Int J Clin Exp Pathol 2013;6(6):1009-1014
www.ijcep.com /ISSN:1936-2625/IJCEP1304001

Review Article

Immune cascades in human intervertebral disc: the pros and cons

Zhen Sun[1*], Ming Zhang[2*], Xu-Hong Zhao[3*], Zhi-Heng Liu[1*], Yang Gao[1], Dino Samartzis[4], Hai-Qiang Wang[1], Zhuo-Jing Luo[1]

[1]Department of Orthopaedics, Xijing Hospital, Fourth Military Medical University, 127 Changle Western Road, Xi'an, P. R. China; [2]Department of Oral and Maxillofacial Surgery, PLA General Hospital, Beijing, P. R. China; [3]Department of orthopaedics, Air Force General Hospital, 30 Fucheng Road, Beijing, P. R. China; [4]Department of Orthopaedics and Traumatology, University of Hong Kong, Pokfulam, Hong Kong, SAR China. [*]Equal contributors.

Received April 2, 2013; Accepted April 28, 2013; Epub May 15, 2013; Published June 1, 2013

Abstract: The unique structural hallmark of the intervertebral disc has made its central composition, the nucleus pulposus (NP), excluded from the immunologic tolerance. Consequently, the intervertebral disc is identified as an immune-privileged organ. Traditionally, local detrimental immune activities caused by NP at the lesion sites of the disc are noted as a significant factor contributing to disc degeneration. However, given the beneficial activities of immune cells in other immune-privileged sites on basis of current evidence, the degenerate disc might need the assistance of a subpopulation of immune cells to restore its structure and lessen inflammation. In addition, the beneficial impact of immune cells can be seen in the absorption of the herniated NP, which is an important factor causes the mechanical compression of nerve roots. Consequently, a modulated immune network in degenerate disc is essential for the restoration of this immune-privileged organ. Until now, the understandings of immune response in disc degeneration still rest on the harmful aspect. Further studies are needed to explore its beneficial influence. Accordingly, there are no absolutely the pros and cons in terms of immune reactions caused by NP.

Keywords: Intervertebral disc degeneration, nucleus pulposus, immune privilege, immune reaction

Introduction

Intervertebral disc degeneration (IDD) is a significant cause of low back pain which accounts for not only greatly individual suffering, but global socioeconomic burden [1-3]. By leading to instability, IDD is also a trigger for a variety of spinal diseases and can cause secondary spinal deformity and spinal canal stenosis [4, 5]. The intervertebral disc plays an important role in the support, durability, and flexibility of the spine. It is composed of three parts: the nucleus pulposus (NP), the annulus fibrosus (AF) and cartilaginous endplates. The central NP is surrounded by concentrically arranged collagen fibrils of the AF and sandwiched between two cartilaginous endplates adjoining the vertebra body [6]. Moreover, it is the largest avascular organ of the body. This unique structural hallmark has made the NP excluded from the development of immunologic tolerance and the intervertebral disc has been identified as an immune-privileged organ with no access to systemic circulation. Accumulating evidence indicates that herniated NP is capable of inducing a specific autoimmune response and plays a role in the pathophysiology of IDD [7-10]. However, studies addressing the immune reactions to NP are still in an early stage, mainly focusing on their detrimental aspect.

Intervertebral disc as an immune-privileged organ

Immune-privileged organs were operationally defined as sites in the body where foreign tissue grafts can survive for extended, often indefinite periods of time, whereas similar grafts placed at regular sites in the body are acutely rejected [11]. Well studied organs include the eye and the brain, as well as the pregnant uterus and testis. It is noteworthy that the intervertebral disc remains less explored [12, 13]. These immune-privileged organs are immune-

