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Nanocomposite hydrogels: an emerging biomimetic platform for myocardial therapy and tissue engineering

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Repairing damaged heart muscles: the challenges

Recent years have seen a significant rise in patient survival rate after myocardial infarction, commonly known as heart attack. This is mainly due to improvement in hospital instrument facilities, clinical management system, surgical tools and technologies. However, many of these patients soon develop heart failure, with 50% mortality rate within 5 years of heart attack [1]. As the regeneration power of the heart muscle is very limited, negative remodeling and nonfunctional scar tissue deposition leads to gradual terminal failure of the heart. Current treatments include heart transplantation and ventricular assist devices, which are both highly invasive and risky surgical procedures with inconsistent results. Stem cell transplantation has recently shown some potential that can improve heart function through several mechanisms such as cardiac differentiation, neoangiogenesis and paracrine effects [2]. Despite promising results, stem cell therapy still remains limited because of economic, timing and logistic issues, particularly when isolating cells from elderly patients under clinical settings. Reduced cell survival and retention at the transplant site further limits their therapeutic potential [3]. Thus, we see an urgent need for new strategies to attenuate the progression of the disease postmyocardial infarction. The following sections highlight the emerging roles of biocompatible nanomaterials and hydrogels and provide insights for further development in cardiac therapy and tissue engineering applications.

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Nanomaterials & injectable hydrogels: how they can help repair damaged cardiac tissues

Although still in its early stage of development, the field of nanomedicine for cardiovascular therapy has evolved rapidly over the years with new discoveries in nanomaterials science [4]. In particular, local intramyocardial delivery of therapeutic nanoparticles, including lipopolymers and viral nanocarriers, has shown impressive *in vivo* results to provide early cardioprotection and enhance neovascularization of injured tissue [5–8]. However, retention of the implanted nanotherapeutics at the target site for an optimal duration is critical for the success of the therapy. And this is particularly challenging when delivering therapeutics to cardiac environment where the wall of the heart is constantly beating driving substantial amount of cargo to other nonessential regions.

Injectable hydrogel that helps retain the nanotherapeutics at the target site may offer a viable solution to this problem. Compared to other procedures, hydrogel with compatible rheological properties aids in reducing the damage to the surrounding tissues along with the added capability to preserve the encapsulated drug at injected site. In general, therapeutic approaches of injectable hydrogels mainly include epicardial and endocardial injections. Main benefits of such delivery methods is that they allow direct access to the damaged tissue site, accurate placement and retention of the therapeutics compared with other methods. Injectable extracellular matrix (ECM) hydrogel from Ventrix Inc. (CA, USA), which is now going for clinical trial for myocardial therapy, is one such example [9]. Importantly, the liquid hydrogel precursor can be delivered in a single bolus or in multiple injection forms, where the later can subsequently get transitioned *in situ* into hydrogel state by shift in salt concentration, pH, temperature, or enzyme concentration. In case of bio-originated materials, such as decellularized ECM matrix, the hydrogel can additionally provide structural support and biochemical cues to the injured site which may induce endogenous stem cell homing for natural healing.

A smart selection of such drug carrying nanoparticles and injectable hydrogel can complement each other's strengths and help develop the next generation therapeutics with multifunctional effects. Recently, it has been reported that DNA carrying nanomaterials in combination with naturally derived methacrylated gelatin (GelMA) hydrogel, can efficiently deliver DNA to the infarcted site when administered intramyocardially [10]. We also noticed that *VEGF* gene-activated nano graphene oxide (GO), suspended in injectable GelMA, can effectively deliver *VEGF* genes to the myocardial tissue in peri-infarct region which eventually leads to neovascularization, attenuation of cardiac dysfunction and scar formation. In fact GelMA alone, as a major ECM derivative, exhibit potential to induce functional benefits to the tissues because of its inherent biological cues. miRNA analysis of the tissues at injected site further confirmed the biocompatibility of the developed nanocomposite GelMA/GO hydrogel. Other studies have shown beneficial effects of injectable shear thinning hydrogels to deliver therapeutics to target site by its shear-induced flow properties commonly induced by syringes and catheters [11,12]. The shear-thinning materials recover back into hydrogel state immediately after delivery and retain the encapsulated therapeutics at the target site. Purcell *et al.*, in an interesting study,

