

Guest Editorial: Vascularization in Tissue Engineering

Laxminarayanan Krishnan

Parker H. Petit Institute for Bioengineering and Bioscience, Georgia Institute of Technology, 315 Ferst Dr. NW, Atlanta, GA 30332; lkrishnan@gatech.edu

KEY WORDS: angiogenesis, vascularized tissue constructs, microvascular stability, vessel maturation

Adequate vascular perfusion is a critical factor in tissue regeneration. Several strategies ranging from biomaterial scaffolds, growth factors, and cell delivery, including stem cells and vascular precursors, have been used to promote new blood vessel growth. Encouraging neovascularization and increasing local vessel density remain the focus in addressing ischemia or in engineering tissue constructs; but the importance of effective perfusion, response to physiologically relevant stimuli, and microvascular remodeling (angioadaptation) are now receiving consideration.^{1–7} Mural cells support and stabilize microvascular structures, particularly during maturation of neovessels during angiogenesis, and they are also thought to be involved in other functions ranging from regulation of flow to regeneration.^{8–12} Many studies have already demonstrated the benefits of including support cells in co-culture with endothelial cells in the formation of engineered microvascular structures.^{13–18} From a tissue engineering perspective, it is interesting that perivascular cells may also impart tissue-specific characteristics to the microvascular bed.¹⁹ Further, microvascular stabilization has also been proposed in relation to cancer therapy to “normalize” aberrant vasculature, and may additionally open avenues to treat other diseases with microvascular dysfunction.^{20–22} The three reviews in this series cover cardiovascular repair strategies in varying depths, provide insights into the status of the field, and explore some of the future directions for engineered tissues as well as for therapies focused on correcting the underlying microvascular dysfunction. Wang et al.²³ provide a concise review of the efforts in improving perfusion using cells and growth factors, the use of natural and synthetic scaffolds, including decellularized myocardium, and the use of complex bioreactors, for cardiac tissue engineering (Issues 5–6, Page 455). An engaging and timely commentary on the need

for uniform standards in tissue-engineered therapeutics is also provided. LeBlanc et al.²⁴ discuss the coronary microvasculature in the pathophysiology of myocardial ischemia in their review of the field, and highlight relevant clinical facets of coronary microvascular dysfunction, the diagnostic and therapeutic challenges, current state of experimental treatments, and the role of animal models in investigating these therapies (Issues 5–6, Page 473). Sun et al.²⁵ explore interactions of microvasculatures and their perivascular cells in relation to vessel stability and maturity, both in pathologies as well as in revascularization strategies aimed at repair and regeneration, and also discuss the importance of formation of hierarchical or organized vascular structures in engineered tissues (Issues 5–6, Page 433). Overall, this collection of three articles explores relevant techniques and considerations for engineering vascularized tissues, promoting microvascular stability, and provides an important discussion on the need for quality standards as we consider clinical translation of experimental therapeutic strategies.

REFERENCES

1. Morris ME, Beare JE, Reed RM, Dale JR, LeBlanc AJ, Kaufman CL, Zheng H, Ng CK, Williams SK, Hoying JB. Systemically delivered adipose stromal vascular fraction cells disseminate to peripheral artery walls and reduce vasomotor tone through a CD11b+ cell-dependent mechanism. *Stem Cells Transl Med.* 2015;4(4):369–80.
2. Pries AR, Secomb TW. Making microvascular networks work: angiogenesis, remodeling, and pruning. *Physiology (Bethesda).* 2014;29(6):446–55. 4280154.
3. Leblanc AJ, Touroo JS, Hoying JB, Williams SK. Adipose stromal vascular fraction cell construct sustains coronary microvascular function after acute myocardial infarction. *Am J Physiol Heart Circ Physiol.* 2012;302(4):H973–82.
4. Hoying JB, Utzinger U, Weiss JA. Formation of microvascular networks: role of stromal interactions directing angiogenic growth. *Microcirculation.* 2014;21(4): 278–89.