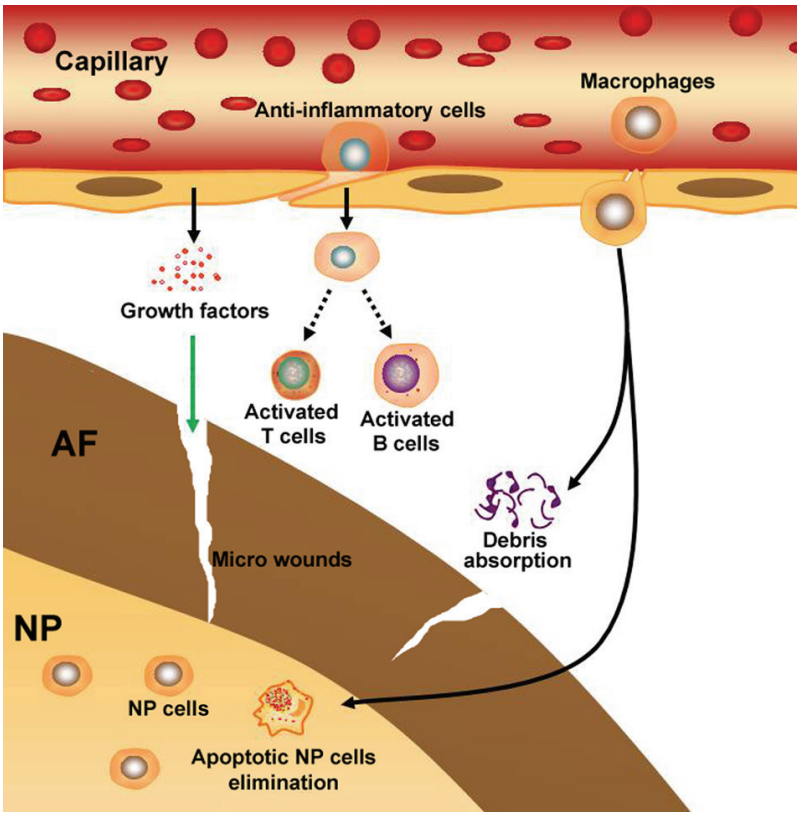

Figure 1. Schematic summary demonstrates immune cascades in human intervertebral disc. Immune reaction of the intervertebral disc is induced by the micro wound of the disc, which exposes the NP to the host immune system. Whereas the downstream of the inflammatory reactions can cause immune destruction, the beneficial aspects of immune cascades might play an important role in the restoration of disc immune balance. AF, annulus fibrosus; NP, nucleus pulposus.

cell-forbidden sites maintained by specialized physical barriers and various molecular mechanisms. In the case of intervertebral disc, the blood-tissue barrier makes the central NP isolated from the immune system of the host, which includes the avascular collagen fibrils of the AF and the adjacent cartilaginous endplates. Meanwhile, FasL, which predominantly expresses in activated T lymphocytes and stromal cells of immune-privileged sites, has also been noted in normal NP cells and plays an important role in the maintenance of immune privilege of the NP [14-16]. As a type II membrane protein of 40 kDa, FasL belongs to the tumor necrosis factor family. Once binding to its receptor Fas, it will kill the infiltrating Fas-bearing immune cells within hours [17-19]. Several lines of evidence imply a decreasing expression of FasL in degenerate NP and indicate close relationship between disc degeneration and immune privilege destruction [20-23].

Traditionally, immune cascades caused by NP have long been renowned ever since its discovery. Local detrimental immune activities seen at the lesion site of the intervertebral disc is thought to be a significant factor contributing to disc degeneration [24, 25]. During the pathological process of IDD, both the passive and active immune privilege barriers are damaged through various mechanisms [26]. Briefly, the tear of AF and the diminishing amounts of fibrocartilage expose the NP to the immune system. Once the NP extrudes from the AF to host circulation, the immune system recognizes it as a foreign body, which may induce the antigen capture. The autoimmune reactions proceed with activation of B cells with the production of auto-antibodies and T cells with cytotoxicity. On the other hand, the decreasing FasL expression weakens the NP cells' ability to clear the invading Fas-positive activated cytotoxic T-lymphocytes (CTLs). Taken together, these mechanisms destroy the immune balance of the microenvironment of the disc. The multiple amplification of the downstream cascades from the immune system attract various specific and nonspecific immune cells to the region, together with the cytokines they secret, aggravate the condition, hinder the recovery and cause pain. Meanwhile, with an increasing expression of growth factors and inflammatory agents, neovascularization and neurogenesis occur in the autoimmune region [27, 28]. These views have been well established that are supported by many lines of evidence. In fact, Anti-TNF therapy has been used as a treatment option for sciatica [29]. However, whether the immune reactions in IDD caused by NP are totally harmful still remains unknown.

