Turk Neurosurg, 2023

Original Investigation

DOI: 10.5137/1019-5149.JTN.42017-22.2

Received: 12.08.2022
Accepted: 01.12.2022

Published Online: 02.05.2023

Role of the MyD88 Dependent Pathway in Degenerative Disc Disease

Mehmet Yigit AKGUN[1], Sibel AKYOL[2], Fatma OZLEN[3], Orkhan ALIZADA[4], Semih Can CETINTAS[3], Okan TURK[5], Murat HANCI[3]

[1]Koc University Hospital, Department of Neurosurgery, Istanbul, Turkey
[2]Istanbul University-Cerrahpasa, Cerrahpasa Medical Faculty, Department of Physiology, Istanbul, Turkey
[3]Istanbul University-Cerrahpasa, Cerrahpasa Medical Faculty, Department of Neurosurgery, Istanbul, Turkey
[4]Baskent University, Department of Neurosurgery, Istanbul, Turkey
[5]Istanbul Health Sciences University, Istanbul Education and Research Hospital, Department of Neurosurgery, Istanbul, Turkey

Corresponding author: Mehmet Yigit AKGUN ✉ myigitakgun@gmail.com

ABSTRACT

AIM: To define the substantial role of the TLR4 signaling pathway in the MyD88-dependent pathway and evaluate the results of TLR4 activation in nucleus pulposus cells. Moreover, we aim to associate this pathway with intervertebral disc degeneration and magnetic resonance imaging (MRI) findings. Additionally, the clinical differences among patients and the effects of their drug use will be evaluated.

MATERIAL and METHODS: Eighty-eight adult male patients with lower back pain and sciatica underwent MRI studies, which showed degenerative changes. Disc materials were obtained intraoperatively from those who underwent surgery for lumbar disc herniation. These materials were kept in freezers at –80°C without any delay. Then, the collected materials were examined using enzyme-linked immunosorbent assays.

RESULTS: Modic type I degeneration had the highest values of all markers, whereas Modic type III degeneration had the lowest values. These results verified that this pathway plays an active role in MD. Moreover, contrary to the current knowledge on which Modic type inflammation is more dominant, we showed that it is the Modic type I phase.

CONCLUSION: The most intense inflammatory process was observed in Modic type 1 degeneration, and the MyD88-dependent pathway was found to play a key role. While the most intense molecular increase was detected in Modic type 1 degeneration, the lowest levels were observed in Modic type III degeneration. It has been observed that the use of nonsteroidal anti-inflammatory drugs affects the inflammatory process through the MyD88 molecule.

KEYWORDS: Toll-like receptor, MyD88, Modic degeneration, Back pain, Degenerative disc disease, Immune system

INTRODUCTION

It is thought that the Toll-like receptor (TLR)-mediated immune and inflammatory process affects the vertebral end plates. TLR/myeloid differentiation primary response 88 (MyD88)-dependent pathway's important role in disc degeneration continues within the Modic degeneration (MD) in the same manner. The importance of this subject is increasing even more considering the lack of studies showing this process in human disc specimens. The proof of this pathway's effect in the MD will directly affect the management process and potential treatment targets (15).

The interaction between lipopolysaccharide (LPS), TLR4 ligand, and TLR4 activates two downstream intracellular signaling pathways in mammals: MyD88-dependent and MyD88-independent pathways (7).

Mehmet Yigit AKGUN : 0000-0003-1342-7663
Sibel AKYOL : 0000-0002-6294-706X
Fatma OZLEN : 0000-0003-0925-8748
Orkhan ALIZADA : 0000-0003-0942-9906
Semih Can CETINTAS : 0000-0001-6036-164X
Okan TURK : 0000-0002-9514-6891
Murat HANCI : 0000-0001-9261-6686

TLR4 is a transmembrane receptor that links the innate immunity with adaptive immunity. With the ligands binding to TLR4, nuclear factor-kappa B (NF-κB) is activated, and the gene expression related to immunity is regulated. When the TLRs are coupled with damage-associated molecular patterns (DAMPs), this complex activates an immediate downstream pathway and transcription factors. Thus, the initiation and progression of inflammation are induced (3,13).

