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Account/Revue

Recent advances in synthetic polymer based hydrogels for spinal cord repair

Hydrogels à base de polymères synthétiques pour la réparation médullaire

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ABSTRACT

In spinal cord repair, the challenge consists in combining various therapies that account for multiple deleterious effects in order to induce an efficient recovery. In that context, biomaterial implantation seems to be highly relevant. Indeed, biomaterials not only serve as a growth support to promote sectioned axonal fibers, but are also used for cell transplantation and drug delivery. In this review, we discuss and put into perspective the recent results obtained in the field of spinal cord repair by synthetic hydrogel implantation. The versatility of those biomaterials is presented through the latest chemical strategies developed to enhance their therapeutic effects.

RÉSUMÉ

Face au défi de la réparation médullaire, une polythérapie visant un grand nombre d'effets délétères est susceptible d'entraîner une récupération importante. Dans ce contexte, l'implantation de biomatériaux semble être particulièrement adaptée. En effet, les biomatériaux ne servent pas seulement à fournir un support de repousse pour les axones lésés, mais sont également utilisés pour la transplantation cellulaire et la libération de molécules pharmacologiques. Dans cette revue, nous abordons et mettons en perspective les derniers développements obtenus dans le domaine de la réparation médullaire par l'implantation d'hydrogels synthétiques. La versatilité de ces biomatériaux est présentée au travers des dernières stratégies développées pour accroître leurs effets thérapeutiques.

1. Introduction

The debilitating effects of spinal cord injuries (SCI) are not only induced by direct disruption of spinal cord ascending and descending pathways, but also by post-traumatic complications, known as the second injury, which in part encompasses ischemia, hematotoxicity, excitotoxicity, inflammatory reactions and release of molecules inhibiting axonal regrowth [1]. As a result, both acute and chronic therapeutic interventions have been

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designed to potentiate the limited spontaneous recovery that is sometimes observed in SCI patients. They usually consist in limiting secondary injury, promoting plasticity or axonal regrowth through rehabilitation, cell transplantation [2], or molecule administrations (e.g. neurotrophic factors and antagonists for neurite growth inhibitors) [3]. Although promising results have been obtained in animal studies, no efficient clinical therapy, except rehabilitation, is yet available [4]. This poor translation from animal research evidence to effective clinical treatments could be, in part, caused by the shortcomings of cell transplantation and molecule administration. Indeed, it was noted that a majority of cells undergoes apoptosis after implantation due to the hostility of the lesion site environment and the lack of cell adhesion [5]. In addition, direct molecule injection leads to uncontrolled molecule release kinetics [6].

An alternative strategy is to fill the spinal cord cavity with a polymer biomaterial in order to reduce the glial scar, which is known to impede axonal regrowth, and to increase axonal regeneration by supplying a substrate for growth support [7]. However, to efficiently repair the spinal cord the characteristics of implanted biomaterials should properly match the ones of the nervous tissue's extracellular matrix (ECM) as it was shown that the ECM played a key role in the migration, the morphology, the phenotype and the survival of cells [8]. A recent study even demonstrated that the implantation of an acellular spinal cord scaffold, obtained through a simple series of detergent, induced functional recovery in hemisected rats [9]. In that context, hydrogels, which are three-dimensional networks formed by hydrophilic cross-linked polymers swollen in water, seem to be well suited for both spinal cord and brain repair [10]. Hydrogels can easily be cast into various shapes in order to properly fill the lesion site or to present pores and microchannels [11]. Moreover, by adjusting the synthesis process it is possible to obtain hydrogels with modulus of elasticity that closely fits the soft mechanical properties of the nervous tissue [12]. Hydrogel mechanical properties are not only known to profoundly affect the neuronal morphology such as neurite branching [13] but also to regulate the self-renewal and the differentiation of the neural stem cell (NSC) [14]. In fact, hydrogels are well suited to be used as cell carriers as it was shown that cells delivered via a biocompatible scaffold presented high survival rates than transplanted cells through simple injection [5].

To date, various polymers from both natural and synthetic origins have already induced therapeutic effects in different animal models [15–17]. Nevertheless, synthetic hydrogels are particularly attractive as they present a low batch-to-batch variability and can be manipulated to have a wider range of physico-chemical properties than natural ones. Additionally, implantation of synthetic materials avoids disease transmission and reduces allergenic and immunogenicity risks [16, 18]. Synthetic hydrogels used in spinal cord repair principally consist of polymethacrylates/methacrylamides and polyethers whose cross-linking is based on different chemistry approaches (e.g. radical polymerization and click reactions). They have been extensively studied and brought promising results. Indeed, functional improvement, tissue recovery and axonal regeneration have been observed after implantation of poly [*N*-(2-hydroxypropyl)methacrylamide] (PHPMA) [19], poly(2-hydroxyethyl methacrylate) (PHEMA) [20], and poly(ethylene glycol) (PEG) hydrogels, respectively [21]. Although hydrogel implantation induces therapeutic effects by itself, synergistic outcomes are generally observed with cell-seeded scaffolds [22]. Indeed, Hejčl et al. only observed significant functional improvement after the implantation of the mesenchymal stem cell (MSC)-seeded PHPMA hydrogel in a chronic SCI model [23]. Other authors studied injectable *in situ*-forming hydrogels in order to limit the surgical invasiveness of conventional implantation [16].

Many well-written reviews already discussed the therapeutic effects induced by the implantation of biomaterials after a spinal cord injury [3, 15–17]. In those reviews, the biomaterials were either classified depending on their nature or their characteristics and both advantages and drawbacks of each biomaterial were debated. In particular, the review of Straley et al. in 2010 has thoroughly listed the desired characteristics of hydrogels for use in spinal cord repair. Besides complex questions about mechanical compliance, adapted porosity/topography, injectability and cell encapsulation, the authors pointed out the crucial importance of cell adhesion, biomolecule delivery and degradability in the design of hydrogel scaffolds. In this short review, we precisely focus on the chemical strategies recently developed to obtain synthetic hydrogels displaying these three key features for use in spinal cord repair, namely (i) improved surface biofunctionality regarding cell adhesion, (ii) drug delivery ability, and (iii) degradability properties so as to avoid chronic complications [3, 18]. We included both *in vivo* and *in vitro* studies on tissue regeneration obtained with these scaffolds. Although each section of this review deals with definite characteristics, it is important to keep in mind that they are all intertwined.

2. Bioadhesion promoting strategies

In spite of exhibiting the interesting above-mentioned features, synthetic polymer-based biomaterials do not generally present inherent surface properties that can provide a suitable environment for biological processes (primarily cell adhesion). Therefore, many efforts have been devoted to modify the bioinert surface of these biomaterials by ECM proteins (e.g. laminin, fibronectin, and collagen), which have the specific advantage of possessing cell-adhesive or signaling domains. Such strategy is not only known to increase tissue integration and viability of transplanted cells but also to improve axonal regeneration. Indeed, after a complete spinal cord transection, a higher number of regenerating axons were observed in fibrin-filled poly(2-hydroxyethyl methacrylate-co-methyl methacrylate) (PHEMA-MMA) implanted channels than in unfilled channels [24]. Similarly, an increase in neurite growth was noticed *in vitro* on the PEG hydrogel coated with fibronectin (i.e. an ECM glycoprotein) [25]. However, ECM-derived proteins

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