Immune reactions in other immune-privileged organs

Inflammation is the body's adaptive response to any mechanical, biochemical, or immune-mediated insult. However, it could be beneficial only under the circumstance that it ends in an active resolution [30]. Studies on injury healing out-side immune privilege organs indicate the distinct subpopulation of macrophages that infiltrate the site of wound and exhibit different functions corresponding to the changing needs of the tissue along with the course of healing [31-33]. Inflammation consists of the elimination of dead cells and tissue debris at the first stage, and the secretion of anti-inflammatory cytokines and growth factors at the later stage [34]. This physiological process can aid tissue regeneration and finally lead to restoration of immune homeostasis [35, 36].

Indeed, in other immune-privileged organs, a subset of monocyte-derived macrophages can exert an immune-resolving function. They are crucial for the resolution of inflammation following sterile insults in models of spinal cord injury and retinal glutamate intoxication [37, 38]. These macrophages are essential for healing on the basis of the measure by a functional motor scale after spinal cord injury and the cell survival in the retina. Despite these organs are classified as immune privilege sites, they benefit from the regulated recruitment of innate immune cells from the outside circulation to assist in their healing.

Beneficial aspects of modulated immune cascades on the intervertebral disc

When it comes to the case of the intervertebral disc, harmful factors such as hyper-physiological loading or overload, low nutrition and oxygen, contribute to an increased number and extent of clefts and tears of the intervertebral disc [3, 39, 40]. These micro lesions might expose antigenic substances of the NP to the immune system and cause an initial immune response. Similar to the aforementioned immune-privileged organs, these wounds might need the assistance of a subpopulation of immune cells to restore structure and reduce inflammation. Although the relevant infiltration of massive inflammatory cells, growth factors and cytokines might be harmful and aggravate the degeneration, at least some groups of immune cells might be beneficial to the regrowth of the intervertebral disc wounds and the immune privilege maintenance in the early stage. The involved immune cells with various phenotypes and function could be necessary factors in the elimination of cell debris as well as the secretion of anti-inflammatory cytokines. Peng et al noted abundant macrophages and mast cells in the granulation tissue zones of painful discs and indicated the key roles in the repair of the injured AF and subsequent disc degeneration [41]. In an experimental study in pig, Geiss et al found a subpopulation of immune cells were elevated in subcutaneous NP chambers [42] These cells include activated T cells (CD4, CD8 and CD45RC) as well as activated B cells expressing immunoglobulin kappa (Ig). Moreover, Murai et al reported natural killer (NK) cells and macrophages may have an immunological function in the early phase of disc herniation [9]. Consequently, a controlled immune reaction involved by some specific immune cells might be helpful (**Figure 1**).

On the other hand, while the other immune-privileged organs contain their own population of immune cells, there have been no studies addressing the resident immune cells in the intervertebral disc. Although phagocytic activity was observed in NP by a subset of cells [43], the mission of clearing dead cell and noxious substance may not be fulfilled without the assistance of extraneous immune cells. Meanwhile, as some inflammatory agents could be secreted by degenerate NP cells, the infiltrating blood-derived macrophages are essential for anti-inflammatory activities in IDD [44-46]. Therefore, we assumed that the infiltrating cells might fulfill specialized functions in the healing and anti-inflammatory process of the disc, which the local phagocytic-associated cells either fail to manifest at sufficient levels or at the right time.

In addition, the beneficial influence of immune cells can also be seen in the absorption of the herniated NP, which is an important factor contributing to the compression of nerve roots. Using a co-culture system of herniated lumbar disc specimens and peripheral blood mononuclear cells, Doita et al implicated immune cells, with enhanced production of matrix metalloproteinases, play an essential role in spontaneous regression of disc materials [47]. Ikeda et al investigated infiltrated cells consisting of mac-

rophages and a small number of T cells, and proposed that extruded or sequestrated disc material has the potential to be absorbed by phagocytes [48]. Indeed, one of the initial purposes of inflammatory is to eliminate dead cells and tissue debris, which in the case of herniation absorption, exert a beneficial function in the nerve root decompression at least in some degree. However, the downstream inflammatory reactions of this uncontrolled process might lead to the detrimental effect, which is so notable that covers its primal impact.

Summary

Available evidence indicates that a modulated immune response in degenerate disc is essential for the recovery of this immune-privileged organ. A suitable time point, duration, and cell phenotype are vital in this restoration. Although the downstream amplified inflammatory reactions are detrimental, the immune response might be re-judged for their beneficial involvement. Accordingly, there are no absolutely the pros and cons in terms of immune reactions caused by NP. It is all a matter of their control and coordination. Actually, an acute autoimmune response caused by the NP tissue and the chronic immune related restoration, might be confused by current studies. Until now, the understandings of immune response in IDD still rest on the harmful aspect. Further studies are needed to explore its beneficial influence. In conclusion, comprehensive understandings of the immune reactions of NP will definitely deepen our knowledge in the immune aspects of IDD and laid a foundation for its treatment.