Studies showed that TLR mediation is essentially mediated by the MyD88-dependent NF-κB pathway. Pattern recognition receptors recognize pathogen-associated molecular patterns (PAMPs) and activate the signaling pathways that induce the production of interferon type I, other inflammatory cytokines, and innate immunity reactions (18,21).

Each TLR contains a leucine-rich ectodomain-mediating PAMP and a Toll/IL-1 receptor (TIR) domain region, which initiates downstream signal transduction. Upon recognition of DAMPs and PAMPs, TLRs bind to adapter proteins containing TIR domains, such as MyD88 and TRIF. This interaction activates NF-κB, interferon regulatory factors, or mitogen-activated protein kinases (MAPKs) for host protection, with the expression of interferon type I, cytokines, and chemokines (20).

It is thought that the TLR4 gene is expressed in NP cells and plays a key role in the molecular mechanism of intervertebral disk (IVD) degeneration. Nevertheless, which signal transduction activates TLR4 in NP cells has not been explained up to this date (23). Moreover, the balance between the matrix anabolism and catabolism is disrupted in IVD degeneration (14,19).

In this study, the TLR4/MyD88-dependent pathway, where adapter proteins, such as CD4, IKKα, NF-κBα, and TRAF6, play a prominent role, which is considered to contribute to degenerative disc diseases, was evaluated, and its association with MD was also assessed. Furthermore, this study was designed to elaborate the role of the MyD88-dependent pathway in IVD degeneration and to pioneer the investigation of other molecular pathways in IVD degeneration.

MATERIAL and METHODS

This study was conducted at the Department of Neurosurgery and Physiology, Istanbul University-Cerrahpasa. This study has been approved by the Institutional Review Board, and all subjects provided informed consent (or the need for written informed consent was waived). Patients with severe comorbidities; those who were unconscious or confused rendering them unable to provide consent; and those who did not want to participate in this study were excluded.

Eighty-eight adult male patients who presented to the outpatient clinic with complaints of low back pain and sciatica and had degenerative findings on magnetic resonance imaging MRI were included in this study. Those patients were operated with respect to the presence of surgical indication for lumbar disc herniation (LDH). Operations were performed by the same surgeon with the aid of a microscope with the patients placed in the prone position.

Female patients were excluded from this study because of the hormonal exposure, which can cause potential differences in the immune response. Additionally, those who had a history of LDH surgery, chronic systemic disease, acute infections, and endocrinological diseases were excluded. Furthermore, patients who received preoperative steroid injections were excluded from this study.

In the preoperative course, the patients were classified into three groups according to the Modic changes. MD is characterized by bone marrow lesions seen within a vertebral body on MRI, suggestive of being associated with back pain. It is accepted that Modic type I degeneration is characterized by bone marrow edema and inflammation, Modic type II degeneration is characterized by fatty replacements of the red bone marrow within a vertebral body secondary to ischemia, and Modic type III degeneration is characterized by subchondral bone sclerosis.

Furthermore, the patients were classified according to the use of nonsteroidal anti-inflammatory drugs (NSAIDs) and the presence of radicular pain in addition to the lower back pain. Thus, the disc materials were evaluated under three conditions: 1) according to MD, 2) according to NSAID usage (yes/no), and 3) according to the presence of radicular pain accompanying low back pain (yes/no).

Disc materials were obtained intraoperatively from the patients who underwent LDH surgery. These materials were kept in freezers at −80°C without any delay via transfer in nitrogen tanks with a temperature of −196°C. All samples were analyzed using enzyme-linked immunosorbent assay (ELISA) at the Cytokines and Receptors Research Laboratory, Cerrahpasa Medical Faculty, Department of Physiology.

The materials taken out of the freezers were thawed gradually and centrifuged at 6,000 g for 2 min. Disc material extracts were analyzed using ELISA. Then, 350-μL supernatant was diluted with sample diluent in a 1:1 ratio. After the addition of 150-μL standard diluent, serial dilution was made from the stock standard tube. Pipetting was performed after each step for even distribution. Next, 30× washing solution was diluted with distilled water, and this solution was used in washing steps.

All materials were subjected to the immunoassay protocol. Optical density values were detected at 450 nm using a Multiskan™ GO Microplate Spectrophotometer (Thermo-Fisher Scientific™).

