Aging progressively narrows the functional reserve of several organs and tissues, in association with variable degrees of morphological changes. Current views strongly indicate that resident stem and progenitor cells contribute to tissue homeostasis throughout life in virtually all organs and tissues, even those traditionally considered as postmitotic. In the aging human heart, the progressive loss of cardiomyocytes is balanced by an increased myocyte turnover through cardiac stem cells. However, this balance is compromised, and net cardiomyocyte loss is accelerated when cardiovascular risk factors are present, either nonmodifiable, such as male sex, or modifiable, such as diabetes mellitus. Similarly, an endothelial damage is normally repaired by resident endothelial cells and endothelial progenitors (EPCs), but this mechanism is impaired by cardiovascular risk factors and age, per se. Several authors have documented that bone marrow-derived EPCs from aged animals or humans are quantitatively reduced and dysfunctional, thus predisposing to atherosclerosis.

This has important pathophysiological and therapeutic implications, because autologous EPCs are being used in cell therapy trials that often involve aging individuals. Aging is a major determinant of bone marrow function, which can explain the reduced EPC levels in the elderly. On the other side, the mechanisms accounting for EPC dysfunction in aging are incompletely understood, but data suggest that they are cell intrinsic and not entirely explained by an aging milieu. Knowing more about these mechanisms is a prerequisite to improve EPC-mediated repair and counter vascular senescence.

In this issue of Hypertension, Xia et al. show that exposure of aged cultured EPCs to shear stress (15 dyne/cm²) restores young properties and improve the ability of EPCs to repair a mechanical endothelial damage. Shear stress is a physiological stimulus for endothelial cells and mediates several surface and intracellular changes through mechanotransduction. Exposure of cultured EPCs to shear stress increased expression of the CXC chemokine receptor type 4 (CXCR4) and improved CXCR4 ligand (stromal cell-derived factor [SDF] 1α)-mediated signaling through Janus kinase (JAK) 2. This is in contrast to a previous report showing that shear stress (15 dyne/cm²) reduced CXCR4 expression and activity in human umbilical vein endothelial cells and improved cell survival. This discrepancy is likely attributable to the fact that EPCs are phenotypically and ontologically distinct from mature endothelial cells and rather share several characteristics with leukocytes. Indeed, although CXCR4 expression in resident endothelial cells mainly reflects activation and inflammation, the role of CXCR4 in circulating EPCs is to direct their homing to the injured endothelium through SDF-1α gradient sensing. In fact, short hairpin RNA-mediated CXCR4 knockdown or JAK-2 inhibition impaired EPC function in vitro and in vivo. Despite the fact that CXCR4 expression was not reduced in aged versus young EPCs, signaling through this pathway was markedly impaired, as evidenced by the low phosphorylation status of JAK-2. Importantly, the shear stress-induced upregulation of CXCR4 was able to restore function of aged EPCs, possibly through forcing ligand-dependent signaling. Therefore, shear stress, by acting on the CXCR4/JAK-2 signaling pathway may improve EPC function not only in the setting of aging.

From a therapeutic perspective, these results indicate that isolation of EPCs for angiogenic cell therapy should use culture conditions with laminar shear stress to improve function of the cells to be transplanted. This holds the potential to reverse EPC dysfunction in patients requiring cell therapies.

From a pathophysiological standpoint, it should be noted that EPCs circulate in the bloodstream, and they are not primarily an adherent cell population. Therefore, the beneficial effects of shear stress on EPCs can take place only once the cells have adhered to the target injured vasculature. However, other than mechanical damage experiments, endothelial injury occurs preferentially at sites of low shear stress, where laminar flow turns turbulent, such as at vascular branching. Therefore, the relevance of this mechanism in vivo remains unclear. Rather, the data by Xia et al broadly identify the SDF-1α/CXCR4/JAK-2 pathway as a target to counter age-associated EPC deterioration (Figure). An application of this has already been shown by the same authors, who reported that the beneficial effects exerted by physical exercise on EPCs from aged individuals are dependent on amelioration of CXCR4 expression and JAK-2 activation.

CXCR4 is a key receptor in EPC biology. Disruption of the SDF-1α/CXCR4 interaction in the bone marrow microenvironment is the primary trigger for progenitor cell mobilization. This can be achieved either by modifying SDF-1α gradients or by directly blocking CXCR4 with the compound AMD3100.
CXCR4 pathway and counter shortage of vascular regenerative cells. Whether this finally translates into improved cardiovascular outcome needs to be ascertained.

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Vascular Rejuvenation Through the Stromal Cell-Derived Factor 1α/CXC Chemokine Receptor Type 4/Janus Kinase 2 Signalling Pathway
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