Editorial

Drug Delivery Design for Regenerative Medicine


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1. INTRODUCTION

There is a growing need for controlled design and release of drugs for regenerative medicine especially for cell/tissue/organ clinical transplantation. Most cells/tissues/organs have limited inherent regenerative capacity in human bodies, with various bioactive agents controlling their fates and functions. For example, myocardial infarction is often followed with noncontractile scar tissue, which can further result in congestive heart failure [1]. Cyocardium repair and wound healing are normal regenerative processes of great importance in clinical medicine with very complex growth factor, cytokine, gene and/or hormone regulation systems [2]. In the case of bone, metabolic disorders could cause abnormal ossium losses, traumatic injuries, and large lesions, which are incapable of self-regeneration without controlled release suitable biomaterials or growth factors [3]. The research has therefore turned to novel ways to stimulate cell/tissue/organ regeneration to address the serious donor shortage issues. It has been proven that bioactive agents, biomaterials, cells, especially multipotential stromal cells or mesenchymal stem cells, are essential elements of regenerative medicine. These elements are usually used as therapeutic drugs with certain controlled design and release protocols. However, individual cell and bioactive agent delivery systems often encounter the quick loss and invalid embarrassments.

Recently, a drug delivery model mimicking nature's organism manufacture approach has emerged with the coordination of cellular self-assembly, cell-cell/matrix/signal interactions and new cell/tissue/organ phenotypes. It has proven that bioactive agents, such as growth factors, cytokines, genes and/or hormones are helpful in counteracting the issues of cell/tissue/organ growth and death. The right choice of bioactive agents with proper release profiles will help bridge the gaps between cell-biomaterial interaction explorations and cell/tissue/organ regenerative therapies [4-12]. In this thematic issue, various *in vitro/in vivo* drug design and delivery models for cell/tissue/organ regeneration have been put forward by leading scientist Prof. Xiaohong Wang from the Center of Organ Manufacturing, Department of Mechanical Engineering, Tsinghua University, China, with her co-contributors, namely Prof. Viness Pillay from the Wits Advanced Drug Delivery Platform Research Unit, Department of Pharmacy and Pharmacology, School of Therapeutic Sciences, Faculty of Health Sciences, University of the Witwatersrand, Johannesburg, South Africa; Prof. Jianping Zhou from the State Key Laboratory of Natural Medicines, Department of Pharmaceutics, China Pharmaceutical University, Nanjing, China; Prof. Soo Hyun Kim from the Biomaterials Research Center, Korea Institute of Science and Technology; Prof. Ling Qin from the Musculoskeletal Research Laboratory, Department of Orthopaedics & Traumatology, The Chinese University of Hong Kong, Hong Kong SAR, China; Prof. Roberta Censi from the University of Camerino, Camerino, The Marches, Italy; Prof. Dong-Woo Cho from the Center for Rapid Prototyping based 3D Tissue/Organ Printing, Kyungbuk, Korea; Prof. Jing Xu, from the CAS Key Laboratory for Biomedical Effects of Nanomaterials and Nanosafety, National Center for Nanoscience and Technology of China; Prof. Banquy Xavier from the Université de Montréal, Montréal, Quebec, Canada, in the pertinent fields, such as biomaterials, stem cells, 3D printing techniques, nanotechnologies, and pharmaceuticals. Each review comprises state-of-the-arts techniques, applications, functionalities, challenges, and perspectives from the targeted cells/tissues/organs. The present drug design and delivery models, which can evaluate and predict the cell/tissue/organ formation and destination, are considered to be promising candidates for concrete cell/tissue/organ regenerative medicines.

2. 2D, 3D, and 4D Active Compound Delivery Systems

At the beginning, Banquy *et al.* proposed a 4D active compound delivery concept in tissue engineering and regeneration medicine [13]. It is demonstrated that controlling cell micro-environment is a key element to the development of successful therapeutic system. Besides two-dimensional (2D) and three-dimensional (3D) techniques that have been used to control the load and release of active compounds to promote cell differentiation and proliferation, active compound delivery systems should include a fourth dimension (i.e. in space and time 4D) to the design of 3D scaffolds.

