Gender differences in susceptibility to coronary heart disease have been firmly established: the incidence of various manifestations of coronary atherosclerosis is less in premenopausal women than age-matched men. The protective role of estrogen covers a broad range of mechanisms including improvement of endothelial regeneration after arterial injury. Mediated primarily by the estrogen receptor alpha (ERα), 17β-estradiol (E2) stimulates migration and proliferation of endothelium. This effect involves among others, eNOS activity, prostacyclin, endothelin, bFGF, and VEGF-R2 signaling. Estradiol also stimulates the recruitment of endothelial progenitor cells (EPCs), which in experimental and emerging clinical studies appear to be important effectors of endothelium repair (for review see Besler et al4). In rodents, E2 increases the adherence capacity as compared to premenopausal female EPCs, during the fertile period. In addition, male EPCs showed a lower homing and adherence to the region of vascular damage. This process is ERα dependent and EPCs are believed to play a nonredundant role in the E2 enhanced reendothelialization. Likewise, in premenopausal women a higher number of circulating EPCs is found when compared to age-matched men. The level of circulating EPCs in E2 enhanced reendothelialization6 and for bone marrow-derived EPCs appear essential for E2-induced enhancement of reendothelialization (see Figure).

OPN is an adhesive protein of the small integrin-binding ligand N-linked glycoprotein (SIBLING) family that is expressed as an extracellularly immobilized (through binding to fibronectin and collagen) or secreted protein by a wide variety of cells including ECs, smooth muscle cells (SMCs), macrophages, bone marrow-derived cells, and osteoblasts. Its expression is upregulated by a plethora of stimuli including interleukin (IL)-1, glucocorticoids, VEGF-A, and bFGF, as well as estrogen and cardiovascular burden. The biological function of OPN can be modified by matrix metalloproteases (ie, MMP-2, -3, -9) and thrombin, which cleave OPN and as such impart a different affinity to integrin members (ie, α5β1, α6β1, and CD44-isoforms with consequences for cell-cell interaction, attachment, migration, and haptotaxis. Based on this binding to integrins and CD44, OPN contains hematopoietic cells in the bone marrow compartment close to the endosteal zone while keeping these cells in a quiescent state. The same linker function might underlie the homing of EPCs to regenerating endothelium. Recently, such a parallel between homing to the bone marrow and to injured endothelium was also established for c-kit and its membrane bound ligand.

The observation that OPN in both the bone marrow and the vascular compartment is required for E2-stimulated EPC homing raises several questions. This observation is based on cross transplantation of bone marrow from OPN+/− and OPN+/+ mice. The difference between these two models in terms of OPN expression in the bone marrow may in fact not be large. Osteoblasts are the primary source of OPN within the bone marrow and may survive irradiation regimens because of their low turnover. The surviving osteoblast population after irradiation and subsequent transplantation should therefore be considered chimeric and, as a consequence, residual OPN expression will persist in the bone marrow. Hence, it can be expected that in both transplantation modes reduced OPN-signaling in the bone marrow will affect the donor EPC-population. Lam Shang Leen and colleagues5 as published in the current issue of Arteriosclerosis, Thrombosis, and Vascular Biology, adds a new dimension to the role of E2 and EPCs in endothelial repair. Their elegant study provides clear evidence for positioning osteopontin (OPN) downstream of E2/ERα-signaling with an unprecedented role for OPN in the homing of EPCs to the region of vascular damage. Intriguingly, OPN expression in both the injured vessel wall and bone marrow-derived EPCs appear essential for E2-induced enhancement of reendothelialization (see Figure).

The presumed clinical relevance of EPC recruitment, for instance in restenosis, is underscored by several strategies to arm stents with integrins or antibody based agents to enhance EPC homing and adherence. The mechanism of EPC enhanced reendothelialization, however, is not fully understood as a structural contribution by direct incorporation and differentiation into endothelial cells seems to be highly variable and probably modest (see Figure). This assumption of minimal structural contribution of EPCs to vascular repair is supported by 2 recent studies, which show a nonsignificant cellular contribution of EPCs in E2 enhanced reendothelialization6 and for bone marrow-derived cells in the adult endothelium. To further understand the possibilities and pitfalls of these strategies, the biology of recruitment, homing, and adherence is of crucial importance.

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Affirmative Action of Osteopontin on Endothelial Progenitors

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cells. E2 stimulates VEGF-R2 expression, and potentially this E2-mediated increase will occur in EPCs as well. It can be expected that increased VEGF-R2 expression on EPC subclasses will enhance their homing to the injured endothelium through VEGF-driven chemotaxis. For OPN, subclass selectivity has been reported as well. OPN inhibits proliferation of CD34+CD38+ bone marrow-derived cells, without affecting CD34+/CD38- cells.3,4 Another layer of complexity may be added to this mechanism by the well known feature of OPN to come in different posttranslationally modified variants (see Figure), for instance as well. MMPs that are known to cleave OPN into OPN products that are released of the mod. EPC to the injured vessel wall.

In conclusion, Lam Shang Lee and colleagues provide evidence for a novel role of OPN in E2-enhanced reendothelialization. While this role in EPC homing is affirmed, several details of the mechanism of action are waiting to be uncovered.

Disclosures

None.

References


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