This process was aimed to associate the MyD88-dependent pathway with IVD degeneration and Modic changes. Additionally, the clinical differences among the patients and the effects of their drug use were evaluated. Furthermore, the relationship of these effects with the MyD88-dependent pathway was assessed.

Statistical Analysis

The disc materials were evaluated under three conditions: 1) according to MD (types I/II/III), 2) according to NSAID usage (yes/no), and 3) according to the presence of radicular pain accompanying low back pain (yes/no).

Because the patients were separated into two cohorts according to their use of NSAIDs and the presence of radicular pain in addition to the lower back pain, statistical analyses were performed using the *independent t-test* in groups with normal distribution and homogenous variance. Groups with non-homogenous variances were compared using the *Mann–Whitney U test*.

Because the patients were divided into three groups and assessed according to the types of MD, statistical analyses were performed using *one-way analysis of variance (ANOVA)*. Because ANOVA statistics do not yield reliable results when variances are different, the *ROBUST test* (Welch and Brown-Forsythe ANOVA) was used to assess.

Post hoc tests were used to specify which groups have differences. The *Tukey, honestly significant difference, Scheffe, and Bonferroni tests* were used when the variances were homogenous, and the *Tamhane, Dunnett T3, Dunnett C, and Games–Howell tests* were used when the variances were not homogenous.

Two-tailed p-values of less than 0.05 were used to indicate statistically significant differences.

RESULTS

The patients consisted of 88 males with a mean age of 47.3 ±19.6 years (range, 19–75 years) at the initial symptom onset.

The patients were classified into three groups according to Modic classification. Twenty-eight (31.8%) patients were evaluated to have Modic type I degeneration, 40 (45.4%) patients were assessed to have Modic type II degeneration, and 20 (22.7%) patients were evaluated to have Modic type III degeneration.

The patients were also examined according to their clinical findings, regardless of their Modic changes. Two types of patients were present according to their reasons for admission. Sixteen (18.1%) patients had low back pain only, and 72 patients (81.8%) had low back pain accompanied by radicular pain.

Additionally, the patients were classified according to their NSAID use in the preoperative period. Forty-nine (55.6%) patients used NSAIDs, whereas 39 (44%) patients did not.

The statistical relationship between the molecules involved in the Myd88-dependent pathway and MD types is shown in Figure 1.

In groups with homogeneous variances, no statistically significant difference in CD4 was observed between the groups (p=0.092). Moreover, no statistically significant difference in NF-κBα was observed between Modic types II and III degeneration (p=0.553). However, a statistically significant difference in NF-κBα was observed between Modic types I and II–III degeneration (p<0.001). The highest NF-κBα values were observed in Modic type I degeneration, and the lowest values were observed in Modic type III degeneration.

In the groups whose variances were not homogeneous, statistically significant differences in IKKα, MyD88, TLR4, and TRAF6 were observed between Modic types I, II, and III degeneration. The detailed p-values for each molecule are shown in Figure 1. The highest values these molecules were observed in Modic type I degeneration, and the lowest values were observed in Modic type III degeneration.

When the patients were evaluated according to whether they used NSAIDs, variances in MyD88 were found to be different, and a statistically significant difference was found between the two groups (p=0.041). When the other molecules were

