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EDITORIAL

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Towards regenerating a fully integrated myocardium: The role of chemical growth factor cocktails in substituting neural stimuli as a novel feat in regenerative medicine

Regenerative medicine approaches to restoring a damaged or dysfunctional myocardium have been reported through various modalities. One approach involves using cells or cell-derived factors as tools; i.e., by transplantation of (a) stem and progenitor cells viz. cardiac stem cells, bone marrow stem cells, adipocyte stem cells, endothelial progenitor cells, and pluripotent stem cells[1,2], (b) cardiomyocytes[3], and (c) by transplanting skeletal myoblast patches[4]. Although exogenous cell transplantation approaches are postulated to be of help through differentiation, transdifferentiation, paracrine effects, etc.[1,2], the regeneration in the myoblast approach is mainly facilitated through paracrine effects[4]. Another approach is through transplanting decellularized extracellular matrices in the damaged portion of the heart[5], into which native cells and their components are expected to grow to form an integrated myocardium. Irrespective of any of the above approaches, the resumption of a fully functional myocardium mandates an anatomical restoration of cells and their components with an optimal environment for viability, while functional restoration has to occur by integration with surrounding tissues at a local tissue level and with central nervous system coordination[6]. Local integration mainly depends on the nutrition supply, whereas central neuronal integration has inputs from the local component of neural regeneration that supplies the concerned region of the tissue or organ, and their ultimate functionality will be restored only when the local neural (motor, sensory, or autonomic) components are connected to their central nervous system counterparts. Such integration has not been very successful for several reasons[7].

Further, in contrast to other organs and tissues in the body, the myocardium has an additional myofiber neural-conduction pathway that runs a locally coordinated functional system aligned with the central command from autonomic and cranial nerves[6]. Therefore, a portion of damaged heart cannot as such; a 3D printed tissue though may be having a nutritional supply for the cells to survive, the syncytium cannot function unless it is in unison with the rest of the myocardium. Otherwise, proper coordination between the conducting system and autonomic nervous system becoming an integral part of the regenerated area cannot be accomplished[8].

Myocardium requires this neural stimulation not only for its function after development, but also during the process of development[9, 10]. Without an appropriate neural stimulus, the regenerated portion remains a neurologically sequestrated region that will not become part of the functional syncytium and will be a foci of ectopic arrhythmia leading to failure of the transplanted portion or even the whole heart[11].

Techniques for neural stimulation involve bioelectric stimulation[12], scaffolds that are wired in[13], etc. To address this issue, Arora et al[13] attempted a cocktail of cardiac developmental growth factors, Wnt3a, BMP4 and Neuregulin (NRG-1), in an ex vivo environment of explant culture of the neonatal myocardium, which has been able to serve as a substitution of the neural stimuli needed during cardiac development.

This is significant because the neuronal stimuli are compensated by these growth factors in dynamic tissue such as the myocardium, which cannot be put to rest during the period of healing, in contrast to tissue such as cartilage, which can be immobilized to give time for healing. The avascular nature of the cartilage along with features such as the possibility of immobilization has led to regenerative approaches such as cell therapies[14] and 3D printing[15] being more successful for cartilage. However, the highly complex neuro-vascular myocardium lacks such advantages, and therefore this attempt by Arora et al[13] is important for future progress. Such chemical cocktails are worth trialing because, at least, preliminary support until growth of actual neurons to sustain further growth of the regenerating or developing tissue can be accomplished.

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