Conflicts of interest statement

The authors declare no competing financial interests.

Acknowledgements

The study was supported by Chinese National Natural Science Foundation grants 30901509, 81270028.

Address correspondence to: Hai-Qiang Wang and Zhuo-Jing Luo, Department of Orthopaedics, Xijing Hospital, Fourth Military Medical University, 127 Changle Western Road Xi'an, P. R. China, 710032. Phone: +86 29 84775285; Fax: +86 29 84775285; E-mail: hqwang@fmmu.edu.cn (Hai-Qiang Wang); zjluo@fmmu.edu.cn (Zhuo-Jing Luo)

References

[1] Freemont AJ. The cellular pathobiology of the degenerate intervertebral disc and discogenic back pain. Rheumatology (Oxford) 2009; 48: 5-10.

[2] Hughes SP, Freemont AJ, Hukins DW, McGregor AH and Roberts S. The pathogenesis of degeneration of the intervertebral disc and emerging therapies in the management of back pain. J Bone Joint Surg Br 2012; 94: 1298-1304.

[3] Salzberg L. The physiology of low back pain. Prim Care 2012; 39: 487-498.

[4] Herkowitz HN, Abraham DJ and Albert TJ. Management of degenerative disc disease above an L5-S1 segment requiring arthrodesis. Spine (Phila Pa 1976) 1999; 24: 1268-1270.

[5] Miyamoto M, Genbum Y and Ito H. [Diagnosis and treatment of lumbar spinal canal stenosis]. J Nippon Med Sch 2002; 69: 583-587.

[6] Mirza SK and White AA 3rd. Anatomy of intervertebral disc and pathophysiology of herniated disc disease. J Clin Laser Med Surg 1995; 13: 131-142.

[7] Gertzbein SD, Tait JH and Devlin SR. The stimulation of lymphocytes by nucleus pulposus in patients with degenerative disk disease of the lumbar spine. Clin Orthop Relat Res 1977; 149-154.

[8] McCarron RF, Wimpee MW, Hudkins PG and Laros GS. The inflammatory effect of nucleus pulposus. A possible element in the pathogenesis of low-back pain. Spine (Phila Pa 1976) 1987; 12: 760-764.

[9] Murai K, Sakai D, Nakamura Y, Nakai T, Igarashi T, Seo N, Murakami T, Kobayashi E and Mochida J. Primary immune system responders to nucleus pulposus cells: evidence for immune response in disc herniation. Eur Cell Mater 2010; 19: 13-21.

[10] Gabr MA, Jing L, Helbling AR, Sinclair SM, Allen KD, Shamji MF, Richardson WJ, Fitch RD, Setton LA and Chen J. Interleukin-17 synergizes with IFNgamma or TNFalpha to promote inflammatory mediator release and intercellular adhesion molecule-1 (ICAM-1) expression in human intervertebral disc cells. J Orthop Res 2011; 29: 1-7.

[11] Medawar PB. Immunity to homologous grafted skin; the fate of skin homografts transplanted to the brain, to subcutaneous tissue, and to the anterior chamber of the eye. Br J Exp Pathol 1948; 29: 58-69.

[12] Crane IJ, Xu H, Wallace C, Manivannan A, Mack M, Liversidge J, Marquez G, Sharp PF and Forrester JV. Involvement of CCR5 in the passage of Th1-type cells across the blood-retina barrier in experimental autoimmune uveitis. J Leukoc Biol 2006; 79: 435-443.

[13] Muldoon LL, Alvarez JI, Begley DJ, Boado RJ, Del Zoppo GJ, Doolittle ND, Engelhardt B, Hallenbeck JM, Lonser RR, Ohlfest JR, Prat A, Scarpa M, Smeyne RJ, Drewes LR and Neuwelt EA. Immunologic privilege in the central nervous system and the blood-brain barrier. J Cereb Blood Flow Metab 2013; 33: 13-21.

[14] Kaneyama S, Nishida K, Takada T, Suzuki T, Shimomura T, Maeno K, Kurosaka M and Doita M. Fas ligand expression on human nucleus pulposus cells decreases with disc degeneration processes. J Orthop Sci 2008; 13: 130-135.