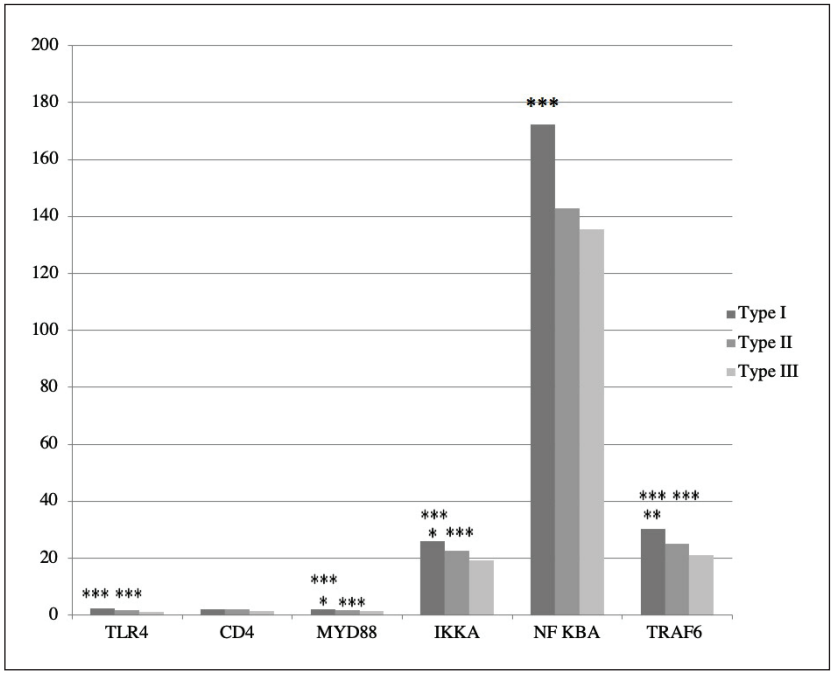

Figure 1: Figure view of the statistical analysis of the parameters according to Modic degeneration types. **TLR4, IKKα:** A statistically significant difference was found between Modic Type 1 degeneration and Modic Type 2 - 3 degeneration [p <0.001 (***)]. In addition, a statistically significant difference was found between Modic Type 2 degeneration and Modic Type 3 degeneration [p <0.001 (***)].
MyD 88 / TRAF6: A statistically significant difference was found between Modic Type 1 degeneration and Modic Type 2 degeneration [p =0.018 (*) / p <0.01 (**)]. Also, a statistically significant difference was found between Modic Type 1 degeneration and Modic Type 3 degeneration [p <0.001 (***)]. In addition, a statistically significant difference was found between Modic Type 2 degeneration and Modic Type 3 degeneration [p <0.001 (***)].

evaluated, no statistically significant difference was found between the groups (p>0.05) (Figure 2). Additionally, the values were lower in the group that used NSAIDs.

When the patients were evaluated according to their clinical conditions, no statistically significant difference in all molecules was found (p>0.05) (Figure 3). The values were lower in the group with accompanying radicular pain.

DISCUSSION

Despite the absence of a certain cause for refractory and nonspecific lower back pain, a correlation between chronic lower back pain and MD has been evaluated with a molecular basis in the literature (10).

Nonetheless, the degree and the exact mechanism of this correlation have not been revealed in any study up to this point. It has been reported that the protrusion of the NP toward the end plate causes inflammation around the IVD, and this incident triggers chronic lower back pain with an excessive cytokine release (17). This immunological reaction has been thought to be associated with MD, particularly Modic type II degeneration (1).

Sterile inflammation, which induces the release of proinflammatory cytokines without infection, appears to be a feature of IVD degeneration. Proinflammatory cytokines, such as interleukin (IL)-1, tumor necrosis factor-alpha (TNF-α), IL-6, and IL-8; angiogenic factors; and neutrophils increase during degeneration (4). In contrast, IL-1 and TNF-α are expressed

