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Research paper

Efficacy of intervertebral disc regeneration with stem cells — A systematic review and meta-analysis of animal controlled trials

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ABSTRACT

Management of intervertebral disc (IVD) degenerative disease is challenging, as it is accompanied by irreversible loss of IVD cells. Stem cell transplantation to the disc has shown promise in decelerating or arresting the degenerative process. Multiple pre-clinical animal trials have been conducted, but with conflicting outcomes. To assess the effect of stem cell transplantation, a systematic review and meta-analysis was performed. A comprehensive literature search was conducted through Week 3, 2015. Inclusion criteria consisted of controlled animal trials. Two reviewers screened abstracts and full texts. Disagreements were resolved by a third reviewer. Random effects models were constructed to pool standardized mean difference (SMD). Twenty two studies were included; nine of which were randomized. Statistically significant differences were found with the stem cell group exhibiting increased disc height index (SMD = 3.64, 95% confidence interval (CI): 2.49, 4.78; $p < 0.001$), increased MRI T2 signal intensity (SMD = 2.28, 95% CI: 1.48, 3.08; $p < 0.001$), increased Type II collagen mRNA expression (SMD = 3.68, 95% CI: 1.66, 5.70; $p < 0.001$), and decreased histologic disc degeneration grade (SMD = −2.97, 95% CI: −3.97, −1.97; $p < 0.001$). There was statistical heterogeneity between studies that could not be explained with pre-planned subgroup analyses based on animal species, study designs, and transplanted cell types. Stem cells transplanted to the IVD in quadruped animals decelerate or arrest the IVD degenerative process. Further studies in human clinical trials will be needed to understand if such benefit can be translated to bipedal humans.

1. Introduction

Low back and neck pain have a point prevalence of 19% of the world's population, a three-month prevalence of 31% in the United States (Strine and Hootman, 2007; Hoy et al., 2012, 2014). They are ranked the first and fourth most common causes for disability in the United States (Murray et al., 2013), and are associated with a tremendous expenditure of hundreds of billions ($80.1 billion to $91.8 billion) of US dollars annually (Martin et al., 2008). Intervertebral disc (IVD) degeneration is ubiquitous and increases with age, with a prevalence of over 70% in the age group of 50 years or younger, and over 90% in those older than 50 (Teraguchi et al., 2014). As an imaging finding, it is simply age-related change, and is frequently asymptomatic (Bogduk, 2012). There is a population, however, in which the disc becomes painful, often termed discogenic pain. Discogenic pain accounts for 25% to 80% of all low back and neck pain (Rogers, 2003; Manchikanti et al., 2009; Gilbert et al., 2013;

Abbreviations: IVD, intervertebral disc; SMD, standardized mean difference; 95% CI, 95% confidence interval; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses; RCT, randomized controlled trial; N-RCT, non-randomized controlled trial; CAMARADES, Collaborative Approach to Meta-Analysis and Review of Animal Data from Experimental Studies; BMSC, bone marrow stromal cell; ADMSC, adipose-derived mesenchymal stem cell; ECM, extracellular matrix.

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Peterson et al., 2013). As a cause of back pain, discogenic pain is more common in relatively young patients (DePalma, 2011).

The degenerative intervertebral disc disease is characterized by cell death and degeneration of extracellular matrix (Urban and Roberts, 2003). Cell death occurs through an apoptosis process associated with aging, genetic propensity, and spinal loading (Lotz and Chin, 2000; Hunter et al., 2003; Livshits et al., 2011; Hirata et al., 2014; Yurube et al., 2014). The decrease of extracellular matrix synthesis and increase of extracellular matrix degeneration are associated with loss of cells and phenotype changes in the surviving cells secondary to local inflammatory responses (Trout et al., 1982; Urban and Roberts, 2003). As a result, the condition presents with dehydration of the nucleus pulposus, fissures of the annulus fibrosus, extrusion of the NP, and a cascade of inflammatory responses that perpetuate the cycle of loss of appropriate matrix (Urban and Roberts, 2003; Gilbert et al., 2013). Micro-environmental changes including neovascularization and nerve growth lead to clinical presentations of pain and altered biomechanical function (Adams et al., 1996; Freemont et al., 1997; Johnson et al., 2002; Chan et al., 2008; Purmessur et al., 2008; Hughes et al., 2012; Richardson et al., 2012).

The treatment of discogenic pain has been particularly challenging due to the irreversible loss of intervertebral disc cells. Current treatment modalities include pain medication (Koes et al., 1997; Van Tulder et al., 2000; Roelofs et al., 2008), therapies (Van Middelkoop et al., 2011; Jang and Lee, 2012), injections (Staal et al., 2009; Lu et al., 2014), nucleoplasty (Welch and Gerszten, 2002; Mirzai et al., 2007; Adam et al., 2013) and surgical discectomy (McCulloch, 1996; Soliman et al., 2014). None addresses the IVD degeneration. Because the extracellular matrix is synthesized and modulated by IVD cells, there has been significant interest in researching cell therapy utilizing stem cells and mesenchymal stem cells for the regeneration of the IVD (Trout et al., 1982; Kalson et al., 2008; Richardson et al., 2008; Henriksson et al., 2009; Benneker et al., 2014).

Multiple pre-clinical randomized controlled animal trials have been performed, but often suffered with small sample size, heterogeneous designs, and conflicting outcomes. Since a consensus on the effect of stem cell transplantation in animals is needed to justify human clinical trials, we conducted a systematic review and a meta-analysis. Specifically, the objective of this study was to evaluate intervertebral disc regeneration due to stem cell transplantation in controlled animal trials. Objective outcomes of disc regeneration included: changes in disc height, nucleus pulposus rehydration on T2 weighted MRI images, histologic disc degeneration grade, and expression of type II collagen regeneration.

2. Methods

The study protocol was finalized in advance of any data collection, which defined objectives, search strategy, inclusion/exclusion criteria, data extraction, outcomes of interest, and analytical approaches. The reporting of this systematic review complies with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement (Moher et al., 2009).

2.1. Search strategy

We conducted a comprehensive search of seven databases, including Ovid Medline In-Process & Other Non-Indexed Citations, Ovid MEDLINE, Ovid EMBASE, Ovid PsycINFO, Ovid Cochrane Central Register of Controlled Trials, Ovid Cochrane Database of Systematic Reviews, and Scopus, from each database's inception to Week 3, 2015. Controlled vocabulary supplemented with keywords was used to search for studies of intervertebral disc height after stem cell transplantation. Search terms were broad and without language or country restrictions. The detailed strategy is available in Appendix 1.

