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Review

Effects of osteogenic protein-1 on intervertebral disc regeneration: A systematic review of animal studies

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ABSTRACT

Osteogenic protein (OP)-1 delivery into discs has achieved some success in disc regeneration in animals, though conflicting outcomes exist. This study aimed to systematically review the animal studies that assessed the effect of OP-1 on disc regeneration. Relevant literature was searched in the following databases: PubMed, MEDLINE, EMBASE, the Cochrane Library, China National Knowledge Internet (CNKI) and Chinese BioMedical Literature Database (CBM). Animal species, disc degeneration model, OP-1 delivery method, and follow-up methodology including disc histology, disc matrix alteration, disc height, MRI T2 signal intensity and OP-1 treatment complications were extracted and reviewed. Among 15 eligible studies, direct OP-1 protein injection into the disc was reported in 10 studies whereas cell-based or viral-based OP-1 gene transfer into the disc was reported in 5 studies. Although one study using a spontaneous canine disc degeneration model reported negative findings, all other studies (10 in rabbit, 1 in canine and 3 in rat) indicated that OP-1 delivery was effective in retarding disc degeneration and regenerating discs. The adverse effect of OP-1 delivery (i.e., extradiscal new bone formation) was reported in one study. In conclusion, OP-1 delivery offers a feasible option to biologically treat degenerated discs in animals, especially in rodent rabbit and rat models. However, more animal studies are needed to test the safety of the current OP-1 delivery means. Additionally, care should be taken when OP-1 delivery is used to treat human disc degeneration due to the differences between human and animal discs.

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Abbreviations: IVD, intervertebral disc; OP-1, osteogenic protein-1; CNKI, China National Knowledge Internet; CBM, Chinese BioMedical Literature Database; LBP, low back pain; IDD, intervertebral disc degeneration; NP, nucleus pulposus; AF, annulus fibrosus; CEP, cartilage endplate; BMP-7, bone morphogenetic protein-7; TGF-β, transforming growth factor-β; PRISMA, preferred reporting items for systematic reviews and meta-analyses; CAMARADES, collaborative approach to meta-analysis and review of animal data from experimental studies; BMSCs, bone marrow mesenchymal stem cells; NPCs, nucleus pulposus cells; ACs, articular chondrocytes; PG, proteoglycan.

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1. Introduction

Low back pain (LBP) is a common cause of physical disability worldwide and brings an enormous social influence to patients [1,2]. Though there is a strong link between the LBP and intervertebral disc degeneration (IDD) [3,4], certain basic points of IDD ranging from the pathogenesis to clinical treatments remain elusive to date.

Macroscopically, the fibrocartilaginous intervertebral disc (IVD) consists of three structurally well-connected parts including the central gelatinous nucleus pulposus (NP), the peripheral lamellar annulus fibrosus (AF) and the thin hyaline cartilage endplate (CEP) [5]. During disc degeneration, several cellular and molecular changes first occur in the NP region, which is described as decreased cell number, increased cell apoptosis and senescence, and decreased content of matrix macromolecules (proteoglycan and collagen II) [6]. Therefore, maintenance of cell viability and the balanced matrix homeostasis may be primary targets in disc regeneration.

Currently, surgical treatment in the form of spinal fusion and disc arthroplasty is the optional therapy to alleviate symptoms and address the disability caused by discogenic LBP [7]. However, the invasive surgical treatments may trigger certain complications and may not be always effective in fully resolving symptoms sometimes. With the rapid development of tissue engineering and regenerative medicine, promising new strategies to biologically intervene disc degeneration are attracting more and more attention. Among these biological strategies for repairing degenerative disc, delivery of growth factors into the central disc by means of direct protein injection and by means of cell-based or viral-based gene transfer is proposed as a minimally invasive form of treatment with a long duration [8–10].

Osteogenic protein-1 (OP-1), otherwise called bone morphogenetic protein-7 (BMP-7), is a member of the transforming growth factor-β (TGF-β) family. In recent years, tremendous research efforts and scientific funds have been employed to investigate the efficiency of OP-1 in treating disc degeneration and the significance of OP-1 within the pathological process of disc degeneration [7,11–16]. Previously, several studies demonstrated that OP-1 expression was down-regulated in degenerative discs [17,18]. Moreover, OP-1 can significantly promote proteoglycan and collagen synthesis in disc cells [13,19,20]. It has also been demonstrated that OP-1 delivery into the central disc stimulates proteoglycan and collagen synthesis, restores disc height and enhances MRI T2 signal intensity [21–31]. Therefore, a consensus on the effect of OP-1 on disc regeneration in animal models is helpful to provide a theoretical basis for human clinical research.

In this paper, we comprehensively reviewed the previous animal studies that investigate the role of OP-1 delivery in disc regeneration. Significant positive and negative findings about the effects of OP-1 on animal disc regeneration were summarized. The benefits and limitations of OP-1 therapy were also discussed.

2. Material and methods

2.1. Inclusion and exclusion criteria for this systematic review

In this systematic review, only the preclinical controlled studies (randomized (RCT) or non-randomized (N-RCT)) that investigated the role of OP-1 in animal disc regeneration were included. We mainly focused on the effects of OP-1 on disc height, disc mechanical function, MRI T2 signal intensity, disc histology, matrix metabolism, production of inflammatory cytokines and disc cell viability. The disc degeneration models induced by needle

Table 1
Quality assessment of the included studies (NA: not available).

Author	Publication in a peer-reviewed journal	Statement of animal temperature control	Randomization of treatment or control	Allocation concealment	Blinded assessment of outcome	Animal anaesthesia without marked intrinsic properties	Sample size calculation	Compliance with regulatory requirements	Statement of possible conflict of interest	Total score
An et al.	1	NA	NA	NA	NA	1	NA	1	1	4
Kawakami et al.	1	1	NA	NA	NA	1	NA	1	NA	4
Miyamoto et al.	1	NA	1	NA	NA	1	NA	1	NA	4
Masuda et al.	1	NA	NA	NA	NA	1	NA	1	1	4
Imai et al.	1	NA	NA	NA	NA	1	NA	1	1	4
Chubinskaya et al.	1	NA	NA	NA	NA	1	NA	1	NA	3
Zhao et al.	1	NA	1	NA	1	1	NA	1	NA	5
Zhao et al.	1	NA	1	NA	NA	1	NA	1	NA	4
Liu et al.	1	NA	1	NA	NA	1	NA	1	NA	4
Ren et al.	1	NA	1	NA	NA	1	NA	1	NA	4
Xu et al.	1	NA	NA	NA	NA	1	NA	1	NA	3
Liu et al.	1	NA	NA	NA	NA	1	NA	1	NA	3
Willems et al.	1	NA	1	NA	NA	1	NA	1	NA	4
Zhang et al.	1	NA	1	NA	NA	1	NA	1	NA	4
Gu et al.	1	NA	NA	NA	NA	1	NA	1	NA	3