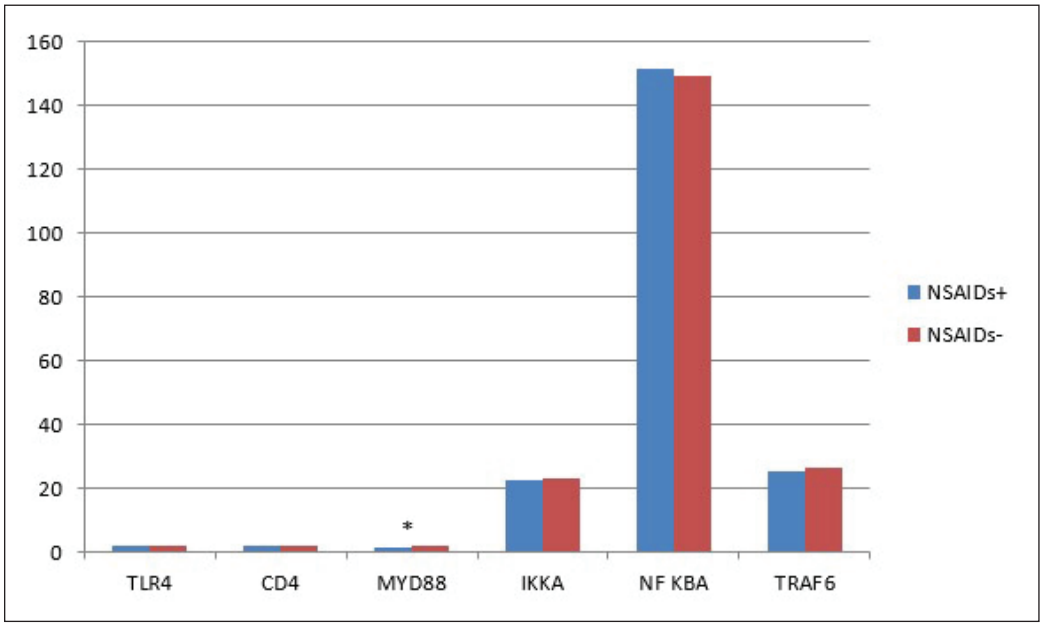

Figure 2: Figure view of the statistical analysis of the parameters according to NSAIDs use.
TLR4, CD4, IKKα, NF-κBα, TRAF6: When the patients were evaluated according to whether they used NSAIDs or not, no statistically significant difference was found between the groups (p>0.05).
MyD 88: When the patients were evaluated according to whether they used NSAIDs or not, a statistically significant difference was found between the two groups (p=0.041).

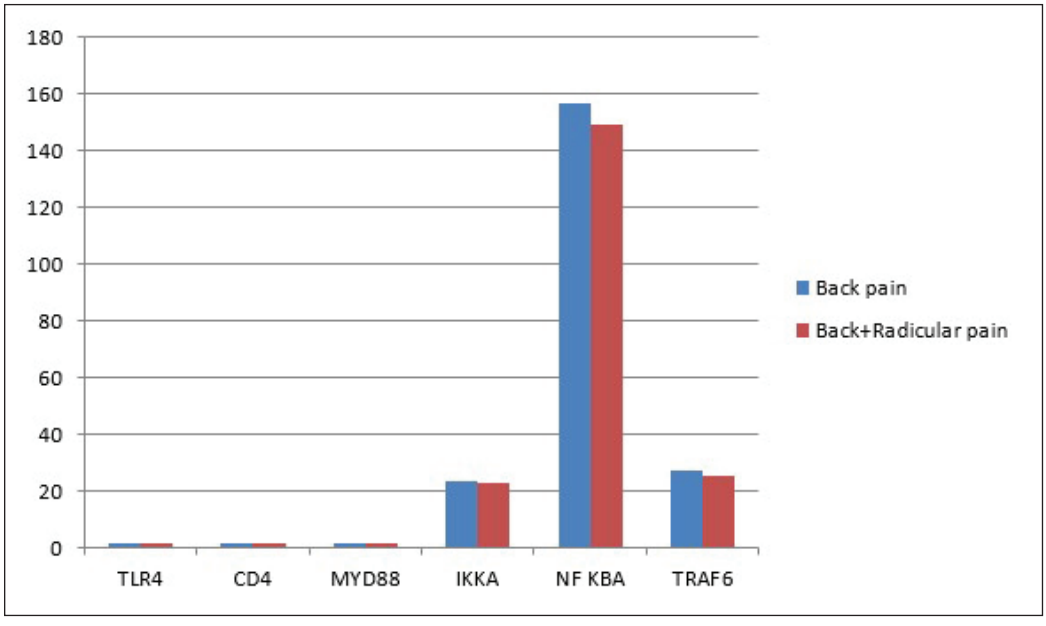

Figure 3: Figure view of the statistical analysis of the parameters according to clinical conditions.
TLR4, CD4, MyD 88, IKKα, NF-κBα, TRAF6: When the patients were evaluated according to their clinical conditions (accompanying radicular pain), no statistically significant difference was found (p>0.05).

in non-degenerated IVDs. Thus, cytokines do not explain the sterile inflammation in the early phases of IVD degeneration. Furthermore, TLRs are activated during the early phases of degeneration due to the increased release of proinflammatory cytokines.