2.2. Inclusion and exclusion criteria

We included pre-clinical controlled trials (randomized controlled trials (RCTs), and non-randomized controlled trials (N-RCTs)) that evaluated stem cell transplantation on experimental regeneration of the intervertebral disc in animals. We focused on the outcomes that were pertinent to the effect and mechanism in IVD regeneration (disc height index, MRI T2 signal intensity, Type II collagen expression, and histologic disc degeneration grade). Animals with any type of model in IVD degeneration secondary to IVD trauma by changing mechanical loading, puncture incision or gamma irradiation, or chemical assault with chemonucleolysis by chondroitinase ABC, chymopapain or fibronectin fragments were included regardless of species/breeds of animal. We did not restrict the type of intervention in control groups. Studies were excluded if they combined multiple treatments (e.g., stem cells and Rho-GTPase inhibitory agents) or if models of nontraumatic spinal cord injury were used. We also excluded studies without original data (e.g., clinical reviews, editorials, letters, or erratum) or without the outcomes of interest.

2.3. Data extraction

Two independent reviewers reviewed the abstracts and full texts of potentially relevant studies. Discrepancies between the reviewers were resolved through discussion and consensus. The same two reviewers extracted study details from the full text studies using a standardized pilot-tested form. The following data were extracted: the author, year of publication, animal species, disc degeneration model (traumatic or chemical), cell type, interventions in control groups, and outcomes of interest. When outcomes of interest were assessed serially, we extracted data for the final time point. Where multiple arms were included in the study, the control group and the stem cell transplantation group were selected.

2.4. Quality assessment

We applied the Collaborative Approach to Meta-Analysis and Review of Animal Data from Experimental Studies (CAMARADES) checklist to assess the methodological quality of the included studies (Sena et al., 2007). A 9-point-item check list was used to assess the risk for bias, including: (1) published in a peer-reviewed journal; (2) control of animals' temperature; (3) randomized treatment allocation; (4) treatment allocation concealment; (5) blinded assessment of outcome; (6) use of anesthetics other than ketamine; (7) reporting of a sample size calculation; (8) statement of compliance with regulatory requirements; and (9) statement of potential conflict of interest.

2.5. Statistical analysis

We calculated standardized mean difference (SMD) and related 95% confidence interval (CI) for each study using Cohen's d method to normalize for the different animal species. We then combined outcomes of interest across the included studies using the DerSimonian and Laird random effect methods. The heterogeneity was estimated using the Mantel–Haenszel model. We conducted subgroup analyses based on animal species (rabbit, dog, rat, pig, and sheep), study designs, and cell types (bone marrow stromal cells (BMSCs), and adipose-derived stem cells (ADMSCs)) to investigate potential sources of heterogeneity and the robustness of our findings. Heterogeneity across individual studies was assessed using the I^2 index and Cochran's Q statistical test, where $I^2 > 50\%$ and/or $p < 0.10$ suggest high heterogeneity. All meta-analyses were conducted using STATA version 13.1 (StataCorp, College Station, TX).

3. Results

3.1. Study characteristics

We identified 642 unique citations, of which 566 were excluded by title/abstract screening (Fig. 1). 22 studies were included in this review, including 9 (40.91%) RCTs and 13 (59.09%) N-RCTs. Animals used for studies included rabbits in 11 studies (50.00%), rats/mice in 6 (27.27%), dogs in 3 (13.64%), pigs in 1 (4.55%), and sheep in 1 (4.55%) (Table 1). Overall, 626 discs were studied, of which 313 were transplanted with stem cells and 313 were controls. The types of transplanted cell used in the studies included 18 BMSCs (81.82%), and 4 ADMSCs (18.18%). Mean maximal follow-up time was 16.79 weeks after transplantation (range: 5–56 weeks).

3.2. Risk of bias

Risk of bias of the included studies was high to moderate (Fig. 2). Most of the included studies did not report sufficient information to assess overall quality. Though all studies were peer-reviewed, 13 studies did not use randomization and no study reported methods of treatment concealment. Of the included studies, 44.44% reported compliance with regulatory requirements and 36.11% provided a statement on conflict of interest. Assessment of publication bias was not conducted due to the limited number of studies included in analysis and high heterogeneity ($I^2 > 50\%$) in all analyses (Serigano et al., 2010).

3.3. Outcomes

We identified 13 studies for the meta-analysis on disc height index (Fig. 3). We found that disc height index in the stem cell transplantation group was significantly higher than the control group (SMD = 3.64, 95% CI: 2.49, 4.78, $p < 0.001$, $I^2 = 91.3\%$). There were 14 studies that reported MRI T2 signal intensity outcomes (Table 2). A significant increase of MRI T2 signal intensity was found in the stem cell transplantation group compared with the control (SMD = 2.28, 95% CI: 1.48, 3.08, $p < 0.001$, $I^2 = 88.5\%$). 11 studies of stem cell transplantation were also found to significantly reduce histologic disc degeneration grade compared to the control group (SMD = −2.97, 95% CI: −3.97, −1.97, $p < 0.001$, $I^2 = 80.1\%$). Moreover, increased expression of type II collagen was identified in 9 studies (SMD = 3.68, 95% CI: 1.66, 5.70, $p < 0.001$, $I^2 = 95.8\%$).

3.4. Subgroup analysis

We conducted subgroup analyses based on animal species, cell types, and study design. We found no significant changes between subgroups and our main analysis in all, except one, of the subgroup analyses

