk for cardiovascular events had higher rates of in vitro senescence than cells from subjects at low risk. Werner et al reported that increased levels of CPCs appearing as CD34+KDR+ or CD133+ are associated with a decreased risk of major cardiovascular events and hospitalization in patients with CAD. The level of CPCs predicts the occurrence of cardiovascular events and death from CAD.

In this issue of the Journal, Turan et al investigate the relationship between the number of CPCs characterized by CD133+CD45+ and the number of diseased coronary arteries in patients with ischemic heart disease (IHD). They enrolled 120 patients with IHD and 40 healthy subjects without heart disease. The patients were allocated to groups according to the number of diseased coronary vessels: IHD1 (n=40), IHD2 (n=40) and IHD3 (n=40). Subjects with acute heart failure classified into New York Heart Association class IV were excluded. Using flow cytometry, they identified CPCs as CD34+CD45+ cells and showed that the number of CPCs was significantly reduced in patients with IHD3 compared with healthy subjects, IHD1 patients and IHD2 patients, but there was no difference in the number of CPCs between the IHD1 and IHD2 groups. Moreover, to accurately assess the severity of IHD, they calculated the SYNTAX score in all the IHD patients and divided them into 3 groups: low score (0–22), intermediate score (23–32) and high score (>33). The relationship between CPC number and severity of IHD was investigated and they found that the number of CPCs was significantly reduced in high-score patients compared with low-and intermediate-score patients.

They also investigated whether CPC number was affected by cardiovascular risk factors (CVRF) by using a score that included age>40 years, male sex, hypertension, diabetes, smoking, positive family history and hypercholesterolemia. No significant difference between IHD groups was recognized among the total number of CVRFs. However, in the univariate analysis, only the number of subjects with diabetes mellitus (DM) was significantly higher in the IHD3 group than in the IHD1 and IHD2 groups. Furthermore, multivariate analysis identified the severity of the diseased coronary artery and DM as independent predictors of the number of CPCs. Moreover, they demonstrated that CPC number inversely correlated with the level of HbA1c in IHD patients with DM.

In contrast, there are several controversial reports regarding impaired EPC mobilization by cardiovascular risk. Xiao

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**Evaluation of Circulating Endothelial Progenitor Cells in Cardiovascular Risk**

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The opinions expressed in this article are not necessarily those of the editors or of the Japanese Circulation Society.

Received September 20, 2011; accepted September 20, 2011; released online October 1, 2011

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et al reported that the number of EPCs defined as Dil–Ac-LDL+‘Lectin’ cells increased with the cardiovascular risk estimated by the Framingham risk score.\textsuperscript{15} Arao et al found no association between the baseline number of CPCs characterized by CD34\textsuperscript{+}CD133\textsuperscript{+} and risk factors such as DM, hypertension or dyslipidemia.\textsuperscript{16} We speculate there are 2 main reasons for the discrepancy among studies. One reason is that, as mentioned before, there is no standard marker of EPCs and, therefore, different methods have been used to identify and quantify them. Although the exact definition of EPCs remains unclear, comparison of studies using different methods to assess EPCs is indispensable. An alternative evaluation of EPCs can be used. Instead of surface marker identification of EPCs, biological assessment is further essential to evaluate the quality and quantity of EPCs. Although there is a lack of consensus on estimating the number of biological EPCs in culture, a new EPC colony assay was developed recently.\textsuperscript{17} This assay discriminates colony-forming EPCs and counts primitive and definitive EPC colony-forming units. This functional assay for qualifying and quantifying EPCs in clinical situations will contribute to further enlightenment of EPC kinetics in pathological states. The other reason is the different severity and type of CAD in individual patients. Thus, both exact methods of identifying EPCs and large-scale studies are necessary to evaluate whether EPC number could predict CAD prognosis.

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