However, whether TLR activation is sufficient to cause degenerative changes in the human IVD has not been clarified. Krock et al. reported that TLR inhibition reduced the release of proinflammatory cytokines and IVD degeneration in mouse models (16). In another study, early inflammatory and morphological changes induced by intradiscal LPS injection were investigated in the rat IVD. The increase in TNF-α, IL-1β, and IL-6 production was thought to be due to the expression of TLR4. Thus, in different publications, degenerative changes in the rat IVD have been demonstrated to be induced by both LPS injection and TLR4 activation (2,8).

However, in IVD degeneration, the nature of the MyD88-dependent signal transduction pathway, which activates TLR4 in NP cells, remains unknown. Determining whether the TLR4 signal pathway is MyD88-dependent or MyD88-independent may generate evidence supporting the hypothesis that the MyD88-dependent TLR4 signal pathway is the target pathway underlying IVD degeneration (12,26).

Animal degeneration models, which involve lesions created by lacerations, generally cause morphological changes in the IVD. These animal models were also associated with temporary increases in proinflammatory cytokines; however, these models are incompatible with human degenerative IVD disease. In humans, IVD degeneration is related to chronic increases in multiple proinflammatory cytokines (27,29).

In a rare study, which showed extensive expression and regulation of TLRs, two proinflammatory cytokines, IL-1β and TNF- α, were found to induce the gene and protein expression of TLR2. The fact remains that IL-1β and TNF-α were also found to activate NF-κB transcription factor via the nuclear translocation of p65. No tangible data were revealed about the role of TLR4 in IVD degeneration, and the information about the role of TLR2 in inflammation was explicated with accumulation of knowledge from the literature. It has been reported that TLR–ligand interactions would lead to NF-κB and MAPK activation in IVD cells both *in vitro* and *in vivo* (22).

In our study, the disc specimens from patients who under surgery for degenerative disc disease were examined. The obtained data were attempted to be presented clearly. According to our study, TLR4, which has been previously shown to play an important role in IVD degeneration (28), also contributes to MD and uses the MyD88-dependent pathway to induce an immunological reaction chain.

The advances made in the diagnosis of both inflammatory and degenerative diseases with the advancement of molecular diagnostic techniques are gratifying. However, publications on the molecular basis of common radiological findings, such as MD, are limited (11,24).

Chen et al. reported significant rises in IL-1, GM-CSF, ENA-78, and TNF-α levels in Modic type II degeneration. Hereby, both IL-1β and TNF-α were shown to be highly correlated with lower back pain (9). On the contrary to the efforts to determine the role of the immune system in the process, the correlation of the immune system with MRI, an imaging modality frequently used in neurosurgical practice, has never been studied.

While the causes and mechanisms of MD remain unclear, it has been strongly linked to low back pain by many authors (6). Exposing the relationship between MD and immune pathways and explaining the inflammatory process will play a decisive role in the following process. We analyzed the relationship of the TLR4/MyD88-dependent pathway with MD.

Unlike the literature, with these values, it is possible to say that the current pathway plays an active role in MD. Additionally, in the literature, studies have suggested that inflammation is more dominant in the MD type II phase (5). Contrary to the current knowledge, we found that inflammation was more dominant in the MD type 1 phase. It is thought that by preventing this pathway, preventing inflammation and low back pain can be achieved.

Even though lower back pain secondary to IVD degeneration after immunological reactions is a subject that has been mentioned, no studies have discussed the impact TLRs on pain. It is particularly remarked that if there is more inflammation, more pain will be present (25). Our study demonstrated that the relief of low back pain with the use of NSAIDs can be achieved by inhibiting the current pathway. The only statistically significant difference detected in MyD88 suggests that the parent molecule in the inflammatory process is MyD88.

Therefore, in degenerated IVDs with concurrent root compression, more inflammation is present, and the radicular pain accompanying lower back pain in those patients could be associated with inflammatory conditions. In our study, we could not find a statistically significant difference when the patients were evaluated according to the presence or absence of accompanying radicular pain. However, the MyD88-independent pathway may play an important role in this special topic. We think that comparative analysis of the two pathways will lead to clearer information.

In our study, the role of the MyD88-dependent pathway in disc tissue degeneration has been clearly demonstrated, and this pathway was correlated with imaging modalities. MRI findings and disc degeneration rates were correlated with the immune system. The fact that the study was conducted using samples obtained from human disc tissue also reveals one of its different aspects from the literature. To summarize, the correlation between MRI and the samples obtained from human disc tissue play an important role in distinguishing our study from those in the literature. Additionally, the path of clinical findings and NSAID use in the inflammatory process and their effect on the immune system were also revealed.