3. Multifunctional Therapeutic Delivery Strategies for Neuro-Regeneration

Traumatic spinal cord regeneration present several interventional challenges, such as extensive inflammation, scar formation, axonal tethering, neuronal degeneration and functional loss, even before a slight neuronal recovery can be achieved [14]. Pillay *et al.* indicated that investigational approaches include a combination of "support and therapeutic" strategies are capable of providing localized delivery of therapeutic molecules along with specialized architecture to allow axonal growth and conformal repair. Combinatorial approaches, i.e. multifunctional therapeutic delivery strategies, employing two-or-more delivery systems such as microspheres-in-conduits, nanoparticles-in-hydrogels, cells-in-scaffolds and fibres-in-films are increasingly being adopted to maintain the stability of neurotrophic factors throughout the release period, to provide conformal filling and repair, to co-deliver cellular and mutifactor components, to sequentially control degradation and dissolution of the scaffold, and to support the neuronal tissue proliferation in and across the lesion cavity. It is suggested that a multifunctional combinatorial device assimilating the molecular, cellular, biomaterial, structural and functional aspects altogether is the best way forward for effective neuroregeneration applications.

4. Reconstituted High Density Lipoprotein-Based Nanoparticles

In the past two decades, polymeric nanoparticles have emerged as a most promising and viable technology platform for targeted and controlled drug delivery [15]. With programmed site-specific drug delivery feature, dual and multi-stimuli responsive nanoparticulate drug formulations have tremendous potential for targeted cell/tissue/organ regeneration. Zhou *et al.* made a systematic review on reconstituted high density lipoprotein (rHDL)-based nanoparticles (rHDL-based NPs) as drug delivery systems [16]. The review highlights four aspects of rHDL-based NPs: current applications in preparation methods, regenerative medicine, conventional assays which are employed to evaluate rHDL-based NPs, and future trends on co-delivery of drugs mediated by rHDL-based NPs to achieve synergic effect. Studies reviewed showcase that rHDL-based NPs holds a bright future for a variety of applications, ranging from drug delivery design in regenerative medicine or other fields, from basic mechanism studies to transmembrane protein accommodation and promising therapies.

5. Advances in Cartilage Regeneration

Hydrogels are a family of biocompatible materials with a high content rate of water. Recently, hydrogels have emerged as promising growth factor and cell delivery systems in regenerative medicine. Nearly all the drugs can be loaded in a water contained hydrogel and subsequently released in a controlled fashion. Censi *et al*. reported the importance of growth factors incorporated into hydrogels and their synergistic interplay in cartilage development [17]. The injection bolus seems to be ineffective and potentially harmful due to the short duration of action and the supraphysiological doses. A better understanding of the biological processes underlying cartilage repair led to the establishment of new drug delivery approaches which comprise the combination of appropriate cells, biodegradable scaffolds and specific environmental cues, such as growth or adhesive factors or genetic materials. Hydrogel delivery platforms can be easily designed to deliver multiple growth factors, cells or genes with independent release rates, by varying hydrogel composition, cross-link density and polymer content. Further efforts in the design or optimization of materials with sufficient stiffness, minimal tissue response, appropriate degradation and release profiles are needed in order to translate drug loaded hydrogels from the bench to the clinic.

6. Material Couture for Wound Healing

Kaur *et al.* indicated that natural, synthetic or modified polymers alone or in combinations are commonly used as dressing couture for wound healing [18]. Good biocompatibility, biodegradability and mechanical strength, in addition to protection, antibacterial nature and facilitated healing and cell regeneration are some of the key properties, which define a good dressing. Localised delivery of therapeutic active agents, such as antimicrobial, soothing minerals, vitamins and growth factors, at the site of injury/trauma/wound could significantly increase the regenerative abilitie and therapeutic effects. [18]. The couture can be deigned to suit various requirement and may thus be in the form of foams, films, composites, nanofibers, hydrocolloids, hydrogels and particulates. This article offered a clear overview on a vast of biomaterials that have been used to design and develop wound dressings or couture.