5. Chang CC, Krishnan L, Nunes SS, Church KH, Edgar LT, Boland ED, Weiss JA, Williams SK, Hoying JB. Determinants of microvascular network topologies in implanted neovasculatures. *Arterioscler Thromb Vasc Biol.* 2012;32(1):5–14.
6. Pilia M, McDaniel JS, Guda T, Chen XK, Rhoads RP, Allen RE, Corona BT, Rathbone CR, Transplantation and perfusion of microvascular fragments in a rodent model of volumetric muscle loss injury. *Eur Cell Mater.* 2014;28:11–23; discussion 23–4.
7. Secomb TW, Alberding JP, Hsu R, Dewhirst MW, Pries AR. Angiogenesis: an adaptive dynamic biological patterning problem. *PLoS Comput Biol.* 2013;9(3):e1002983. 3605064.
8. Gerhardt H, Betsholtz C. Endothelial-pericyte interactions in angiogenesis. *Cell Tissue Res.* 2003;314(1):15–23.
9. Rundhaug JE. Matrix metalloproteinases and angiogenesis. *J Cell Mol Med.* 2005;9(2):267–85.
10. Jain RK. Molecular regulation of vessel maturation. *Nat Med.* 2003;9(6):685–93. 12778167.
11. Kutcher ME, Herman IM. The pericyte: cellular regulator of microvascular blood flow. *Microvasc Res.* 2009;77(3):235–46.
12. Armulik A, Genove G, Betsholtz C. Pericytes: developmental, physiological, and pathological perspectives, problems, and promises. *Dev Cell.* 2011;21(2):193–215.
13. McFadden TM, Duffy GP, Allen AB, Stevens HY, Schwarzmaier SM, Plesnila N, Murphy JM, Barry FP, Gulberg RE, O'Brien FJ. The delayed addition of human mesenchymal stem cells to pre-formed endothelial cell networks results in functional vascularization of a collagen-glycosaminoglycan scaffold in vivo. *Acta Biomater.* 2013;9(12):9303–16.
14. Kaully T, Kaufman-Francis K, Lesman A, Levenberg S. Vascularization--the conduit to viable engineered tissues. *Tissue Eng Part B Rev.* 2009;15(2):159–69.
15. Levenberg S, Rouwkema J, Macdonald M, Garfein ES, Kohane DS, Darland DC, Marini R, van Blitterswijk CA, Mulligan RC, D'Amore PA, Langer R. Engineering vascularized skeletal muscle tissue. *Nat Biotechnol.* 2005;23(7):879–84.
16. Boyd NL, Nunes SS, Jokinen JD, Krishnan L, Chen Y, Smith KH, Stice SL, Hoying JB. Microvascular mural cell functionality of human embryonic stem cell-derived mesenchymal cells. *Tissue Eng Part A.* 2011;17(11-12):1537–48.
17. LeBlanc AJ, Krishnan L, Sullivan CJ, Williams SK, Hoying JB. Microvascular repair: post-angiogenesis vascular dynamics. *Microcirculation.* 2012;19(8):676–95.
18. Boyd NL, Nunes SS, Krishnan L, Jokinen JD, Ramakrishnan VM, Bugg AR, Hoying JB. Dissecting the role of human embryonic stem cell-derived mesenchymal cells in human umbilical vein endothelial cell network stabilization in three-dimensional environments. *Tissue Eng Part A.* 2013;19(1-2):211–23.
19. Nunes SS, Krishnan L, Gerard CS, Dale JR, Maddie MA, Benton RL, Hoying JB. Angiogenic potential of microvessel fragments is independent of the tissue of origin and can be influenced by the cellular composition of the implants. *Microcirculation.* 2010;17(7):557–67.
20. Jain RK. Normalizing tumor vasculature with anti-angiogenic therapy: a new paradigm for combination therapy. *Nat Med.* 2001;7(9):987–9.
21. Pries AR, Cornelissen AJ, Sloot AA, Hinkeldey M, Dreher MR, Hopfner M, Dewhirst MW, Secomb TW. Structural adaptation and heterogeneity of normal and tumor microvascular networks. *PLoS Comput Biol.* 2009;5(5):e1000394.
22. Carmeliet P, Jain RK. Principles and mechanisms of vessel normalization for cancer and other angiogenic diseases. *Nat Rev Drug Discov.* 2011;10(6):417–27.
23. Wang B, Patnaik SS, Brazile B, Butler RJ, Claude A, Zhang G, Guan J, Hong Y, Liao J. Establishing early functional perfusion and structure in tissue engineered cardiac constructs. *Crit Rev Biomed Eng.* 2016.
24. LeBlanc AJ, Nevitt CD. Targeting the vessel underdogs: therapeutic approaches for microvessel dysfunction in the heart. *Crit Rev Biomed Eng.* 2016.
25. Sun X, Evren S, Nunes SS. Blood vessel maturation in health and disease and its implications for vascularization of engineered tissues. *Crit Rev Biomed Eng.* 2016.