CONCLUSION

The most intense inflammatory process was observed in Modic type I degeneration, and the MyD88-dependent

pathway was found to play a key role in this process. While the most intense molecular increase was detected in Modic type I degeneration, the lowest levels were observed in Modic type III degeneration. It has been observed that the use of NSAIDs affects the inflammatory process through the MyD88 molecule. Moreover, the molecular values were lower in the group using NSAIDs. A better understanding of the role of the innate immune system in IVD degeneration and its correlation with MD will provide serious developments in patient management and treatment in the future.

DISCLOSURE

This study was funded by Scientific Research Projects Coordination Unit of Istanbul University-Cerrahpasa (Project number: 25405). On behalf of all authors, the corresponding author states that there is no other conflict of interest.

AUTHORSHIP CONTRIBUTION

Study conception and design: MYA, SA, MH
Data collection: MYA, SA, OA, SCC, OT
Analysis and interpretation of results: MYA
Draft manuscript preparation: MYA
Critical revision of the article: MH
Other (study supervision, fundings, materials, etc...): SA, OA, SCC, OT, MH
All authors (MYA, SA, FO, OA, SCC, OT, MH) reviewed the results and approved the final version of the manuscript.

REFERENCES

1. Ahmed-Yahia S, Decousser JW, Flouzat-Lachaniette CH, Dervin G, Roubineau F, Audureau E, Hourdille A, Royer G, Eymard F, Chevalier X: Is the discopathy associated with Modic changes an infectious process? Results from a prospective monocenter study. PLoS One 14(8):e0221030, 2019
2. Akieda-Asai S, Ma H, Date Y: Palmitic acid induces guanylin gene expression through the toll-like receptor 4/nuclear factor κB pathway in rat macrophages. Am J Physiol Cell Physiol 317(6):C1239-C1246, 2019
3. Akira S, Uematsu S, Takeuchi O: Pathogen recognition and innate immunity. Cell 124(4):783-801, 2006
4. Akyol S, Eraslan BS, Etyemez H, Tanriverdi T, Hanci M: Catabolic cytokine expressions in patients with degenerative disc disease. Turk Neurosurg 20(4):492-499, 2010
5. Albert HB, Kjaer P, Jensen TS, Sorensen JS, Bendix T, Manniche C: Modic changes, possible causes and relation to low back pain. Med Hypotheses 70(2):361-368, 2008
6. An Y, Li J, Li Y, Shen Y: Characteristics of Modic changes in cervical kyphosis and their association with axial neck pain. J Paif Res 10:1657-1661, 2017
7. Beutler BA: TLRs and innate immunity. Blood 113(7):1399-1407, 2009
8. Cao W, Du Y, Gao L, Che N, Zhang Q, Luo J, Cao W, Fu X, Wang R: Lipopolysaccharide/Toll-like receptor 4 signaling pathway involved Qingdu decoction treating severe liver injury merging with endotoxemia. J Tradit Chin Med 37(3):371-377, 2017
9. Chen L, Hu X, Zhang J, Battié MC, Lin X, Wang Y: Modic changes in the lumbar spine are common aging-related degenerative findings that parallel with disk degeneration. Clin Spine Surg 31(7):312-317, 2018
10. Chen Y, Bao J, Yan Q, Wu C, Yang H, Zou J: Distribution of Modic changes in patients with low back pain and its related factors. Eur J Med Res 24(1):34, 2019
11. Dudli S, Fields AJ, Samartzis D, Karppinen J, Lotz JC: Pathobiology of Modic changes. Eur Spine J 25(11):3723-3734, 2016
12. Ge J, Chen L, Yang Y, Lu X, Xiang Z: Sparstolonin B prevents lumbar intervertebral disc degeneration through toll like receptor 4, NADPH oxidase activation and the protein kinase B signaling pathway. Mol Med Rep 17(1):1347-1353, 2018
13. Janeway CA Jr, Medzhitov R: Innate immune recognition. Annu Rev Immunol 20:197-216, 2002
14. Jensen OK, Andersen MH, Østgård RD, Andersen NT, Rolving N: Probiotics for chronic low back pain with type 1 Modic changes: A randomized double-blind, placebo-controlled trial with 1-year follow-up using Lactobacillus Rhamnosis GG. Eur Spine J 28(11):2478-2486, 2019
15. Karppinen J, Solovieva S, Luoma K, Raininko R, Leino-Arjas P, Riihimäki H: Modic changes and interleukin 1 gene locus polymorphisms in occupational cohort of middle-aged men. Eur Spine J 18(12):1963-1970, 2009
16. Krock E, Millecamps M, Currie JB, Stone LS, Haglund L: Low back pain and disc degeneration are decreased following chronic toll-like receptor 4 inhibition in a mouse model. Osteoarthritis Cartilage 26(9):1236-1246, 2018
17. Li N, Whitaker C, Xu Z, Heggeness M, Yang SY: Therapeutic effects of naringin on degenerative human nucleus pulposus cells for discogenic low back pain. Spine J 16(10):1231-1237, 2016
18. Medzhitov R: Recognition of microorganisms and activation of the immune response. Nature 449(7164):819-826, 2007
19. Mok FPS, Samartzis D, Karppinen J, Fong DYT, Luk KDK, Cheung KMC: Modic changes of the lumbar spine: prevalence, risk factors, and association with disc degeneration and low back pain in a large-scale population-based cohort. Spine J 16(1):32-41, 2016
20. Park BS, Song DH, Kim HM, Choi BS, Lee H, Lee JO: The structural basis of lipopolysaccharide recognition by the TLR4–MD-2 complex. Nature 458(7242):1191-1195, 2009
21. Pasare C, Medzhitov R: Toll-like receptors and acquired immunity. Semin Immunol 16(1):23-26, 2004
22. Quero L, Klawitter M, Schmaus A, Rothley M, Sleeman J, Tiaden AN, Klasen J, Boos N, Hottiger MO, Wuertz K, Richards PJ: Hyaluronic acid fragments enhance the inflammatory and catabolic response in human intervertebral disc cells through modulation of toll-like receptor 2 signalling pathways. Arthritis Res Ther 15(4):R94, 2013