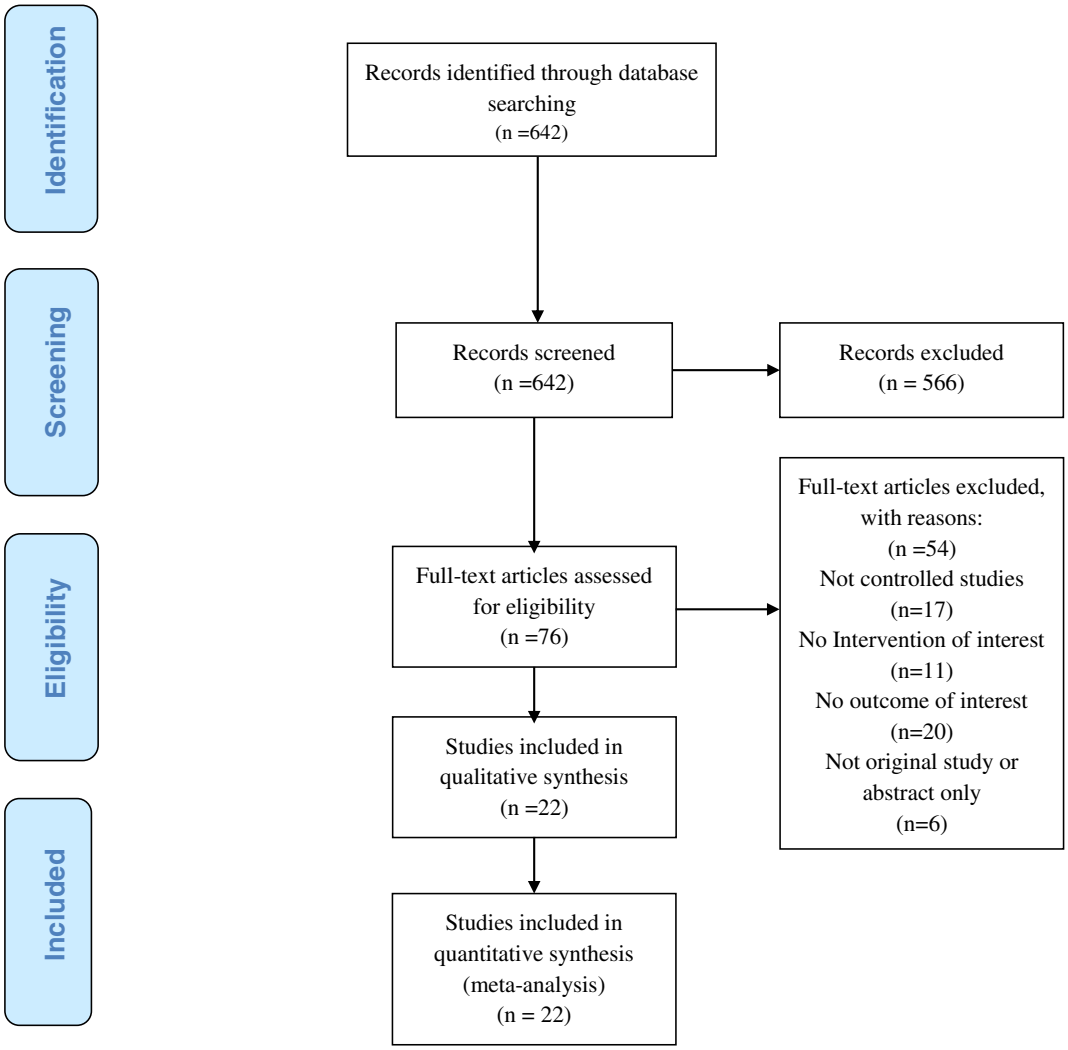

Fig. 1. Flow diagram sketches the current system review identified, screened, included and excluded in meta-analysis.

Table 1
Characteristics of the included studies.

Author	Year	Country	Animal	Disc degeneration model	Study design	Types of cell	Follow-up (weeks)
Allon et al. (2010)	2010	USA	Rat	Partial nucleotomy	N-RCT	BMSC	5
Chen et al. (2012)	2012	China	Rabbit	Needle puncture	N-RCT	ADMSC	2
Liang et al. (2013)	2013	China	Rat	Needle puncture	RCT	ADMSC	24
Wu et al. (2011)	2011	China	Rabbit	Nucleus pulposus aspiration	RCT	BMSC	10
Yang et al. (2009)	2009	China	Mouse	Needle puncture	N-RCT	BMSC	24
Zhang et al. (2007)	2007	China	Rabbit	No	RCT	BMSC	24
Zhang et al. (2005)	2005	China	Rabbit	No	RCT	BMSC	24
Zhao et al. (2008)	2008	China	Rabbit	Needle puncture	RCT	BMSC	12
Feng et al. (2011b)	2011	China	Rabbit	Nucleus pulposus aspiration	N-RCT	BMSC	16
Ganey et al. (2009)	2009	USA	Dog	Partial nucleotomy	RCT	ADMSC	48
Ghosh et al. (2012)	2012	Australia	Sheep	Chondroitinase induction	N-RCT	BMSC	24
Hiyama et al. (2008)	2008	Japan	Dog	Nucleus pulposus aspiration	N-RCT	BMSC	8
Ho et al. (2008)	2008	Hong Kong	Rabbit	Needle puncture	N-RCT	BMSC	28
Jeong et al. (2009)	2009	Korea	Rat	Blade injury	N-RCT	BMSC	8
Jeong et al. (2009)	2010	Korea	Rat	Needle puncture	N-RCT	ADMSC	6
Jiang et al. (2011)	2011	China	Rabbit	Needle puncture	N-RCT	ADMSC	8
Sakai et al. (2006)	2006	Japan	Rabbit	Nucleus pulposus aspiration	N-RCT	BMSC	24
Serigano et al. (2010)	2010	Japan	Dog	Nucleus pulposus aspiration	N-RCT	BMSC	12
Wu et al. (2007)	2007	China	Rat	Chondroitinase induction	N-RCT	BMSC	2
Yang et al. (2010)	2010	USA	Rabbit	Nucleus pulposus aspiration	RCT	BMSC	12
Subhan et al. (2014)	2014	Malaysia	Rabbit	Needle puncture	RCT	BMSC	16
Cai et al. (2015)	2015	China	Rabbit	Needle puncture	RCT	BMSC	10

Note: BMSC, bone marrow stromal cell; ADMSC, adipose-derived mesenchymal stem cell; RCT, randomized controlled trial; N-RCT, non-randomized controlled trial.

(Tables 3, 4, 5). One study reported disc height index in sheep and found a significant reduction of disc height index in the treated group (SMD = −2.75, 95% CI: −4.40, −1.09) (Ghosh et al., 2012). However, other studies reported significant increases in disc space height in dog, pig, rabbit, and rat models.

4. Discussion

We conducted a systematic review and meta-analysis to evaluate intervertebral disc regeneration with stem cells in animal controlled trials. Twenty two studies were included in the analysis. Stem cell transplantation was associated with significantly increased disc height index, T2 weighted MRI signal intensity, type II collagen expression, and significantly reduced histologic disc degenerative grade.

The degenerative IVD is the result of a series of changes in metabolism, biomechanics and morphology. The degeneration processes are closely related to cell loss, extracellular matrix (ECM) breakdown with collagen fiber denaturation and degradation, decreased disc osmotic pressure with dehydration and cleft formation, anabolic and catabolic unbalance with increased inflammatory cytokines and infiltrated immune cells, and neovascularization and nociceptive nerve ingrowth (Trout et al., 1982; Adams et al., 1996; Urban and Roberts, 2003; Zhang et al., 2005; Hughes et al., 2012; Gilbert et al., 2013). Since Pittenger et al. first demonstrated that the MSCs isolated from bone marrow possessed the potential of the multi-lineage differentiation (Pittenger et al., 1999), stem cells have been successfully distinguished and derived from many adult tissues, such as adipose, muscle, dermis, synovial membrane, synovial fluid, and cartilage (Barry and Murphy, 2004; Richardson et al., 2010). In this meta-analysis, the studies explored the strategy of cell-based IVD regeneration by means of stem cell transplantation in different animal models. It is noteworthy that these regeneration processes after stem cell transplantation seem to

