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PREVIEWS

Previews highlight research articles published in the current issue of STEM CELLS TRANSLATIONAL MEDICINE, putting the results in context for readers.

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Pericytes are multifunctional cells that wrap around the endothelial cell layers that form capillaries and provide structural support and regulate both endothelial cell functions (eg, blood vessel integrity and permeability) and blood flow via direct cell-to-cell interactions and the secretion of paracrine acting factors.[1] Multiple studies have provided evidence for the existence of a multipotent stem cell-like pericyte population, thereby suggesting that capillaries function as a stem cell reservoir that contribute to tissue maintenance and repair/regeneration following injury. Multipotent pericytes also possess huge therapeutic potential, with target conditions including limb ischemia, ischemic heart disease, muscular dystrophy, and retinal vasculopathy.[2] Furthermore, alongside neural and vascular cells, pericytes represent a key element in the blood-brain barrier (BBB)/neurovascular unit, (NVU)[3] and multipotent pericytes may represent an important cell type that could contribute toward repair/regeneration in certain pathological situations, such as stroke.[4] However, we do not have a complete understanding of the unique phenotypes and markers associated with pericytes[1]; hence, we currently lack the means to efficiently identify or isolate multipotent pericytes from a heterogeneous population. In our first Featured Article this month from *STEM CELLS Translational Medicine*, Yoshida et al employ a novel cell surface protein, EphA7, to isolate multipotent pericytes with capillary forming ability and cross-germ layer plasticity that may prove useful to the development of disease models and in regenerative therapies.[5] In a Related Article from *STEM CELLS*, Nakagomi et al described how brain vascular pericytes acquire multipotential differentiation capabilities and differentiate into major components of the BBB/NVU in response to an ischemic insult, similar to that which occurs in ischemic stroke patients.[6]

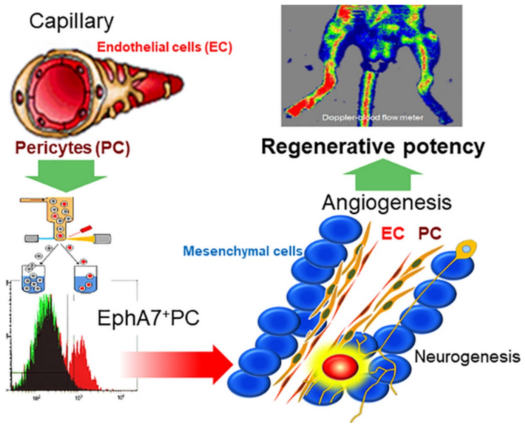
The existence of human endogenous cardiac progenitor cells (CPCs) has recently fallen into some doubt, mainly as a consequence of concerns surrounding high impact studies from the laboratories of Piero Anversa who first suggested that c-kit expressing stem-like cells present in the heart could regenerate damaged heart muscle (see the original articles and the accompanying *Expression of Concern*[7,8]). Even given this setback, many laboratories have independently provided evidence for rare putative progenitor populations with limited cardiomyogenic potential that may contribute to cardiac repair via several mechanisms, including differentiation into relevant cell types and the secretion of paracrine acting regenerative factors. Harnessing the power of CPCs may permit the development of strategies that enhance cardiac repair/regeneration in heart failure patients; however, we first require a deeper understanding of the underlying mechanisms controlling CPC proliferation and differentiation. Encouragingly, the establishment of protocols that permit the differentiation of pluripotent stem cells into large numbers of putative CPCs will allow for said studies as well as cardiac regenerative approaches.[9] In our second Featured Article this month from *STEM CELLS Translational Medicine*, Drowley et al report on their identification of retinoic acid receptor (RAR) agonists as potent proliferation enhancers of induced pluripotent stem cell (iPSC)-derived CPCs in the hope that their findings will enhance regenerative approaches for conditions such as myocardial infarction.[10] In a Related Article from *STEM CELLS*, Salabei et al established how the glutamine-induced enhancement of mitochondrial function and mTOR signaling pathway stimulation induced CPC proliferation in a study that may provide a means to improve cardiac regenerative therapies.[11]

