New Definition of Aging?
Measuring Regenerative Capacity in Patients

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In cardiovascular disease risk profiling, age trumps all other factors. Yet age, like beauty, has proven to be difficult to define. Every cardiovascular clinician knows that not all 60-year-olds are of the same cardiovascular age; however, we have lacked the tools to define age with more precision from a medical standpoint.

In this issue of *Circulation Research*, Quyyumi et al provide evidence that regenerative capacity, as measured by circulating progenitor cell counts, may better define the aging process, refining our ability to define age-related cardiovascular risk according to a metric other than years.

Nearly 20 years ago, Asahara et al identified CD34 cells as a population enriched for cells with endothelial lineage potential, so-called endothelial progenitor cells (EPCs). There have been many subsequent attempts to rediscover the EPC using different markers or culture methods; however, no surface marker of a circulating cell has supplanted CD34 for the identification of EPCs.

Over the past 2 decades, there have been several reports revealing an association between cardiovascular health and CD34 cell or EPC numbers and function. In 2001, Vasa et al documented an inverse relationship between EPC numbers and migratory activity and risk factors (RFs) for cardiovascular disease. In 2005, Werner et al showed a striking relationship between EPC counts and 1-year survival after acute myocardial infarction, with a cardiovascular mortality of 1.8% in patients with the highest tertile of EPC counts and 8.3% with the lowest tertile (P=0.01). More recently, Povsic et al showed that circulating EPC counts were associated with and could predict physical function.

In this context, why is the work of Al Mheid et al so important? The authors recruited 2800 patients at their centers, enabling the analysis of progenitor cells in a large, diverse population at a single core laboratory. The population was 47% female and 34% African American, with a wide range of cardiovascular RFs defined as hypertension, hyperlipidemia, diabetes mellitus, and smoking (18% had no RF, 37% had 1–2 RF, and 45% had ≥3 RF).

As expected, there was a decline in EPC numbers with increasing age. However, a deeper analysis reveals 2 critical observations, which warrant further investigation. The authors show that (1) in the absence of cardiovascular disease or RF, there is no significant decline in EPC numbers with age and (2) increasing RF burden is associated with an increase in certain progenitor cell populations in younger patients.

This led the authors to conclude that vascular injury resulting from hypertension, smoking, hyperlipidemia, or diabetes mellitus acts as a trigger for the release of EPCs in younger patients, presumably for reparative purposes. Furthermore, the authors posit that the consumption of EPCs results in depletion of these cells later on in life in patients with multiple RF, whereas those without an ongoing assault on the vasculature maintain their reparative potential.

There are several questions that arise from these observations.

Is it possible that progenitor cell populations become exhausted, and the depletion of the EPC population is accelerated by the burden of cardiovascular RF? Although this is one relatively straightforward interpretation of the data, the cause–effect relationship is not clearly established by these observational data.

The corollary questions are even more fascinating to consider, specifically, is progenitor cell depletion a factor that leads to the advent of vascular disease, and if so, does progenitor cell replenishment have the potential to attenuate the progression of disease?

There are data to suggest that the answers to these questions may be “Yes”! Statin therapy, well known to reduce clinical events in patients with multiple RFs or clinically evident atherosclerosis, has been shown to increase circulating EPCs and to accelerate EPC-driven vascular repair. More recently, direct administration of CD34 cells has been associated with improved function and outcomes in patients with advanced cardiac disease and peripheral vascular disease, providing further evidence that the availability of EPCs is a determinant of disease progression. The benefit of statin therapy within 1 month of initiation post-myocardial infarction (too soon for antiatherosclerosis effects) provides more evidence to consider the impact of statins on EPCs. This may represent the pharmacological equivalent of the natural mobilization of EPCs noted in the Werner study.

The accurate quantification of cardiovascular risk plays a central role in clinical practice because it guides the use of medications, invasive and noninvasive tests, frequency of follow-up, and so on. Age has been at the foundation of quantifying cardiovascular risk for decades.
The work by Quyyumi et al forces us to step back and ask a fundamental question: What is aging? We all know what it means at a personal level—we do not bounce back as quickly as we used to. The scientific answer is the declining ability to regenerate damaged tissue may be the sine qua non of aging. Should quantification of EPCs become part of the risk profile of our patients is the logical next question.

Disclosures

None.

References


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