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Progenitor Cells and Age: Can we Fight Aging with Exercise?

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CHANGES IN VASCULAR MORPHOLOGY and function with increasing age clearly are significant contributors to age-related increases in cardiovascular disease (CVD). In addition, the presence of CVD risk factors, such as hypertension, hyperlipidemia, diabetes, and smoking, have been shown to cause endothelial dysfunction, an early marker of atherosclerosis and CVD. Regular physical activity is not only important in the primary prevention of CVD but, as an intervention, aerobic exercise training decreases the incidence of diagnosed CVD and improves prognosis following cardiovascular events. Although regular aerobic exercise attenuates intimal-medial thickening, arterial stiffness, and endothelial dysfunction with age, the mechanisms by which exercise contributes to vascular health are still unknown.

In 1997, Asahara et al. (1) characterized a novel group of cells by cell surface antigens ($CD34^+$/Flk-1^+) found in circulation that differentiated into endothelial cells and were incorporated into sites of angiogenesis. Soon thereafter, it was demonstrated that these cells, endothelial progenitor cells (EPCs), were released from the bone marrow and were also responsible for re-endothelialization (13). These cells are commonly identified by cell surface markers such as CD34, CD133, and vascular endothelial growth factor 2 (VEGFR2 or KDR). Since the identification of EPCs, there has been an exponential expansion in our knowledge relative to EPCs, including characteristics of the cell population, their effects, and regulators of their release, function, and incorporation. Experimental evidence shows that compared with healthy controls, EPC number is reduced with most CVD risk factors, including systolic blood pressure, diabetes, hypercholesterolemia, and smoking (15). Additionally, the number of circulating EPCs has been found to independently predict atherosclerotic disease progression in patients with CVD, and the number of circulating EPCs has been correlated with event-free survival in CVD (14). Recent clinical trials show that EPC transplantation may be a useful therapy to improve cardiac function and reduce poor outcomes following myocardial infarction (9). Importantly, acute exercise (6) and exercise training (7, 10) have been shown to increase the numbers of circulating EPCs in both healthy individuals and patients with CVD or CVD risk factors.

In this issue of the *Journal of Applied Physiology*, Hoetzer et al. (4) report important and novel findings relative to EPCs, age, and exercise. Their study reports that two measures of EPC function, clonogenic capacity (EPC-CFUs) and EPC migration toward VEGF, were decreased in older healthy individuals compared with young healthy subjects. Specifically, they found that EPC-CFU count was lower in middle-aged (36–55 yr) and older (56–75 yr) subjects compared with young subjects (22–35 yr) and that EPC migration was lower in older men compared with the young and middle-aged groups. Hoetzer et al. (4) also report that both EPC-CFU count and EPC migration were significantly increased in a group of middle-aged and older men (59 ± 3 yr) following a 3-mo endurance exercise training program. These findings are important not only in their contribution to the available literature on EPC function and aging in humans but also because they provide evidence for a mechanism by which exercise may attenuate the age-related decline of endothelial integrity and function, thereby decreasing CVD risk.

Evidence for changes in EPCs with age is equivocal. Although age has been related to decreases in EPC number in patient populations (12), no age-related decline in EPC number has been found in studies on healthy individuals (2). However, physical activity has been shown to increase EPC numbers; therefore when physical activity status is controlled, a clearer picture of the relationship between EPC number and age is likely to emerge. Indeed, in a recently published report, EPC number in healthy sedentary older men was lower compared with healthy sedentary young men (11). Therefore, age may be independently and inversely related to EPC number.

Measures of EPC migration, EPC proliferation, and EPC-CFU count have become in vitro indicators of EPC function. Although these techniques may not reflect what is occurring in vivo, they may lend some evidence of the ability of EPCs to localize to an area of endothelial damage, multiply, and create a cellular patch, which would be necessary for the repair of vessel wall damage. Therefore, information on EPC function provides a more complete understanding of how EPCs are affected by certain conditions beyond simple number. Disease has been shown to increase EPC senescence (5) and may directly affect precursor cells in the bone marrow (17). Hoetzer et al. (4) provide the first evidence in humans that age, independent of physical activity status and CVD risk factors, leads to decreased EPC colony-forming capacity and migration. Therefore, decreased EPC function in conjunction with or perhaps separate from decreased EPC bioavailability with age may lead to an imbalance in the ratio between ongoing endothelial damage and the capacity for repair. This disparity is one likely mechanism by which age may confer increased CVD risk (8).

In their paper, Hoetzer et al. (4) also show that 3 mo of endurance exercise training in middle-aged and older men can improve EPC function independent of CVD risk factors. Studies have demonstrated increases in EPC number with acute exercise and exercise training in persons with CVD, CVD risk factors, and healthy subjects; however, this study is the first to show that exercise training can improve EPC function, thereby attenuating the age-related decline in EPC function. Exercise training induced an ~120% increase in EPC-CFU count and an ~50% increase in EPC migration. Notably, 3 mo of exercise training in the older men were able to recover almost one-half of the age-related decline in EPC clonogenic capacity and resulted in a migratory capacity similar to that of the young sedentary volunteers. Therefore, it appears that exercise training may diminish decreases in EPC function that occur with age, which may be a novel mechanism by which exercise maintains endothelial function and decreases the vulnerability of the endothelium to damage and atherosclerosis.

Another difficulty that still remains in this emerging area is the characterization of endothelial progenitors. Hoetzer et al. (4) define EPCs via three cell surface antigens ($CD34^+$/$CD133^+$/KDR^+). The definition of "early" EPCs with this profile is common; however, there is recent evidence that there may be subpopulations of bone marrow progenitors that may have more potent effects on the vasculature (3) and that progenitors targeted toward the vessels may be found outside

the bone marrow (16). Therefore, as we begin to understand more about vascular progenitor cells, their origin, differentiation, maturation, and targets, it will be important to determine how these subpopulations are affected by exercise training and age independently.

Finally, although increased EPC number and function may emerge as a mechanism by which exercise training can maintain endothelial integrity with aging, it is unclear what causes decreases in EPC number and function with aging, as well as the mechanisms by which they may be increased via exercise training. There are numerous proposed mechanisms that may alter EPC signaling and function. Changes in oxidative stress, nitric oxide bioavailability, VEGF, and genetic factors may contribute to modulation of EPC release from the bone marrow or their function in the circulation. Aging is well recognized as a CVD risk factor. Until recently, the mechanisms underlying this interaction were not understood. The current study supplies evidence that while advancing age is a nonmodifiable risk factor, changing an older person's lifestyle habits with physical activity will result in a markedly enhanced, "younger" vascular health profile.

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