FEATURE ARTICLES

EphA7 Identifies Multipotent Pericytes With Regenerative Potential

Although reporter gene analyses have aided the initial characterization of multipotent pericytes,[12] we still lack pericyte-specific cell surface markers that would facilitate the identification and isolation of multipotent cells from a heterogeneous cell population. Previous studies led by Jun-ichi Kawabe (Asahikawa Medical University, Hokkaido, Japan) established immortalized pericyte cell lines derived from microvessels in remodeling mouse tissues that maintain their multipotent characteristics during long-term subculture, allowing for the in-depth analysis of distinct pericyte populations.[13] Reporting in *STEM CELLS Translational Medicine*, the team subsequently employed microarray analysis of several clonal pericyte lines with differing degrees of multipotency to identify EPH Receptor A7 (EphA7), a member of the ephrin receptor subfamily of the protein-tyrosine kinase family, as a potential cell surface marker of multipotent pericytes.[5] Yoshida et al employed an anti-EphA7 antibody to isolate EphA7-expressing pericytes from peripheral tissues, including subcutaneous adipose tissues, which they named capillary stem cells (CapSCs); importantly, CapSCs displayed both mesenchymal and neuronal

differentiation propensities when compared with EphA7 nonexpressing pericytes. Furthermore, CapSCs also differentiated into endothelial cells and pericytes to form capillary-like structures and significantly improved blood flow recovery in a hind limb ischemia mouse model via enhanced vascular formation when compared with EphA7-negative pericytes and adipose-derived stem cells. Overall, this encouraging study highlights EphA7 as a means to isolate multipotentpericytes, a finding with enormous potential for both the understanding of tissue development and regenerative therapeutic approaches.



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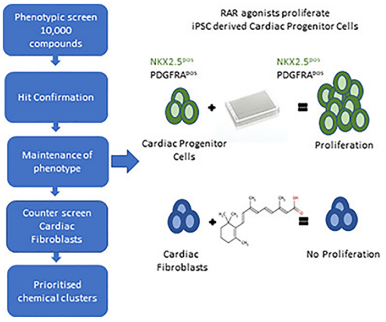
Retinoic Acid Receptor Agonists Boost the Proliferation of Cardiac Progenitor Cells

A recent *STEM CELLS Translational Medicine* article from the research group of Jane McPheat (AstraZeneca, Gothenburg, Sweden) described the sequential differentiation of human pluripotent stem cells into a population of CPCs and then into cardiomyocytes and reported on their use as a drug discovery tool.[9] The team hoped that this their approach may allow for an increase in the reported number of chemical mediators of cardiogenesis.[14] In their new *STEM CELLS Translational Medicine* article,[10] Drowley et al now report on their application of a phenotypic screen to identify compounds that boost the proliferation of human iPSC-derived CPCs to enhance their number while inhibiting the loss of their progenitor cell phenotype. The authors screened CPCs with a 10 000-compound library containing molecules known to modulate the phenotype of stem or primary cells, which revealed RAR agonists as potent CPC proliferation-inducing agents. However, the studied RAR agonists maintained the CPC-phenotype, as evidenced by the expression of CPC markers such as NKX2.5. While biochemical and agonist-antagonist competition experiments confirmed the activity and pharmacology of RAR agonists on CPCs, the same agonists failed to induce the proliferation of cardiac fibroblasts, a numerous and critical cell type in the human heart. The authors highlight the utility of phenotypic screening in the study of stem cell biology and cardiac regeneration and hope to next evaluate RA signaling and CPC activation in vivo to discover whether boosting the proliferation of rare CPCs can promote enhanced cardiac regeneration.

