Another angiogenesis-independent role for VEGF: SDF1-dependent cardiac repair via cardiac stem cells

Filip Claes¹, Wouter Vandevelde¹, Lieve Moons², and Marc Tjwa¹*

¹Laboratory of Vascular Hematology/Angiogenesis, Institute for Transfusion Medicine, Goethe University Frankfurt, Frankfurt, Germany; and ²Research Group Neural Circuit Development and Regeneration, Biology Department, University of Leuven, Leuven, Belgium

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This editorial refers to ‘VEGF/SDF-1 promotes cardiac stem cell mobilization and myocardial repair in the infarcted heart’ by J.-M. Tang et al., pp. 402–411, this issue.

Mounting evidence indicates that the vascular endothelial growth factor gene (encoding the secreted growth factor VEGF) is one of those few truly essential genes in the mammalian genome. Indeed, genetic haploinsufficiency of one VEGF allele is incompatible with life and birth due to severe embryonic defects in the conversion of single endothelial cells into a network of blood vessels, thereby establishing VEGF as one of the most important angiogenic growth factors.¹

Furthermore, over the past decade, pleiotropic roles of VEGF in multiple angiogenesis-(in)dependent processes were identified. VEGF was shown to affect an ever-growing list of non-endothelial cell types derived from all three embryonic lineages, including—to name a few—pneumocytes, retinal pigment epithelial cells, renal podocytes, chondrocytes, osteoblasts, osteoclasts, cardiomyocytes, various neuronal cell types, pancreatic duct cells, and haematopoietic/muscle/dental pulp stem cells.² Tang et al. add further evidence that VEGF also affects resident adult cardiac stem cells (CSCs) and stimulates cardiac repair after myocardial infarction (MI), effects that are at least in part independent of its angiogenic properties.³

VEGF and the diseased heart³ remains a very popular research topic for further development into clinically applicable therapeutic paradigms. For almost two decades now, attempts have been made to stimulate revascularization of the chronically ischaemic heart by various forms of VEGF therapy (therapeutic angiogenesis), with mixed results.⁴ Gradually, the applied strategy of this innovative treatment concept shifted towards the use of cell therapy, co-opted from the rapidly developing evolution of regenerative medicine, i.e. the cardiac injection/infusion of certain autologous cell types, and harvested from bone marrow or other sources, with the aim not only to amplify the endogenous revascularization capacity, but also to (potentially) regenerate cardiovascular cell types, including cardiomyocytes. Although the beneficial effects of cell therapy in some of the clinical trials might be explained by enhanced revascularization, the overall effect of cell therapy to combat ischaemic cardiac disease remains controversial, and the direct regenerative capacity of these injected cells is disputed. Among the many challenges to be addressed are the long-term engraftment of injected cells, their regenerative capacity, and the choice of cell type⁴—although one of the favourable cell types for injection seems to be marrow-derived mesenchymal stem cells (MSCs), as recently suggested in Cardiovascular Research.⁵

In the present article, Tang et al.⁶ demonstrate the therapeutic efficacy of a combinatorial approach of the aforementioned strategies. Using a rat model of established MI, they show that cardiac injection of MSCs, genetically engineered to express VEGF, stimulates revascularization and reduces infarct size, thereby ameliorating cardiac dysfunction.⁷ As recently shown in a parallel study by Kim et al.,⁸ the beneficial effects of VEGF-expressing MSCs vs. control MSCs might be explained at least in part by the increased engraftment of VEGF-expressing MSCs, by (i) creating well-vascularized ‘cardiogenic niches’ that are permissive for engrafting transplanted stem cells,⁹ and/or (ii) stimulating the Akt pathway inside MSCs—previously shown to be critical for MSC engraftment in the ischaemic heart.⁷ Likely, the VEGF-expressing MSCs might also secrete cardioprotective factors, preventing loss of injured cardiomyocytes in a paracrine fashion.⁸

Interestingly, Tang et al.⁶ also provide evidence of a new effect of VEGF: the recruitment of resident adult CSCs to the ischaemic area. In a previous study, the authors already showed that VEGF stimulates CSC migration via the Akt pathway.⁹ In the present study, they demonstrate that VEGF-promoted migration might involve the tyrosine kinase receptors VEGFR-1 and VEGFR-3, expressed on CSCs—but not VEGFR-2 (despite expression of all three receptors on CSCs).¹⁰ Hence, this finding also further reinforces the (simplified) concept that VEGF signals in endothelial cells vs. non-endothelial cells through VEGFR-2 vs. VEGFR-1/3, respectively.¹⁰ Moreover, Tang et al. provide evidence, via a combination of cardiac injection of MSCs with elegant adoptive transfer of labelled...
CSCs in vivo, that VEGF-mediated CSC recruitment is dependent on the SDF1/CXCR-4 axis. Indeed, forced overexpression of VEGF (e.g. via engineered MSCs) increases the expression of SDF1 and its canonical (G-protein-coupled) receptor CXCR-4 in the ischemic heart and on CSCs, respectively, resulting in increased recruitment of CXCR-4+ CSCs via SDF1 (also known as CXCL-12) and presumably enhanced cardiac repair of the ischemic/necrotic area. The latter is suggested by the observation of a reduced infarct size, but this is not formally proven as the reduced infarct size can also be explained alternatively, for instance by improved revascularization of the ischemic area via VEGF (and/or SDF1). However, the authors also showed that in vivo genetic knock-down of SDF1 in the myocardium and systemic administration of CXCR-4 antagonists abolished the therapeutic effects of VEGF-expressing MSCs on cardiac function and CSC recruitment, whereas the effects on revascularization were only partially blocked. Even though these experimental strategies have their intrinsic deficits precluding conclusive proof (e.g. an alternative explanation of reduced engraftment of VEGF-expressing MSCs cannot be excluded), these data—together with the isolated in vitro migration experiments—strongly support a concept in which VEGF promotes CSC-mediated cardiac repair via activating an SDF1/CXCR-4 axis and which is not dependent on VEGF-driven angiogenesis.

VEGF was previously shown to be an upstream regulator of SDF1 expression. Novel is the finding that the biological activity of VEGF might be abolished via inhibiting the SDF1/CXCR-4 axis. These data not only further emphasize the complex cross-talk between tyrosine kinase receptors and G-protein-coupled receptors, but also suggest some therapeutic implications for VEGF/anti-VEGF therapies.

Moreover, the study by Tang et al. indicates that CXCR-4 (also known as CD184) might be considered as a novel phenotypic marker of CSCs. This expands the potential implications of SDF1 therapy in cardiac disease, now primarily focused on promoting the marker of CSCs. This expands the potential implications of SDF1 (also known as CD184) might be considered as a novel phenotypic

References