Myometrium: another candidate for cell-based myocardial angiogenesis

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CARDIOVASCULAR DISEASE is the leading cause of death, disability, and health care expenditure in the United States and other developed countries (8). Although advances in medical, percutaneous, and surgical treatments have greatly advanced the treatment of ischemic coronary disease, up to one-third of patients presenting with advanced coronary disease receive incomplete revascularization with conventional percutaneous and surgical techniques due to the presence of diffuse disease and unsuitable coronary anatomy (2, 5). These patients suffer from disabling symptoms and increased risk of cardiovascular mortality (3). Thus treatment of end-stage coronary disease represents a significant unmet clinical need.

Over the past decade, numerous attempts have been made to stimulate the growth of new blood vessels to increase perfusion to the ischemic myocardium. The early approaches to myocardial angiogenesis applied protein or gene-based delivery of angiogenic growth factors, whereas cell-based therapies have been the focus of recent investigations. A plethora of different cell types have been proposed as potential candidates, including hematopoietic progenitor cells, skeletal myoblasts, mesenchymal stem cells, and endothelial progenitors (6). In this issue of American Journal of Physiology-Heart and Circulatory Physiology, Huang et al. (4) propose yet another candidate for inducing angiogenesis and myocardial functional improvement.

Myometrial cells, under physiological conditions, are intimately involved in vasculogenesis in the uterus and, therefore, are potential candidates for the induction of myocardial angiogenesis and perhaps even arteriogenesis. The authors have nicely demonstrated that these cells express vascular endothelial growth factor, which is enhanced by progesterone in a dose-sensitive manner. These cells induced greater vessel formation compared with endothelial or smooth muscle cells on a matrigel assay. Injection of myometrial cells led to increased vessel density, reduced scar size, and improved functional recovery in the cryoinjured myocardium. This study adds to the growing number of candidate cell types that may eventually be used for therapeutic angiogenesis. However, a number of questions remain. What are the effects of other endogenously produced sex steroids like estrogen and testosterone on the angiogenic potential of these cells? How do myometrial cells perform in the setting of myocardial ischemia? What is the eventual fate of myometrial cells when transplanted into the heart? Can the results of these experiments, conducted in female animals, be extrapolated to male recipients? Further work is required to better characterize the interesting and novel findings reported by the authors.

Although cell-based angiogenesis appears to be a promising therapeutic option for patients with end-stage coronary artery disease, there are numerous obstacles that must be overcome before these treatments become a clinical reality. In this context, it is important to note that the significant improvements in angiogenesis and myocardial function that were observed in preclinical models of growth factor delivery did not translate into similar benefits in subsequent clinical trials (7). One of the reasons for this lack of translation from preclinical models using young, healthy animals to patients with end-stage coronary disease is the milieu within which these therapies operate. Patients with end-stage coronary disease have numerous comorbidities like diabetes, hypercholesterolemia, and endothelial dysfunction that can impair the response to angiogenic therapy. These disease states are associated with reduced nitric oxide bioavailability and endothelial dysfunction, impaired growth factor signaling, and increased expression of antiangiogenic proteins (1). A better understanding of these antiangiogenic influences may allow for the modulation of the response to angiogenic therapy in these patients.

Recent studies from animal models of cell delivery have suggested that only a small percentage (between 1 and 10%) of delivered cells is actually retained in the target tissue in the days to weeks after implantation (6). The relatively low retention rate may be a function of various cell-related or host tissue-related factors. The dose of cells delivered as well as the timing and method of delivery may affect cell survival rates. Other strategies to increase cell survival, currently being studied, include genetic modification of cells to secrete growth factors, coadministration of different cell types, as well as delivery of cells within a matrix that provides a more favorable environment for growth.

Finally, a better understanding of the fate of the delivered cells as well as the mechanisms through which they improve myocardial function is required. Whether these cells differentiate and participate in the formation of new vascular structures or enhance the endogenous angiogenic response through a paracrine effect of growth factor secretion remains unclear. One of the major limitations in obtaining this understanding is our limited ability to track cells once they are delivered into the target tissue. Advances in cell tracking and in vivo imaging of implanted cells will undoubtedly further our understanding of the mechanisms through which these cells exert their therapeutic effects.

The eventual translation of cell-based angiogenic therapy into tangible benefits for patients with coronary artery disease will require a better understanding and novel solutions to these issues.

GRANTS

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