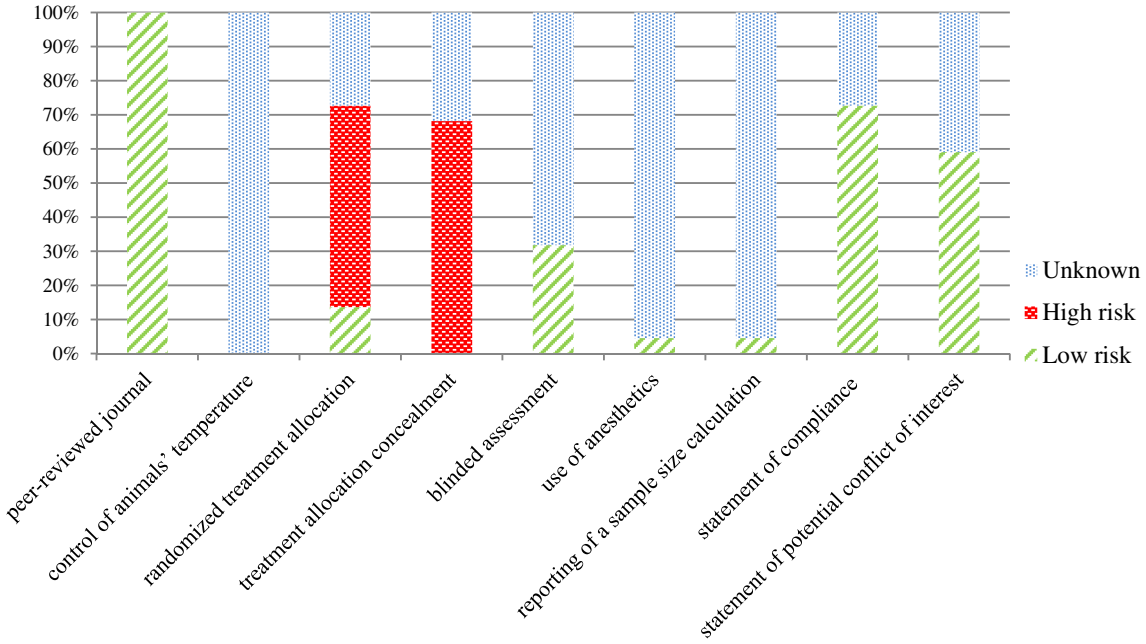

Fig. 2. Risk of bias of the included studies.

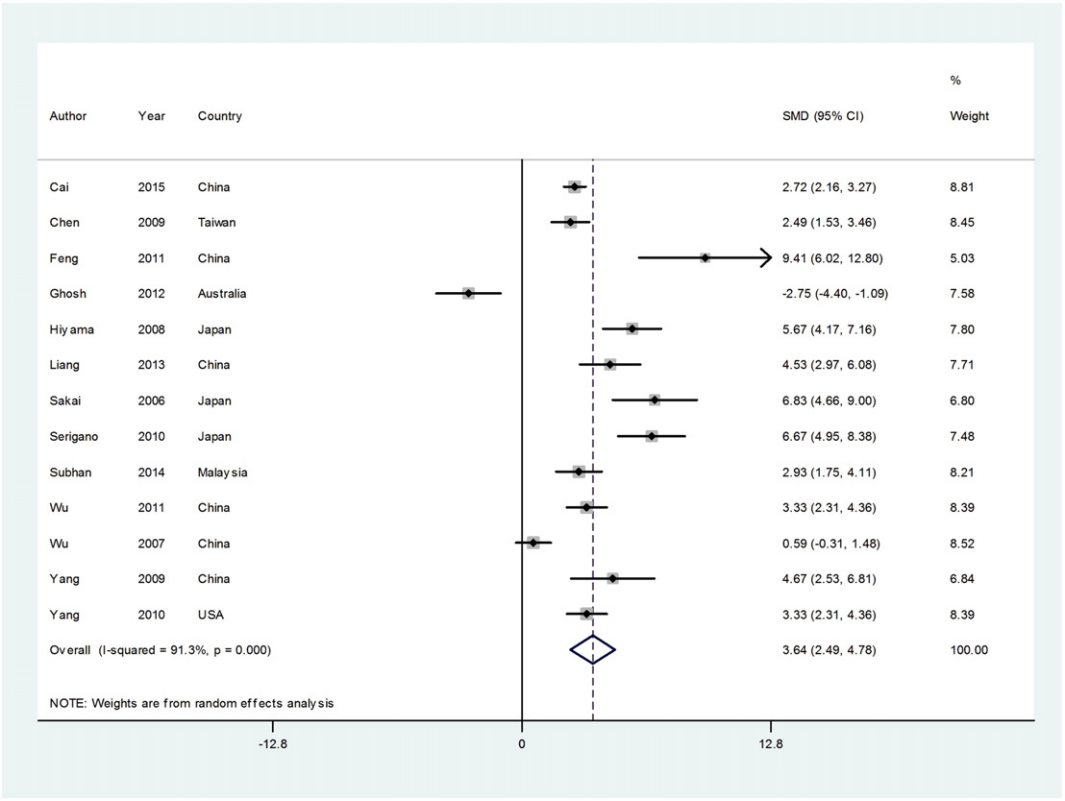

Fig. 3. Forest plot shows the effect of stem cell transplantation on disc height index. The solid squares denote standardized mean difference, the horizontal lines represent the 95% confidence interval (CI), and the diamond denotes the DerSimion Laird (DL) weighted mean differences.

be closely connected to a cascade of changes and can be expressed as follows: enhanced intra-discal cell phenotype induction (Pittenger et al., 1999; Zhang et al., 2007; Richardson et al., 2008; Gilbert et al., 2013; Hirata et al., 2014; Yurube et al., 2014), increased gene and protein expression of type II collagen (Zhang et al., 2005, 2007; Sakai et al., 2006; Yang et al., 2010; Feng et al., 2011a), restored intra-discal hydration (Zhao et al., 2008; Jeong et al., 2009, 2010; Feng et al., 2011a; Jiang et al., 2011; Wu et al., 2011; Liang et al., 2013), ameliorated ongoing disc degeneration processes (Sakai et al., 2006; Ho et al., 2008; Jeong et al., 2009; Yang et al., 2009; Allon et al., 2010; Feng et al., 2011a; Liang et al., 2013), and prevention of loss of disc height (Sakai et al., 2006; Wu et al., 2007, 2011; Yang et al., 2009, 2010; Liang et al., 2013).

Moreover, our study also sheds light on the mechanism of disc regeneration with stem cell transplantation. Stem cells have been known to maintain a regenerative capacity and have the ability to decelerate or arrest the degenerative processes by means of differentiating towards NP-like cells. It is hypothesized that the regeneration effect are the results of processes involving the production of intra-discal matrix by induced stem cells in vivo, stimulation of the progenitor cells of the disc by the trophic factors released by the stem cells, and decreased inflammatory response as a response to immunomodulating cytokines released by stem cells (Barry and Murphy, 2004; Richardson et al., 2010; Schmitt et al., 2012; Gilbert et al., 2013).

