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Stem cell niches as clinical targets: the future of anti-ischemic therapy?

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SUMMARY

This article provides context for the research presented by Napoli *et al.*, reported in this journal. Treatment strategies that target stem cell niches are promising avenues for stimulating inducible angiogenesis in many vascular diseases, such as diabetes mellitus and atherosclerosis. Here we discuss the study carried out by Napoli and colleagues—an analysis of the effects of parathyroid hormone on the vascular stem cell niche in peripheral ischemia. Napoli *et al.* demonstrate that parathyroid hormone administered in combination with granulocyte colony-stimulating factor induces angiogenesis in a hindlimb ischemia mouse model. This treatment seems to mobilize and localize endothelial cell progenitors specifically to ischemic vascular cell beds. We explore the mechanisms through which the multiple cells within the vascular niche respond to ischemia. The interaction between parathyroid hormone and granulocyte colony-stimulating factor in humans is also discussed. Further assessment is needed to elucidate the factors involved in migration and differentiation of endothelial cell progenitors in ischemia-damaged tissues.

Preliminary investigations have shown the great potential of bone-marrow-derived stem cells as a novel therapeutic tool for tissue regeneration. Among the primary targets for stem cell therapy is cardiovascular disease, which is characterized by various abnormalities, including microvascular ischemia. Vascular tissue repair, mediated by proliferation and differentiation of stem cells, offers the most promising method to reverse ischemic damage. This potential repair system relies on the relationship between the vascular niche of the bone-marrow-based hematopoietic cell system and the endothelial cells of the microvasculature.

Ischemia, whether caused by arteriosclerosis, inflammation or vessel obstruction, compromises microvascular function in multiple ways. Vascular endothelial cells have a strategic role in maintaining blood pressure and capillary function.[1,2] When ischemic damage becomes severe or irreversible, endothelial cells, and in turn capillaries, are damaged, reducing considerably the number of functional vessels.[1–3] Blood vessel damage due to ischemia also interferes with vessel responsiveness to vasodilatory stimuli, such as nitric oxide, potentially leading to intraluminal thrombosis.[2–5] Continued immune response triggered by vessel damage can also produce intraluminal thrombosis.[2] Inducible angiogenesis is, therefore, essential for the restoration of blood flow to ischemic tissue and/or organs.[1,6,7]

Ischemia-induced neovascularization requires the mobilization and migration of endothelial progenitor cells (EPCs) from the vascular niche of the bone marrow system to the immediate area of tissue damage, as well as the proliferation of these migrating endothelial cells.[8] The progenitors of EPCs, hematopoietic stem cells (HSCs), reside in stable, complex microenvironments within bone, and control the self-renewal of the microvasculature, particularly that of damaged vascular endothelium. Ischemic tissues produce angiogenic cytokines that stimulate proliferation and homing of the EPCs to the damaged area, where they ultimately differentiate into endothelial cells. Another possible initiator of angiogenesis following ischemia is damaged perivascular cells, such as pericytes, which associate with the walls of small blood vessels and can release chemokines that direct EPC localization.[5] Cells in the vascular niche microenvironment respond to stimuli such as ischemia and interact with one another, leading to angiogenesis.

The therapeutic challenge is to augment the natural self-renewal mechanisms that exist between the vascular niche and the damaged microvasculature. Available treatments fall short in repairing vascular damage; therefore, strategies to activate neovascularization in ischemic tissue are needed. Understanding the mechanisms of interactions between the bone marrow and the microcirculatory systems will provide an opportunity

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for therapeutic intervention in patients with myocardial infarction and stroke, as well as those with peripheral ischemia.[2]

Reporting in *Nature Clinical Practice Cardiovascular Medicine*, Napoli *et al.*[9] demonstrate that targeting the vascular niche with parathyroid hormone (PTH) in conjunction with granulocyte colony-stimulating factor (G-CSF) improves stem-cell-based therapy in an experimental model of hindlimb ischemia. The locus of treatment in the ischemic cascade in peripheral ischemia and related conditions of ischemic etiopathogenesis is provided in Supplementary Figure 1 online. In humans, G-CSF is routinely administered before bone marrow transplantation, as this growth factor is known to mobilize HSCs to the location of ischemic injury. The addition of PTH to the regimen in the mouse model used by Napoli and co-workers improved the cellular responses observed with G-CSF treatment. They demonstrated increases in blood flow, capillary density and circulating cell numbers in the ischemic area, as well as a reduced number of inflammatory and apoptotic cells in response to PTH/G-CSF administration. If these effects could be reproduced in patients with vascular diseases worldwide morbidity and mortality could be substantially reduced. Determining the role of PTH in affecting endothelial cell proliferation and migration and stimulating hematopoiesis presents a strategic opportunity for targeting the vascular niche in angiogenesis.[6,10–12]

The relationship between PTH and G-CSF in humans is unclear. Certain evidence indicates that patients with hyperparathyroidism have increased numbers of circulating EPCs but no change in G-CSF levels.[13] PTH does not, therefore, seem to affect the production of G-CSF in humans. However, PTH might affect the levels of vascular endothelial growth factors, which are known to be associated with vascular development.[13] Dissecting the cross-talk between the multiple cell types within the vascular niche may further our understanding of the mobilization of EPCs stimulated by PTH/G-CSF.

How do we move forward? First, a series of translational studies must be carried out to determine certain safety and efficacy issues in humans. These include determining the effects of PTH on tumor development, the effects of PTH/G-CSF in patients with peripheral ischemic diseases caused by atherosclerotic plaques and on larger peripheral vessels. Furthermore, as vascular diseases tend to develop with age, these studies should assess the effect of age on angiogenesis and the various parameters listed earlier. However, promising data are emerging from a phase I trial showing that PTH is well tolerated for 14 days in patients of various ages with Hodgkin and non-Hodgkin lymphoma.[14] Obviously, the treatment period and patient population must be expanded in further tests. If the results of future studies are positive, PTH/G-CSF therapy could provide clinical practitioners with more effective options for the treatment of vascular disease beyond the existing treatments—combination drug therapies, endothelial progenitor cell transplantation and locally administered chemokines and growth factors.

Supplementary information in the form of a figure is available on the *Nature Clinical Practice Cardiovascular Medicine* website.

Competing interests
The authors declared no competing interests.

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