Task for Today: Complete the Puzzle of Circulating Stem Cells and the Atherosclerotic Burden

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“The art of simplicity is a puzzle of complexity”
—Douglas Horton

Atherosclerosis is a systemic disease, and it often affects multiple arterial beds at the same time. Why atherosclerosis hits first at the coronary, cerebral, or peripheral level in different patients is unknown. Also, few data are available on how the disease spreads to multiple sites, whether plaque growth progresses linearly over time or if it accelerates suddenly. The recent discovery that acute vascular events, such as myocardial infarction and stroke, are both consequences and causes of atherosclerosis acceleration, is groundbreaking.1 A neuroendocrine loop has been described as responsible for plaque growth after acute ischemia in animals and humans. This pathway primarily involves bone marrow (BM)–derived precursors, generating inflammatory cells that propagate to the plaque. Organs such as the BM and the spleen were not considered to play a significant role in the pathophysiology of atherosclerosis. Now we know that many actors of the atherosclerotic process are born in the BM and traffic through the spleen before reaching the artery wall.2 Studies using F-18-fluorodeoxyglucose–positron emission tomography show that metabolic activation of the BM and spleen takes place after acute coronary syndromes,3,4 and spleen metabolic activity also predicts future cardiovascular events.3 Enhanced BM myelopoiesis, extramedullary seeding of myeloid precursors, and monocytosis are consistent features observed in murine models of atherosclerosis and myocardial infarction, as well as in patients with atherosclerosis or risk factors.2,5

A parallel line of research has produced a wealth of experimental and clinical findings on alterations of circulating BM-derived stem and progenitor cells in the scenario of atherosclerotic cardiovascular disease.6 Pioneered by the discovery that BM-derived cells help regenerate the vasculature through a hematopoiesial intermediate,7 this field has moved to a more general consideration of the interplay among the BM, hematopoietic stem cells, and atherosclerosis.8 Leaving aside the never-ending diatribe on endothelial progenitor cells, there is evidence that a shrinking in the physiological pool of circulating stem cells goes side by side with atherosclerotic disease. Circulating CD34+ stem cells are so rare in peripheral blood (=0.05% of white blood cells in healthy patients) that one may hardly believe that a further decline in such number has any clinical meaning. Yet, these cells play roles in hematopoiesis, immunosurveillance, and peripheral tissue homeostasis. A recent meta-analysis of prospective studies, including >4000 patients, shows that a reduction in circulating stem/progenitor cells, mainly CD34+, is an independent predictor of cardiovascular events and death, as well as all-cause mortality.9

In this issue of Circulation Research, Hayek et al10 provide a new piece to complete the puzzle of circulating stem cells in atherosclerosis. Taking advantage of the Emory Cardiovascular Biobank prospective registry, the authors evaluated 1497 patients with angiographically proven coronary artery disease (CAD) to explore associations of circulating progenitor cells with prevalence and outcomes of peripheral arterial disease (PAD). As such, this is the largest cross-sectional and longitudinal study on circulating progenitor cells to date reported. Hayek et al10 show that the presence versus absence of PAD was associated with lower CD34+ and CD34+KDR+ progenitor cells in patients with CAD. As a diagnostic tool, progenitor cells performed well beyond and above risk factors in discriminating patients with PAD from those without. Furthermore, a below-median CD34+ or CD34+KDR+ progenitor cell level was associated with adverse outcomes, but only CD34+KDR+ cells predicted PAD-related events and were independently associated with outcomes in fully adjusted models including PAD as a covariate.10 Although this study confirms that progenitor cells have a prognostic value, it differs slightly from the results of a recent meta-analysis wherein CD34+ and CD34+CD133+ cells seem to be provided with stronger predictive power.9 It had been already shown that CD34+KDR+ cells (sometimes referred to as an endothelial progenitor cell phenotype) may be more closely related to PAD than CD34+ cells,11 but their prognostic power was thought to be limited by the large variability of their measure, as they circulate in the bloodstream at an even rarer frequency than hematopoietic stem cells.7 Reasons for this discrepancy are unclear and deserve further investigation because the identity of CD34+KDR+ endothelial progenitor cells is continuously being scrutinized. It has been recently shown that a careful enumeration of CD34+KDR+ cells by polychromatic flow cytometry yields different results when compared with the traditional analysis although this does not necessarily lead to different qualitative conclusions.12 That said, do we really need to undertake such a complex measure to detect PAD in CAD patients? Probably not, as long as PAD diagnosis relies on a routine, widespread, and reliable clinical-instrumental

The opinions expressed in this article are not necessarily those of the editors or of the American Heart Association.

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DOI: 10.1161/CIRCRESAHA.116.309315.)
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Circulation Research is available at http://circres.ahajournals.org
DOI: 10.1161/CIRCRESAHA.116.309315
workup. In addition, in Hayek et al.\textsuperscript{10} the CD34+KDR+ cell count did not actually improve PAD discrimination based on C statistics, which is a more stringent reclassification metric than integrated discrimination improvement and continuous net reclassification improvement.

So, what message do we take home from the last piece of Hayek et al\textsuperscript{10}? This is where our ability to put the puzzle together and see simplicity in complexity is important. Robust data now tell us that multisite atherosclerosis (PAD and CAD) is accompanied by a more profound and multilineage depletion of stem/progenitor cells than CAD alone.\textsuperscript{10} If atherosclerosis acceleration relies on myelopoiesis, monocytosis, and inflammation, what drives an exhaustion of circulating progenitor cells? Studies in the field of diabetes mellitus show that circulating stem cells are reduced because of an impaired mobilization from the BM, and both PAD and diabetes mellitus are characterized by extensive BM remodeling.\textsuperscript{13} Recently, expansion of BM macrophages has been described as a new feature of the diabetic BM, which prevents stem cell mobilization by the production of Oncostatin-M.\textsuperscript{14} Oncostatin-M inhibition restores stem cell mobilization and homing and improves vascular recovery after limb ischemia.\textsuperscript{14} Furthermore, excess macrophage generation has been shown to also retain stem cells in the spleen, which functions as a reservoir of proatherosclerotic inflammatory cells.\textsuperscript{15} Thus, we hypothesize that inflammatory and extramedullary myelopoiesis is intimately linked with depletion of circulating stem cells, both being related to atherosclerosis development and progression (Figure).

Peripheral blood progenitor cell levels perform well as biomarkers, but we still do not know whether such a rare population is a true housekeeper of organismal health, or whether progenitor cell depletion is a bystander phenomenon of pathological changes ongoing in the BM of high-risk patients. Although experimental models show that BM-derived cells contribute to homeostasis of the cardiovascular system, this evidence has often been considered insufficiently conclusive. This challenging question can be addressed by implementing therapies that raise circulating stem cells by interrupting the molecular interactions that keep them attached to an inflamed BM niche. CXCR4 antagonism and Oncostatin-M inhibition are just some examples of therapeutic approaches that have never been tested in the setting of atherosclerosis. This novel molecular therapy may turn out to be an unexpected life-saving approach in the field of cardiovascular disease.

Sources of Funding
Dr Fadini was supported by a grant from the Italian Ministry of Health (GR-2011-02347600).

Disclosures
None.

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Circ Res. 2016;119:502-504
doi: 10.1161/CIRCRESAHA.116.309315

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Print ISSN: 0009-7330. Online ISSN: 1524-4571

The online version of this article, along with updated information and services, is located on the World Wide Web at:
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