demonstrated that an on-demand matrix metalloproteinase (MMP) inhibition is possible using such injectable bioresponsive hydrogel which releases recombinant tissue inhibitors of MMPs only when MMP activity is increased postmyocardial infarction [13]. In recent years, several other bioresponsive materials for cardiac applications have been developed which, in combination with nanovectors, can deliver oxygen-releasing agents, small molecules, drugs and growth factors at injured site [14,15]. The technology can be further improved using nanoparticles which can bind to specific target sites. For this the nanoparticles must be surface functionalized with high density ligand molecules which can identify a substantially overexpressed molecular target at the injured tissue site. It is also important to mention here that these nanohybrids can be surgically implanted at any site in patients with minimal prior knowledge of the geometry of the injured site.

Engineering miniaturized cardiac tissues: role of biomimetic nanocomposite hydrogels

The last few years have seen significant thrust in designing *in vitro* miniaturized healthy and diseased cardiac tissue models also known as 'heart on-a-chip' [16,17]. To achieve this goal tissue engineering is now entering a new era where it merges the insights of microscale technologies with stem cell biology, in particular induced pluripotent stem cells. So far the cardiac and stem cell originated *in vitro* cardiac tissue prototypes have demonstrated that they can help better understand the cell–drug interactions, drug resistance and cytotoxicity, pharmacological profiling and instigate personalized medicine practice. Moreover, such bioengineered cardiac constructs can also be used as cardiac patches for functional tissue replacement therapy. However, one of the main challenges to develop such a clinically relevant tissue engineered cardiac structure is replicating the unique morphological, physiological and functional properties of the native myocardium.

In a classical approach, cardiac cells are combined with hydrogels, and cultivated in perfusable bioreactors which provide mechanical and electrical stimulation. Yet, poor conductive nature of commonly used biomaterials result in cardiac constructs with suboptimal performance. Incorporation of electroconductive nanomaterials such as carbon nanotubes (CNTs) and GO nanosheets can potentially solve this problem. CNT-reinforced hybrid GelMA hydrogel has been shown to improve mechanical and electrical properties of hydrogel [18]. The resulting nanocomposite hydrogel significantly improved cardiomyocyte alignment, maturation and electrophysiological functions. Developing such biomimetic nanocomposite hydrogels can facilitate proper electroconductive network and establish spontaneous beating behavior within the cardiac cells. Toward the same goal Dvir *et al.* demonstrated that the addition of gold nanowires and nanoparticles to biomaterial-based hydrogels can significantly enhance electrical communication between neighboring cardiac cells in a 3D microenvironment [19,20]. As a result, the adjacent cardiac cells exhibited a synchronous response to electrical pacing and generated proper excitation–contraction coupling with each beat. Thus it can be stated that the ability to fabricate functional cardiac tissues depends on engineering hydrogels which closely represents cardiac cell niche and biomimetic microarchitecture.

Future perspective

It can be envisaged from the recent studies articulated in this editorial that nanohybrid hydrogels can be highly useful for cardiac tissue engineering and therapeutics. Although new nanocomposite biomaterials are consistently being developed, we need to prioritize these materials as per biomedical applications. Studies with generally-recognized-as-safe materials and hydrogels will have the greatest chances for clinical translation. However, several challenges need to overcome before considering them fit for clinical realization. This includes inventing methods to vascularize the engineered cardiac tissues, optimization of microfabrication technique to consistently develop identical cardiac constructs for high-throughput screening and drug discovery applications. Other concerns related to application of nanocomposite injectable hydrogel include long-term biosafety of the implants, easy integrateability of hydrogel to host tissue and knowledge about fate of implanted nanomaterials postimplantation. While these are few of the many parameters that need to be investigated in designing nanocomposite hydrogels for specific cardiac applications, clearly many unique opportunities and challenges await equally for the clinicians and academic research communities. The demand for new class of clinical therapies for cardiovascular diseases is rapidly rising and these encouraging results offer a promising future.

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