[15] Takada T, Nishida K, Doita M and Kurosaka M. Fas ligand exists on intervertebral disc cells: a potential molecular mechanism for immune privilege of the disc. Spine (Phila Pa 1976) 2002; 27: 1526-1530.

[16] Wang HQ, Yu XD, Liu ZH, Cheng X, Samartzis D, Jia LT, Wu SX, Huang J, Chen J and Luo ZJ. Deregulated miR-155 promotes Fas-mediated apoptosis in human intervertebral disc degeneration by targeting FADD and caspase-3. J Pathol 2011; 225: 232-242.

[17] Bellgrau D, Gold D, Selawry H, Moore J, Franzusoff A and Duke RC. A role for CD95 ligand in preventing graft rejection. Nature 1995; 377: 630-632.

[18] Greil R, Egle A and Villunger A. On the role and significance of Fas (Apo-1/CD95) ligand (FasL) expression in immune privileged tissues and cancer cells using multiple myeloma as a model. Leuk Lymphoma 1998; 31: 477-490.

[19] Griffith TS, Brunner T, Fletcher SM, Green DR and Ferguson TA. Fas ligand-induced apoptosis as a mechanism of immune privilege. Science 1995; 270: 1189-1192.

[20] Park JB, Chang H and Kim KW. Expression of Fas ligand and apoptosis of disc cells in herniated lumbar disc tissue. Spine (Phila Pa 1976) 2001; 26: 618-621.

[21] Park JB, Kim KW, Han CW and Chang H. Expression of Fas receptor on disc cells in herniated lumbar disc tissue. Spine (Phila Pa 1976) 2001; 26: 142-146.

[22] Wang F, Jiang JM, Deng CH, Wang FL, Fu ZZ and Zhang ZF. Expression of Fas receptor and apoptosis in vertebral endplates with degenerative disc diseases categorized as Modic type I or II. Injury 2011; 42: 790-795.

[23] Tschoeke SK, Hellmuth M, Hostmann A, Robinson Y, Ertel W, Oberholzer A and Heyde CE. Apoptosis of human intervertebral discs after trauma compares to degenerated discs involving both receptor-mediated and mitochondrial-dependent pathways. J Orthop Res 2008; 26: 999-1006.

[24] Tsuru M, Nagata K, Ueno T, Jimi A, Irie K, Yamada A, Nishida T and Sata M. Electron microscopic observation of established chondrocytes derived from human intervertebral disc hernia (KTN-1) and role of macrophages in spontaneous regression of degenerated tissues. Spine J 2001; 1: 422-431.

[25] Tapia-Perez H. [Intervertebral disc pathologies from an immunological perspective]. Rev Neurol 2008; 46: 751-757.

[26] Wan J and Zhang XS. Pre-operative blood test for antibody to nucleus pulposus may distinguish types of lumbar disc herniation. Med Hypotheses 2010; 75: 464-465.

[27] Kauppila LI. Ingrowth of blood vessels in disc degeneration. Angiographic and histological studies of cadaveric spines. J Bone Joint Surg Am 1995; 77: 26-31.

[28] Roberts S, Evans H, Trivedi J and Menage J. Histology and Pathology of the Human Intervertebral Disc. J Bone Joint Surgery Am 2006; 88: 10-14.

[29] Karppinen J, Korhonen T, Malmivaara A, Paimela L, Kyllonen E, Lindgren KA, Rantanen P, Tervonen O, Niinimaki J, Seitsalo S and Hurri H. Tumor necrosis factor-alpha monoclonal antibody, infliximab, used to manage severe sciatica. Spine (Phila Pa 1976) 2003; 28: 750-753; discussion 753-754.

[30] Gronert K. Resolution, the grail for healthy ocular inflammation. Exp Eye Res 2010; 91: 478-485.

[31] Nishihira J. Novel pathophysiological aspects of macrophage migration inhibitory factor (review). Int J Mol Med 1998; 2: 17-28.

[32] Arakawa T, Watanabe T, Tanigawa T, Tominaga K, Fujiwara Y and Morimoto K. Quality of ulcer healing in gastrointestinal tract: its pathophysiology and clinical relevance. World J Gastroenterol 2012; 18: 4811-4822.

[33] Gethin G. Understanding the inflammatory process in wound healing. Br J Community Nurs 2012; Suppl: S17-18, S20, S22.