7. Systemic Drug Delivery Systems for Bone Tissue Regeneration

Musculoskeletal metabolic diseases such as osteoporosis have become the major public health problems worldwide in our aging society [19]. One of the innovative approaches for osteoporosis treatment is developing bone-targeting drug delivery technologies to improve the pharmacokinetic profile and therapeutic efficacy of the chemical drugs. This paper reviewed the current available bone targeting drug delivery systems with emphasis on bone-targeting moieties, including the bone-surface-site-specific (bone formation dominant or bone resorption dominant) and cell-specific ones. Additionally, the connections of drug-bone-targeting moieties-carrier, the newly developed liposomes and nanoparticles were all summarized for their potential use for therapeutic agent delivering to bone tissues.

8. Myocardial Regeneration

Heart failure is one of the most prominent causes of morbidity and mortality, which responses more than 29% of deaths worldwide [20]. Current treatment methods include coronary artery bypass grafting, cellular therapy, organ transplantation, ventricular remodeling, and cardiomyoplasty. Each of these methods has inherent risks and benefits. For instance, cellular cardiomyoplasty can decrease the fibrosis of infarct scars and adverse post-ischemic remodeling and improve heart function. However, the shortage of cell sources and donors, low rate of cell survival, ethical issues and tumorigenesis hamper full exploitation of this therapic treatment. Consequently, the mobilization and recruitment of endogenous stem/progenitor cells from peripheral circulation, bone marrow, and cardiac tissues have emerged through harnessing the host's own reparative capacities from interplaies among cytokines, chemokines, and adhesion molecules. Therapeutic treatments to enhance the mobilization and homing of stem cells are under development. In this review, the authors presented state-of-the-art approaches that are being pursued for stem cell mobilization and recruitment to regenerate infarcted myocardium. Furthermore, the potential delivery strategies and therapeutic interventions have been discussed in detail.

9. DSPE-PEG Delivery Systems

As an aside, 1,2-Distearoyl-sn-glycero-3-phosphoethanolamine-Poly(ethylene glycol) (DSPE-PEG) has been widely used as a phospholipids-polymer conjugation in drug delivery applications. It is biocompatible, biodegradable and amphiphilic and can be functionalized with various biomolecules for special purposes [15]. Recently, the imaging DSPE-PEG has become a very useful tool for the formulation of nanocarriers for achieving prolonged blood circulation time, improved stability and enhanced encapsulation efficiency. In this review, Che *et al.* focused on the relationships between the DSPE-PEG structures and its noticeable effects on nanocarriers' properties, and the recent progress on the DSPE-PEG development and its derivatives in drug delivery systems [15].

10. 3D Printing Technology Over Drug Delivery for Tissue Engineering

Nowadays, many researchers have attempted to use computer-aided design (CAD) and computer-aided manufacturing (CAM) to provide 3D environment for tissue and organ regeneration. Lee *et al.* overview several 3D printing technologies, including stereolithography, deposition modeling, inkjet-based printing and selective laser sintering, which have been adapted to a drug delivery system for tissue engineering [21].

11. Perspectives

Finally, stem cells (SCs), especially induced pluripotent stem cells (iPS), have properties which make them promising for the treatment of chronic non-healing wounds. There is tremendous hope that we can increasingly use stem cells to obtain primary human cells with reliable differentiation protocols. A major so far unmet challenge is the efficient, safe and painless delivery of SCs, iPS and bioactive agents to wounds. Often 3D cultures overcome 2D cultures in dedifferentiation, the loss of specific cell functions typical for primary cells [23,24]. We discussed the future direction of *in vitro* stem cell culture and delivery models and how to extend the lessons learned from stem cells to cell/tissue/organ analogies. By incorporating ideas from how bioactive agent delivery and stem cell responses, we showed that stem cell manipulation (including migration, growth, proliferation, differentiation, variability, and stability) can occur at a much easier and safer way. We are left with even more windows between establishing the 3D culture and critical loss of differentiation. The addition of more dimensions, such as the fourth dimension (4D)-time, fifth dimension (5D)-temperature, and sixth dimension (6D)-intelligent, will definitely make the long-term exposure, temperature-dependent and memory reaction of our target cell/tissue/organ equivalents possible in the near future.

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