4.1. Clinical implications

The meta-analysis suggests that stem cells halt the degeneration processes in IVD and promote IVD regeneration in animal studies. It was hypothesized that those changes are attributed to the trophic, immunomodulating, and matrix producing the ability of the stem cells induced by the local environment after transplantation. Those findings provide a foundation for testing the effect of stem cells in human studies. Currently, a few closed or active clinical trials are listed in ClinicalTrials.gov. Three currently active trials are open label trials. One closed phase 2 clinical trial has not been reported in literature yet. There are more trials being planned for treatment of degenerative disc conditions with stem cells. Whether or not the benefit observed in animal studies could be translated to humans would depend on the outcomes of future trials.

4.2. Future works

Despite the encouraging results of this meta-analysis on the use of stem cells in IVD degeneration, for cell-based regenerative medicine to play a critical role in clinical treatment of discogenic pain, further research is required. Important research includes identification of appropriate transcriptional factors for induction of the MSCs towards nucleus pulposus-like cells, genome modification of the MSCs for

Table 2
The effects of stem cell transplantation on intervertebral disc degeneration.

Outcomes	Number of studies	SMD	95% CI	p value	I^2	Heterogeneity p value
Disc height Index	13	3.64	2.49, 4.78	<0.001	91.3%	<0.001
MRI T2 signal	14	2.28	1.48, 3.08	<0.001	88.5%	<0.001
Histologic disc degenerative grade	11	−2.97	−3.97, −1.97	<0.001	80.1%	<0.001
Type II collagen expression	9	3.68	1.66, 5.70	<0.001	95.8%	<0.001

Note: SMD, standardized mean difference; 95% CI, 95% confidence interval.

Table 3
Subgroup analysis based on animal species.

Outcome	Number of studies	SMD	95% CI	p value	I^2
Disc height Index					
Dog	2	6.10	4.97, 7.23	<0.001	0.0%
Pig	1	2.50	1.53, 3.46	<0.001	n/a
Rabbit	6	4.01	2.89, 5.14	<0.001	81.4%
Rat	3	3.17	0.13, 6.21	0.04	92.2%
Sheep	1	−2.75	−4.40, −1.09	0.001	n/a
MRI T2 signal					
Dog	2	2.48	0.92, 4.03	0.002	83.1%
Rabbit	8	2.42	1.11, 3.73	<0.001	92.9%
Rat	3	2.05	1.03, 3.06	<0.001	51.3%
Sheep	1	2.53	0.95, 4.11	0.002	n/a
Histologic disc degenerative grade					
Dog	2	−3.88	−6.98, −0.77	0.01	88.6%
Rabbit	4	−2.41	−3.15, −1.67	<0.001	10.7%
Rat	4	−3.61	−5.79, −1.42	0.001	84.7%
Sheep	1	−0.75	−1.93, 0.43	0.21	n/a
Type II collagen expression					
Dog	1	2.41	0.86, 3.95	0.002	n/a
Pig	1	5.67	4.02, 7.31	<0.001	n/a
Rabbit	5	3.38	0.37, 6.39	0.03	97.2%
Rat	2	4.26	−0.94, 9.45	0.11	94.4%

Note: SMD, standardized mean difference; 95% CI, 95% confidence interval.

potentiating matrix and trophic factor productions, and stimulation of the MSCs for enhanced immunomodulation activities. This requires better understanding of the genome composition and phenotypical expression of MSCs as well as the nucleus pulposus-like cells. In addition, human clinical trials will be needed to understand if the benefit identified in animal models can be translated to bipedal humans.

4.3. Limitations

Our study suffers several important limitations. First, all of the included studies were quadrupedal animal studies in which the largely non-weight bearing spine may provide a more forgiving environment for the stem cells to survive and function. Second, substantial heterogeneity was observed across the studies in all of the outcomes ($I^2 > 50\%$). We were unable to evaluate potential publication bias due to high heterogeneity and the limited number of studies included. Publication bias is quite likely in animal studies.

Nevertheless, our study has several strengths. We conducted a comprehensive search of multiple databases, selected and appraised studies by independent pairs of reviewers, and followed a priori planned protocol that included several hypotheses for subgroup analysis. Almost all of the included studies show significant benefits across different animal species, cell types and study designs. Therefore, our results provide justification for further evaluation of stem cell transplantation in human trials.

Table 4
Subgroup analysis based on cell type.

Outcome	Number of studies	SMD	95% CI	p value	I^2
Disc height index					
ADMSC	1	4.53	2.97, 6.08	<0.001	n/a
BMSC	12	3.57	2.36, 4.77	<0.001	91.8%
MRI T2 signal					
ADMSC	3	1.82	0.64, 3.00	0.01	71.2%
BMSC	11	2.45	1.46, 3.45	<0.001	90.6%
Histologic disc degenerative grade					
ADMSC	1	−3.62	−4.96, −2.29	<0.001	n/a
BMSC	10	−2.90	−4.00, −1.81	<0.001	81.3%
Type II collagen expression					
ADMSC	2	4.63	0.13, 9.13	0.04	91.0%
BMSC	7	3.42	1.11, 5.73	<0.001	96.4%

Note: SMD, standardized mean difference; 95% CI, 95% confidence interval; BMSC, bone marrow stromal cell; ADMSC, adipose-derived mesenchymal stem cell.

Table 5
Subgroup analysis based on study design.

Outcome	Number of studies	SMD	95% CI	p value	I^2
Disc height Index					
N-RCT	8	4.03	1.72, 6.35	0.001	94.7%
RCT	5	3.14	2.64, 3.65	<0.001	26.5%
MRI T2 signal					
N-RCT	8	2.19	1.40, 2.97	<0.001	66.5%
RCT	6	2.36	0.93, 3.79	0.001	94.4%
Histologic disc degenerative grade					
N-RCT	9	−3.01	−4.29, −1.72	<0.001	83.2%
RCT	2	−2.86	−4.22, −1.49	<0.001	61.9%
Collagen II (mRNA)					
N-RCT	4	3.26	0.98, 5.54	0.01	92.2%
RCT	5	4.12	0.47, 7.77	0.03	97.3%

Note: SMD, standardized mean difference; 95% CI, 95% confidence interval; RCT, randomized controlled trial; N-RCT, non-randomized controlled trial.

5. Conclusion

Stem cells transplanted to the IVD in animals decelerate and arrest the IVD degenerative process. Further studies in human clinical trials will be needed to advance our knowledge of the benefit.

Competing interests

The authors have declared that no competing interest exists.

Acknowledgments

None.

Appendix A. Supplementary data

Supplementary data to this article can be found online at http://dx.doi.org/10.1016/j.gene.2015.03.022.