[34] Weidenbusch M and Anders HJ. Tissue microenvironments define and get reinforced by macrophage phenotypes in homeostasis or during inflammation, repair and fibrosis. J Innate Immun 2012; 4: 463-477.

[35] Arnold L, Henry A, Poron F, Baba-Amer Y, van Rooijen N, Plonquet A, Gherardi RK and Chazaud B. Inflammatory monocytes recruited after skeletal muscle injury switch into antiinflammatory macrophages to support myogenesis. J Exp Med 2007; 204: 1057-1069.

[36] Nahrendorf M, Swirski FK, Aikawa E, Stangenberg L, Wurdinger T, Figueiredo JL, Libby P, Weissleder R and Pittet MJ. The healing myocardium sequentially mobilizes two monocyte subsets with divergent and complementary functions. J Exp Med 2007; 204: 3037-3047.

[37] Shechter R, London A, Varol C, Raposo C, Cusimano M, Yovel G, Rolls A, Mack M, Pluchino S,

Martino G, Jung S and Schwartz M. Infiltrating blood-derived macrophages are vital cells playing an anti-inflammatory role in recovery from spinal cord injury in mice. PLoS Med 2009; 6: e1000113.

[38] London A, Itskovich E, Benhar I, Kalchenko V, Mack M, Jung S and Schwartz M. Neuroprotection and progenitor cell renewal in the injured adult murine retina requires healing monocyte-derived macrophages. J Exp Med 2011; 208: 23-39.

[39] Modic MT. Degenerative disc disease and back pain. Magn Reson Imaging Clin N Am 1999; 7: 481-491, viii.

[40] Singh K, Masuda K and An HS. Animal models for human disc degeneration. Spine J 2005; 5: 267S-279S.

[41] Peng B, Hao J, Hou S, Wu W, Jiang D, Fu X and Yang Y. Possible pathogenesis of painful intervertebral disc degeneration. Spine (Phila Pa 1976) 2006; 31: 560-566.

[42] Geiss A, Larsson K, Rydevik B, Takahashi I and Olmarker K. Autoimmune properties of nucleus pulposus: an experimental study in pigs. Spine (Phila Pa 1976) 2007; 32: 168-173.

[43] Weiler C, Nerlich AG, Schaaf R, Bachmeier BE, Wuertz K and Boos N. Immunohistochemical identification of notochordal markers in cells in the aging human lumbar intervertebral disc. Eur Spine J 2010; 19: 1761-1770.

[44] Ohtori S, Inoue G, Eguchi Y, Orita S, Takaso M, Ochiai N, Kishida S, Kuniyoshi K, Aoki Y, Nakamura J, Ishikawa T, Arai G, Miyagi M, Kamoda H, Suzuki M, Sakuma Y, Oikawa Y, Kubota G, Inage K, Sainoh T, Toyone T, Yamauchi K, Kotani T, Akazawa T, Minami S and Takahashi K. Tumor Necrosis Factor-alpha-Immunoreactive Cells in Nucleus Pulposus in Adolescent Patients With Lumbar Disc Herniation. Spine (Phila Pa 1976) 2013; 38: 459-462.

[45] Yamamoto J, Maeno K, Takada T, Kakutani K, Yurube T, Zhang Z, Hirata H, Kurakawa T, Sakai D, Mochida J, Doita M, Kurosaka M and Nishida K. Fas ligand plays an important role for the production of pro-inflammatory cytokines in intervertebral disc nucleus pulposus cells. J Orthop Res 2013; 31: 608-615.

[46] Andrade P, Hoogland G, Garcia MA, Steinbusch HW, Daemen MA and Visser-Vandewalle V. Elevated IL-1beta and IL-6 levels in lumbar herniated discs in patients with sciatic pain. Eur Spine J 2013; 22: 714-20.

[47] Doita M, Kanatani T, Ozaki T, Matsui N, Kurosaka M and Yoshiya S. Influence of macrophage infiltration of herniated disc tissue on the production of matrix metalloproteinases leading to disc resorption. Spine (Phila Pa 1976) 2001; 26: 1522-1527.

[48] Ikeda T, Nakamura T, Kikuchi T, Umeda S, Senda H and Takagi K. Pathomechanism of spontaneous regression of the herniated lumbar disc: histologic and immunohistochemical study. J Spinal Disord 1996; 9: 136-140.