Austin Journal of Orthopedics & Rheumatology

Austin Publishing Group

Open Access Full Text Article

Editorial

Fibrosis in Intervertebral Disc Degeneration: Knowledge and Gaps

Yan Peng[2#] and Feng-Juan Lv[1,2,3,4*#]

[1]HKU Shenzhen Institute of Research and Innovation, China

[2]Department of Orthopaedics and Traumatology, University of Hong Kong, China

[3]Stem Cell & Regenerative Medicine Consortium, University of Hong Kong, China

[4]Center for Reproduction, Development and Growth, University of Hong Kong, China

[#]These authors contribute equally to this work

***Corresponding author:** Feng-Juan Lv, Department of Orthopedics and Traumatology, University of Hong Kong, Pokfulam Road, Pokfulam, Hong Kong SAR, China

Received: September 18, 2014; **Accepted:** September 22, 2014; **Published:** September 23, 2014

Editorial

Intervertebral disc (IVD) degenerates with aging. It is a major contribution to low back pain [1] which may cause mortality and is one of the most frequent reasons for clinic visits and loss of work hours, leading to considerable economic burden on health care [2]. The molecular pathogenesis of IVD degeneration remains largely unclear. Understanding of these biological changes would help to identify the crucial mediator of IVD degeneration and facilitate future therapeutic development.

It has been reported that degenerated IVD is in a chronic inflammatory state with increased expression of multiple inflammatory cytokines. Examination of surgically degenerated and/or herniated discs has reported the expression of interleukin (IL) -1, matrix metalloproteinase (MMP) -10 [3], IL-8, tumor necrosis factor (TNF) -α, IL-10 [4], and prostaglandin E2 (PGE2) [5]. It is also observed that levels of production of IL-6 and IL-8 were significantly higher in patients undergoing fusion for discogenic low back pain compared to the patients undergoing discectomy for sciatica [6]. Nerve growth factor (NGF) is known to play an important role for pain, including low back pain (LBP), which can be induced by proinflammatory cytokines in IVD cells [3]. Experimentally, acute injury or loading results in a transient inflammation cascades in the IVD, subsequently the disc would either recover or continue to degenerate with time, which might be depended on the degree of initial damage [7,8]. Chronic overloading of the disc leads to significant inflammation coinstantaneous with the annular damage [9]. Repeated injuries in the IVD during the active healing triggers persistent inflammation in the disc [1,10]. Besides, both injury and compression of the disc lead to increase of the neuropeptides in the dorsal root ganglia (DRG), especially the compression in the IVDs could result in the long-lasting nerve injury and afferent fibers regeneration to innervate IVD [10]. Importantly, among these inflammatory factors, TNF-α [11] is shown to act as neuropathic pain mediator. Stimulation of IVD with inflammatory factors, such as IL-1 and TNF-a [12,13], or macrophages [14], also induces degenerative changes.

Chronic inflammation is thought to be the major cause of tissue fibrosis. During IVD degeneration, fibrotic changes appear to occur in the same way as in other tissues. Fibrosis is an exaggerated inflammatory response to injury which results in matrix remodeling and increased mechanical stiffness of the tissue [15,16]. It is represented by increased collagen I, II and fibronectin. Studies have demonstrated that in degenerated IVD, there is an increase in collagens types I, III and fibronectin content, and a loss of proteoglycans [17]. Studies on surgical specimens of discal or peridiscal tissues provide the evidence of abnormal fibrosis in the degenerated discs [18-21]. Degenerated IVD also exhibits elevated expression of connective tissue growth factor (CTGF) [20], a fibrosis marker. In our recent work, puncture-induced disc degeneration in mice and rabbits led to fibrotic changes that were analogous to human IVD degeneration [22-24]. In the degenerated IVD, collagen I and fibronectin expression were upregulated in the NP. We further showed in the rabbit model that such fibrotic transformation is accompanied by a significant increase in collagen fibril diameter and stiffness at nano-structural levels [25]. Moreover, we found that the implantation of mesenchymal stem cells (MSCs) can modulate the fibrotic events within the IVD by reducing the deposition of collagen I, and reducing the fibril thickness and stiffness. We also showed that the treatment of degenerated human NP (nucleus pulposus: the center compartment of IVD) cells with MSCs-conditioned media resulted in the suppression of profibrotic mediators MMP12 and HSP47 (a chaperone for collagen processing) expression [25], suggesting that the anti-fibrotic activity of MSCs is elicited through long-distance signaling to target cells, presumably the profibrotic effector cells such as the macrophage and myofibroblasts, in the degenerating disc [24]. Findings described thus far, strongly implicate fibrosis being involved in the process of IVD degeneration.

Macrophages and myofibroblasts have been implicated as the main mediators in fibrosis [16]. In acute stage of inflammation, 'classically activated' macrophages secret pro-inflammatory cytokines, such as interleukin-1 (IL-1), IL-6, IL-8, and tissue necrosis factor-α (TNF-α), to fight the infection or clear o the necrotic tissue. In late stage, 'alternatively activated' macrophages appear and secrete anti-inflammatory factors, such as IL-10, which stimulate the activation of myofibroblasts, to aid tissue repair and wound healing. Myofibroblasts are the primary source of extracellular matrix in tissue fibrosis including that of lungs, liver, skeletal muscle and kidneys [26-29]. Myofibroblasts characteristically express alpha smooth muscle actin (α-SMA) [28], vimentin, type I collagen and fibronectin [30]. They are the major type of effecter cells in tissue fibrosis which express collagen I and contribute to excessive tissue repair and scar tissue formation [31].

Citation: Peng Y and Feng-Juan Lv. Fibrosis in Intervertebral Disc Degeneration: Knowledge and Gaps. Austin J Orthopade & Rheumatol. 2014;1(1): 3.