References

Adam, D., Pevzner, E., Gepstein, R., 2013. Comparison of percutaneous nucleoplasty and open discectomy in patients with lumbar disc protrusions. Chirurgia (Rom.) 108, 94–98.
Adams, M.A., McNally, D.S., Dolan, P., 1996. 'Stress' distributions inside intervertebral discs. The effects of age and degeneration. J. Bone Joint Surg Ser. B 78, 965–972.
Allon, A.A., Aurouer, N., Yoo, B., Liebenberg, E., Buser, Z., Lotz, J.C., 2010. Structured coculture of stem cells and disc cells prevent degeneration in a rat model. Spine. Conference: 38th Annual Meeting of the Cervical Spine Research Society. CSRS (20101202).
Barry, F.P., Murphy, J.M., 2004. Mesenchymal stem cells: clinical applications and biological characterization. Int. J. Biochem. Cell Biol. 36, 568–584.
Benneker, L.M., Andersson, G., Iatridis, J.C., Sakai, D., Härtl, R., Ito, K., Grad, S., 2014. Cell therapy for intervertebral disc repair: advancing cell therapy from bench to clinics. Eur. Cells Mater. 27, 5–11.
Bogduk, N., 2012. Degenerative Joint Disease of the Spine. Radiol Clin North Am. 50 (4), 613–628.
Cai, F., Wu, X.-T., Xie, X.-H., Wang, F., Hong, X., Zhuang, S.-Y., Zhu, L., Rui, Y.-F., Shi, R., 2015. Evaluation of intervertebral disc regeneration with implantation of bone marrow mesenchymal stem cells (BMSCs) using quantitative T2 mapping: a study in rabbits. Int. Orthop. 39, 149–159.
Chan, C.C.M., Roberts, C.R., Steeves, J.D., Tetzlaff, W., 2008. Aggrecan components differentially modulate nerve growth factor-responsive and neurotrophin-3-responsive dorsal root ganglion neurite growth. J. Neurosci. Res. 86, 581–592.
Chen, J.Y., Jiang, X.H., Cai, Z.X., Zhang, Y., Liu, Z.Z., Liang, B.L., 2012. Magnetic labeled adipose derived stem cells for repair of rabbit degenerated intervertebral disc. Chin. J. Interv. Imaging Ther. 9, 41–45.
DePalma, M.J., Ketchum, J.M., Saullo, T., 2011. What is the source of low back pain and does age play a role? Pain Med. 12 (2), 224–233.
Feng, G., Liu, H., Zhang, H., Chen, X., Shi, R., Liu, X., Zhao, X., Zhang, W., Wang, B., 2011a. Transplantation of mesenchymal stem cells and nucleus pulposus cells in a