23. Sacre SM, Andreakos E, Kiriakidis S, Amjadi P, Lundberg A, Giddins G, Feldmann M, Brennan F, Foxwell BM: The Toll-like receptor adaptor proteins MyD88 and Mal/TIRAP contribute to the inflammatory and destructive processes in a human model of rheumatoid arthritis. Am J Pathol 170:518-525, 2007
24. Teichtahl AJ, Finnin MA, Wang Y, Wluka AE, Urquhart DM, O'Sullivan R, Jones G, Cicuttini FM: The natural history of Modic changes in a community-based cohort. Joint Bone Spine 84(2):197-202, 2017
25. van den Berg R, Jongbloed EM, de Schepper EIT, Bierma-Zeinstra SMA, Koes BW, Luijsterburg PAJ: The association between pro-inflammatory biomarkers and nonspecific low back pain: A systematic review. Spine J 18(11):2140-2151, 2018
26. Yang H, Tian W, Wang S, Liu X, Wang Z, Hou L, Ge J, Zhang X, He Z, Wang X: TSG-6 secreted by bone marrow mesenchymal stem cells attenuates intervertebral disc degeneration by inhibiting the TLR2/NF-κB signaling pathway. Lab Invest 98(6):755-772, 2018
27. Zhang J, Li Z, Chen F, Liu H, Wang H, Li X, Liu X, Wang J, Zheng Z: TGF-β1 suppresses CCL3/4 expression through the ERK signaling pathway and inhibits intervertebral disc degeneration and inflammation-related pain in a rat model. Exp Mol Med 49(9):e379, 2017
28. Zhang L, Chen Q, Wang H, Yang J, Sheng S: Andrographolide mitigates IL-1β-induced human nucleus pulposus cells degeneration through the TLR4/MyD88/NF-κB signaling pathway. Mol Med Rep 18(6):5427-5436, 2018
29. Zhongyi S, Sai Z, Chao L, Jiwei T: Effects of nuclear factor kappa B signaling pathway in human intervertebral disc degeneration. Spine (Phila Pa 1976) 40(4):224-232, 2015