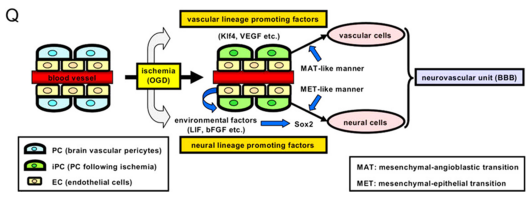


https://doi.org/10.1002/sctm.19-0069

RELATED ARTICLES

Brain Vascular Pericytes Display Multipotential Stem Cell Activity in the Ischemic Brain

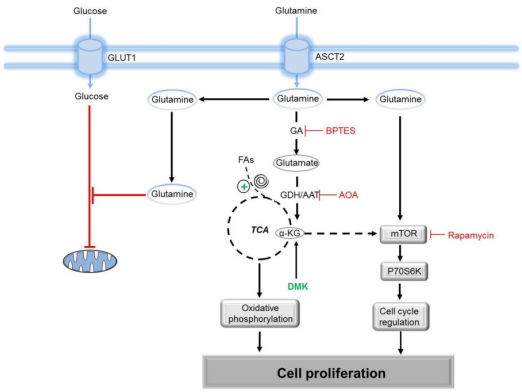
Brain vascular pericytes form an essential element of the BBB/NVU, and studies have suggested that they possess a multipotent nature under normal conditions and can differentiate into cells of vascular and neural lineages. Fascinating research from the laboratory of Takayuki Nakagomi (Hyogo College of Medicine, Hyōgo, Japan) previously established that ischemic insult to the brain prompts the appearance of brain vascular pericyte derivatives, ischemia-induced neural stem cells, that express various stem cell and undifferentiated cell markers.[15,16] The team followed up this research with a *STEM CELLS* article in which they assessed brain vascular pericyte multipotentiality in response to brain pathologies such as ischemic stroke.[6] Through the analysis of brain vascular pericytes extracted from ischemic regions of mouse brains (from a highly reproducible stroke model) and human brain vascular pericytes cultured under oxygen/glucose deprivation, the authors found evidence that pericytes can develop stemness through reprogramming which endows them in addition to their mesenchymal properties, with the ability to differentiate into vascular and neural cells that contribute towards the formation of the BBB/NVU. Overall, this exciting study suggests that brain vascular pericyte can contribute to neurogenesis and vasculogenesis at the site of brain damage, thereby highlighting pericytes an attractive target for therapies aiming to repair damaged central nervous system components.



https://doi.org/10.1002/stem.1977

Improving Cardiac Regeneration by Targeting Cardiac Progenitor Cell Metabolism

The transplantation of CPCs into the damaged heart has the potential to improve myocardial recovery and function[17]; however, the marginal improvements generally observed suggest that this therapeutic approach may require improvements. Furthermore, the mechanisms that contribute to repair still remain poorly understood. Transplanted stem cells can be significantly influenced by host metabolic conditions due to their unique requirements,[18] and this led researchers from the laboratory of Bradford G. Hill (University of Louisville, Kentucky) to search for those metabolic programs that support CPC function and regulate their proliferation. In their *STEM CELLS* article, Salabei et al discovered that rapidly proliferating CPCs isolated from adult mouse heart expressed the Glut1 glucose transporter and increased their glycolytic rate in response to high extracellular glucose concentrations in an insulin-independent manner; however, glucose failed to affect CPC proliferation. Instead, the authors employed high throughput respirometric analyses to establish that the exposure of CPCs to glutamine increased proliferation, promoted survival under conditions of oxidative stress, and enhanced mitochondrial function. Furthermore, glutamine exposure also prompted the activation of the mTOR signaling pathway and the phosphorylation of the retinoblastoma protein and the subsequent induction of the cyclin D1 and Cdk4 cell cycle regulators. Importantly, inhibition of mTOR signaling or glutamine metabolism led to reduced CPC proliferation. Overall, these findings highlight a unique metabolic feature of CPCs and suggest that targeting glutamine metabolism may represent a means to improve CPC-mediated therapies.



https://doi.org/10.1002/stem.2047

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