degenerative disc model in rabbits: a comparison of 2 cell types as potential candidates for disc regeneration. Laboratory investigation. J. Neurosurg. Spine 14 (3), 322–329.
Feng, G., Zhao, X., Liu, H., Zhang, H., Chen, X., Shi, R., Liu, X., Zhao, X., Zhang, W., Wang, B., 2011b. Transplantation of mesenchymal stem cells and nucleus pulposus cells in a degenerative disc model in rabbits: a comparison of 2 cell types as potential candidates for disc regeneration. J. Neurosurg. Spine 14, 322–329.
Freemont, A.J., Peacock, T.E., Goupille, P., Hoyland, J.A., O'Brien, J., Jayson, M.I.V., 1997. Nerve ingrowth into diseased intervertebral disc in chronic back pain. Lancet 350, 178–181.
Ganey, T., Hutton, W.C., Moseley, T., Hedrick, M., Meisel, H.-J., 2009. Intervertebral disc repair using adipose tissue-derived stem and regenerative cells: experiments in a canine model. Spine 34, 2297–2304.
Ghosh, P., Moore, R., Vernon-Roberts, B., Goldschlager, T., Pascoe, D., Zannettino, A., Gronthos, S., Itescu, S., 2012. Immunoselected STRO-3 + mesenchymal precursor cells and restoration of the extracellular matrix of degenerate intervertebral discs. J. Neurosurg. Spine 16, 479–488.
Gilbert, H.T.J., Hoyland, J.A., Richardson, S.M., 2013. Stem cell regeneration of degenerated intervertebral discs: current status (Update). Curr. Pain Headache Rep. 17.
Henriksson, H.B., Svanvik, T., Jonsson, M., Hagman, M., Horn, M., Lindahl, A., Brisby, H., 2009. Transplantation of human mesenchymal stems cells into intervertebral discs in a xenogeneic porcine model. Spine 34, 141–148.
Hirata, H., Yurube, T., Kakutani, K., Maeno, K., Takada, T., Yamamoto, J., Kurakawa, T., Akisue, T., Kuroda, R., Kurosaka, M., Nishida, K., 2014. A rat tail temporary static compression model reproduces different stages of intervertebral disc degeneration with decreased notochordal cell phenotype. J. Orthop. Res. 32, 455–463.
Hiyama, A., Mochida, J., Iwashina, T., Omi, H., Watanabe, T., Serigano, K., Tamura, F., Sakai, D., 2008. Transplantation of mesenchymal stem cells in a canine disc degeneration model. J. Orthop. Res. Off. Publ. Orthop. Res. Soc. 26, 589–600.
Ho, G., Leung, V.Y., Cheung, K.M., Chan, D., 2008. Effect of severity of intervertebral disc injury on mesenchymal stem cell-based regeneration. Connect. Tissue Res. 49, 15–21.
Hoy, D., Bain, C., Williams, G., March, L., Brooks, P., Blyth, F., Woolf, A., Vos, T., Buchbinder, R., 2012. A systematic review of the global prevalence of low back pain. Arthritis Rheum. 64, 2028–2037.
Hoy, D., March, L., Woolf, A., Blyth, F., Brooks, P., Smith, E., Vos, T., Jan, B., Blore, J., Murray, C., Burstein, R., Buchbinder, R., 2014. The global burden of neck pain: estimates from the global burden of disease 2010 study. Ann. Rheum. Dis. 73, 1309–1315.
Hughes, S.P.F., Freemont, A.J., Hukins, D.W.L., McGregor, A.H., Roberts, S., 2012. The pathogenesis of degeneration of the intervertebral disc and emerging therapies in the management of back pain. J. Bone Joint Surg Ser. B 94 (B), 1298–1304.
Hunter, C.J., Matyas, J.R., Duncan, N.A., 2003. The notochordal cell in the nucleus pulposus: a review in the context of tissue engineering. Tissue Eng. 9, 667–677.
Jang, H., Lee, H., 2012. Meta-analysis of pain relief effects by laser irradiation on joint areas. Photomed. Laser Surg. 30, 405–417.
Jeong, J.H., Jin, E.S., Min, J.K., Jeon, S.R., Park, C.-S., Kim, H.S., Choi, K.H., 2009. Human mesenchymal stem cells implantation into the degenerated coccygeal disc of the rat. Cytotechnology 59, 55–64.
Jeong, J.H., Lee, J.H., Jin, E.S., Min, J.K., Jeon, S.R., Choi, K.H., 2010. Regeneration of intervertebral discs in a rat disc degeneration model by implanted adipose-tissue-derived stromal cells. Acta Neurochir. 152, 1771–1777.
Jiang, X.h., Chen, J.y., Cai, Z.x., Ya, Z., Liu, Z.z., Xie, C.m., Wu, Y.p., Wu, P.h., 2011. In vivo tracking superparamagnetic iron oxide labeled adipose derived stem cells to repair rabbit degenerated intervertebral disc. J. Clin. Rehabil. Tissue Eng. Res. 15 (40), 7515–7519.
Johnson, W.E.B., Caterson, B., Eisenstein, S.M., Hynds, D.L., Snow, D.M., Roberts, S., 2002. Human intervertebral disc aggrecan inhibits nerve growth in vitro. Arthritis Rheum. 46, 2658–2664.
Kalson, N.S., Richardson, S., Hoyland, J.A., 2008. Strategies for regeneration of the intervertebral disc. Regen. Med. 3, 715–729.
Koes, B.W., Scholten, R.J.P.M., Mens, J.M.A., Bouter, L.M., 1997. Efficacy of non-steroidal anti-inflammatory drugs for low back pain: a systematic review of randomised clinical trials. Ann. Rheum. Dis. 56, 214–223.
Liang, C.Z., Li, H., Tao, Y.Q., Peng, L.H., Gao, J.Q., Wu, J.J., Li, F.C., Hua, J.M., Chen, Q.X., 2013. Dual release of dexamethasone and TGF-β3 from polymeric microspheres for stem cell matrix accumulation in a rat disc degeneration model. Acta Biomater. 9, 9423–9433.
Livshits, G., Popham, M., Malkin, I., Sambrook, P.N., MacGregor, A.J., Spector, T., Williams, F.M.K., 2011. Lumbar disc degeneration and genetic factors are the main risk factors for low back pain in women: the UK Twin Spine Study. Ann. Rheum. Dis. 70, 1740–1745.
Lotz, J.C., Chin, J.R., 2000. Intervertebral disc cell death is dependent on the magnitude and duration of spinal loading. Spine 25, 1477–1483.
Lu, Y., Guzman, J.Z., Purmessur, D., Iatridis, J.C., Hecht, A.C., Qureshi, S.A., Cho, S.K., 2014. Nonoperative management of discogenic back pain: a systematic review. Spine 39, 1314–1324.
Manchikanti, L., Singh, V., Datta, S., Cohen, S.P., Hirsch, J.A., 2009. Comprehensive review of epidemiology, scope, and impact of spinal pain. Pain Physician 12, E35–E70.
Martin, B.I., Deyo, R.A., Mirza, S.K., Turner, J.A., Comstock, B.A., Hollingworth, W., Sullivan, S.D., 2008. Expenditures and health status among adults with back and neck problems. JAMA J. Am. Med. Assoc. 299, 656–664.
McCulloch, J.A., 1996. Focus issue on lumbar disc herniation: macro- and microdiscectomy. Spine 21, 45S–56S.
Mirzai, H., Tekin, I., Yaman, O., Bursali, A., 2007. The results of nucleoplasty in patients with lumbar herniated disc: a prospective clinical study of 52 consecutive patients. Spine J. 7, 88–92.
Moher, D., Liberati, A., Tetzlaff, J., Altman, D.G., 2009. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. BMJ 339, b2535.
Murray, C.J.L., Abraham, J., Ali, M.K., Alvarado, M., Atkinson, C., Baddour, L.M., Bartels, D.H., Benjamin, E.J., Bhalla, K., Birbeck, G., Bolliger, I., Burstein, R., Carnahan, E., Chen, H., Chou, D., Chugh, S.S., Cohen, A., Colson, K.E., Cooper, L.T., Couser, W., Criqui, M.H., Dabhadkar, K.C., Dahodwala, N., Danaei, G., Dellavalle, R.P., Des Jarlais, D.C., Dicker, D., Ding, E.L., Dorsey, E.R., Duber, H., Ebel, B.E., Engell, R.E., Ezzati, M., Felson, D.T., Finucane, M.M., Flaxman, S., Flaxman, A.D., Fleming, T., Forouzanfar, M.H., Freedman, G., Freeman, M.K., Gabriel, S.E., Gakidou, E., Gillum, R.F., Gonzalez-Medina, D., Gosselin, R., Grant, B., Gutierrez, H.R., Hagan, H., Havmoeller, R., Hoffman, H., Jacobsen, K.H., James, S.L., Jasrasaria, R., Jayaraman, S., Johns, N., Kassebaum, N., Khatibzadeh, S., Knowlton, L.M., Lan, Q., Leasher, J.L., Lim, S., Lin, J.K., Lipshultz, S.E., London, S., Lozano, R., Lu, Y., MacIntyre, M.F., Mallinger, L., McDermott, M.M., Meltzer, M., Mensah, G.A., Michaud, C., Miller, T.R., Mock, C., Moffitt, T.E., Mokdad, A.A., Mokdad, A.H., Moran, A.E., Mozaffarian, D., Murphy, T., Naghavi, M., Narayan, K.M.V., Nelson, R.G., Olives, C., Omer, S.B., Ortblad, K., Ostro, B., Pelizzari, P.M., Phillips, D., Pope Iii, C.A., Raju, M., Ranganathan, D., Razavi, H., Ritz, B., Rivara, F.P., Roberts, T., Sacco, R.L., Salomon, J.A., Sampson, U., et al., 2013. The State of US health, 1990–2010: burden of diseases, injuries, and risk factors. JAMA J. Am. Med. Assoc. 310, 591–608.
Peterson, J.C., Smith, K.A., Khan, T., Arnold, P.M., 2013. The interdisciplinary management of spinal disorders: a review of outcomes. Tech. Reg. Anesth. Pain Manag. 17 (4), 157–162.
Pittenger, M.F., Mackay, A.M., Beck, S.C., Jaiswal, R.K., Douglas, R., Mosca, J.D., Moorman, M.A., Simonetti, D.W., Craig, S., Marshak, D.R., 1999. Multilineage potential of adult human mesenchymal stem cells. Science 284, 143–147.
Purmessur, D., Freemont, A.J., Hoyland, J.A., 2008. Expression and regulation of neurotrophins in the nondegenerate and degenerate human intervertebral disc. Arthritis Res. Ther. 10.
Richardson, S.M., Hughes, N., Hunt, J.A., Freemont, A.J., Hoyland, J.A., 2008. Human mesenchymal stem cell differentiation to NP-like cells in chitosan-glycerophosphate hydrogels. Biomaterials 29, 85–93.
Richardson, S.M., Hoyland, J.A., Mobasheri, R., Csaki, C., Shakibaei, M., Mobasheri, A., 2010. Mesenchymal stem cells in regenerative medicine: opportunities and challenges for articular cartilage and intervertebral disc tissue engineering. J. Cell. Physiol. 222, 23–32.
Richardson, S.M., Purmessur, D., Baird, P., Probyn, B., Freemont, A.J., Hoyland, J.A., 2012. Degenerate human nucleus pulposus cells promote neurite outgrowth in neural cells. PLoS ONE 7.
Roelofs, P.D.D.M., Deyo, R.A., Koes, B.W., Scholten, R.J.P.M., Van Tulder, M.W., 2008. Non-steroidal anti-inflammatory drugs for low back pain: an updated cochrane review. Spine 33, 1766–1774.
Rogers, M.T., 2003. Development of interdisciplinary spinal interventional pain centers. Pain Physician 6, 527–535.
Sakai, D., Mochida, J., Iwashina, T., Hiyama, A., Omi, H., Imai, M., Nakai, T., Ando, K., Hotta, T., 2006. Regenerative effects of transplanting mesenchymal stem cells embedded in atelocollagen to the degenerated intervertebral disc. Biomaterials 27, 335–345.
Schmitt, A., van Griensven, M., Imhoff, A.B., Buchmann, S., 2012. Application of stem cells in orthopedics. Stem Cells Int. 2012, 394962.
Sena, E., van der Worp, H.B., Howells, D., Macleod, M., 2007. How can we improve the preclinical development of drugs for stroke? Trends Neurosci. 30, 433–439.
Serigano, K., Sakai, D., Hiyama, A., Tamura, F., Tanaka, M., Mochida, J., 2010. Effect of cell number on mesenchymal stem cell transplantation in a canine disc degeneration model. J. Orthop. Res. Off. Publ. Orthop. Res. Soc. 28, 1267–1275.
Soliman, J., Harvey, A., Howes, G., Seibly, J., Dossey, J., Nardone, E., 2014. Limited microdiscectomy for lumbar disk herniation: a retrospective long-term outcome analysis. J. Spinal Disord. Tech. 27, E8–E13.
Staal, J.B., De Bie, R.A., De Vet, H.C.W., Hildebrandt, J., Nelemans, P., 2009. Injection therapy for subacute and chronic low back pain: an updated cochrane review. Spine 34, 49–59.
Strine, T.W., Hootman, J.M., 2007. US national prevalence and correlates of low back and neck pain among adults. Arthritis Care Res. 57, 656–665.
Subhan, R.A., Puvanan, K., Murali, M.R., Balaji Raghavendran, H.R., Shani, S., Abdullah, B.J.J., Amir Abbas, A., Mohamed, J.A., Kamarul, T., 2014. Fluoroscopy assisted minimally invasive transplantation of allogenic mesenchymal stromal cells embedded in hystem reduces the progression of nucleus pulposus degeneration in the damaged interverbal disc: a preliminary study in rabbits. Sci. World J. 2014.
Teraguchi, M., Yoshimura, N., Hashizume, H., Muraki, S., Yamada, H., Minamide, A., Oka, H., Ishimoto, Y., Nagata, K., Kagotani, R., Takiguchi, N., Akune, T., Kawaguchi, H., Nakamura, K., Yoshida, M., 2014. Prevalence and distribution of intervertebral disc degeneration over the entire spine in a population-based cohort: the Wakayama Spine Study. Osteoarthr. Cartil. 22, 104–110.
Trout, J.J., Buckwalter, J.A., Moore, K.C., 1982. Ultrastructure of the human intervertebral disc: II. Cells of the nucleus pulposus. Anat. Rec. 204, 307–314.
Urban, J.P.G., Roberts, S., 2003. Degeneration of the intervertebral disc. Arthritis Res. Ther. 5, 120–130.
Van Middelkoop, M., Rubinstein, S.M., Kuijpers, T., Verhagen, A.P., Ostelo, R., Koes, B.W., Van Tulder, M.W., 2011. A systematic review on the effectiveness of physical and rehabilitation interventions for chronic non-specific low back pain. Eur. Spine J. 20, 19–39.
Van Tulder, M.W., Scholten, R.J.P.M., Koes, B.W., Deyo, R.A., 2000. Nonsteroidal anti-inflammatory drugs for low back pain: a systematic review within the framework of the Cochrane Collaboration Back Review Group. Spine 25, 2501–2513.
Welch, W.C., Gerszten, P.C., 2002. Alternative strategies for lumbar discectomy: intradiscal electrothermy and nucleoplasty. Neurosurg. Focus [Electron. Resour.] 13.
Wu, J., Tang, T.S., Wang, G.L., Lai, Z., Yin, H., 2007. Constructing a rabbit model of intervertebral disc degeneration induced by puncture and aspiration. [Chinese]. J. Clin. Rehabil. Tissue Eng. Res. 11 (45), 9116–9119.

Wu, J., Yang, J.H., Yang, Z.H., Wang, X.L., Zhang, W., Shen, F., 2011. Bone marrow mesenchymal stem cells combined with injectable fibrinous gel transforming growth factor-beta 1 transplantation for treatment of intervertebral disc degeneration. J. Clin. Rehabil. Tissue Eng. Res. 15, 478–482.

Yang, F., Leung, V.Y.L., Luk, K.D.K., Chan, D., Cheung, K.M.C., 2009. Mesenchymal stem cells arrest intervertebral disc degeneration through chondrocytic differentiation and stimulation of endogenous cells. Mol. Ther. 17 (11), 1959–1966.

Yang, H., Wu, J., Liu, J., Ebraheim, M., Castillo, S., Liu, X., Tang, T., Ebraheim, N.A., 2010. Transplanted mesenchymal stem cells with pure fibrinous gelatin-transforming growth factor-beta1 decrease rabbit intervertebral disc degeneration. Spine J. 10, 802–810.

Yurube, T., Hirata, H., Kakutani, K., Maeno, K., Takada, T., Zhang, Z., Takayama, K., Matsushita, T., Kuroda, R., Kurosaka, M., Nishida, K., 2014. Notochordal cell disappearance and modes of apoptotic cell death in a rat tail static compression-induced disc degeneration model. Arthritis Res. Ther. 16.

Zhang, Y.-G., Guo, X., Xu, P., Kang, L.-L., Li, J., 2005. Bone mesenchymal stem cells transplanted into rabbit intervertebral discs can increase proteoglycans. Clin. Orthop. Relat. Res. 219–226.

Zhang, Y., Guo, X., Li, T., Wang, S., Li, S., Xu, P., Ren, F., 2007. The effect of injecting bone mesenchymal stem cells into nucleus pulposus on the biochemistry of intervertebral disc. [Chinese]. J. Xi'an Jiaotong Univ. (Med. Sci.) 28 (6), 675–679.

Zhao, X., Huang, S., Yan, N., Liu, C.Q., Hou, T.S., 2008. Alginate scaffold in the repair of lumbar intervertebral degenerative disc by biological method. [Chinese]. J. Clin. Rehabil. Tissue Eng. Res. 12 (1), 73–76.