In the literature, several studies have suggested the detection of macrophages or cells with phagocytic activities in the IVD. In 1994, Gronblad et al. [32] reported that only a few cells positive for CD68, a macrophage marker, were observed in macroscopically normal discs, whereas abundant CD68(+) cells were present in half of the herniated discs. Similarly, in two other studies, CD68(+) cells were detected in the nucleus pulposus of all individuals with histomorphologic signs of disc degeneration [33] or surgical specimens [34], predominantly in discs adjacent to cleft formations, while they were not detected in the discs of fetuses, infants, and adolescents. Additionally, it was found that bovine disc cells were able to ingest latex beads at least as efficiently, if not more so, than cell lines of monocytes/macrophages showing that IVD cells were capable of behaving as competent phagocytes. Despite of the findings of macrophages in IVD degeneration, whether these macrophages are tissue resident cells, or infiltrated through blood vessel ingrowth, is unclear. Moreover, whether the IVD macrophages belong to class I (classically activated, inflammatory) or class II (alternatively activated, anti-inflammatory) macrophages, is a question awaited to be answered.

Different from macrophages, currently, myofibroblasts have not been confirmed to be associated with IVD degeneration. One study [35] reported that cells positive for the expression of α-smooth muscle actin (α-SMA), a marker of myofibroblasts, increased in degenerated IVDs, highlighting the possibility of the detection of myofibroblasts. However, α-SMA is characteristic of, but not limited to, myofibroblasts. To confirm the detection of myofibroblasts in the IVD, studies demonstrating co-expression of α-SMA with other myofibroblasts markers, such as fibroblast specific protein, desmin, or transforming growth factor (TGF) beta 1, will be required.

In the literature, myofibroblasts are postulated to have multiple origins. It may be derived from local mesenchyme cells [36], circulating fibrocytes [37], or epithelial cells [38]. Interestingly, research suggest that myofibroblasts may be also derived from stem/progenitor cells [39]. Coincidently, recently reports about the detection of endogenous stem/progenitor like cells in IVD are emerging. These include the identification of MSC-like progenitor cells in the NP, annulus fibrosus [40-42] or endplate [43,44]. Whether the endogenous IVD stem cells contributes to the generation of myofibroblasts, or on the other hand, whether IVD fibrosis affects the number and properties of IVD endogenous stem cells, remain exclusively in the dark.

Conclusion Remark

Emerging evidence has suggested the involvement of fibrosis in IVD degeneration, mainly based on matrix changes due to remodeling. The involvement of cellular changes, including macrophages and myofibroblasts, in this process is not well documented. Whether the endogenous stem cells contribute to, or are affected by, IVD fibrosis calls for further study.

Acknowledgement

This work was supported by Small Project Funding of the University of Hong Kong (201209176179), and Seed Funding Programme for Basic Research of the University of Hong Kong (201211159148).

References

1. Cheung KM, Karppinen J, Chan D, Ho DW, Song YQ, Sham P, et al. Prevalence and pattern of lumbar magnetic resonance imaging changes in a population study of one thousand forty-three individuals. Spine (Phila Pa 1976). 2009; 34: 934-940.
2. Freemont AJ. The cellular pathobiology of the degenerate intervertebral disc and discogenic back pain. Rheumatology (Oxford). 2009; 48: 5-10.
3. Richardson SM, Doyle P, Minogue BM, Gnanalingham K, Hoyland JA. Increased expression of matrix metalloproteinase-10, nerve growth factor and substance P in the painful degenerate intervertebral disc. Arthritis Res Ther. 2009; 11: R126.
4. Ahn SH, Cho YW, Ahn MW, Jang SH, Sohn YK, Kim HS, et al. mRNA expression of cytokines and chemokines in herniated lumbar intervertebral discs. Spine (Phila Pa 1976). 2002; 27: 911-917.
5. O'Donnell JL, O'Donnell AL. Prostaglandin E2 content in herniated lumbar disc disease. Spine (Phila Pa 1976). 1996; 21: 1653-1655.
6. Burke JG, Watson RW, McCormack D, Dowling FE, Walsh MG, Fitzpatrick JM, et al. Intervertebral discs which cause low back pain secrete high levels of proinflammatory mediators. J Bone Joint Surg Br. 2002; 84: 196-201.
7. Lotz JC, Ulrich JA. Innervation, inflammation, and hypermobility may characterize pathologic disc degeneration: review of animal model data. J Bone Joint Surg Am. 2006; 88 Suppl 2: 76-82.
8. Anderson DG, Izzo MW, Hall DJ, Vaccaro AR, Hilibrand A, Arnold W, et al. Comparative gene expression profiling of normal and degenerative discs: analysis of a rabbit annular laceration model. Spine (Phila Pa 1976). 2002; 27: 1291-1296.
9. Wang YJ, Shi Q, Lu WW, Cheung KC, Darowish M, Li TF. Cervical intervertebral disc degeneration induced by unbalanced dynamic and static forces: a novel in vivo rat model. Spine (Phila Pa 1976). 2006; 31: 1532-1538.
10. Miyagi M, Ishikawa T, Kamoda H, Suzuki M, Murakami K, Shibayama M, et al. ISSLS prize winner: disc dynamic compression in rats produces long-lasting increases in inflammatory mediators in discs and induces long-lasting nerve injury and regeneration of the afferent fibers innervating discs: a pathomechanism for chronic discogenic low back pain. Spine (Phila Pa 1976). 2012; 37: 1810-1818.
11. Igarashi T. 2000 Volvo Award winner in basic science studies: Exogenous tumor necrosis factor-alpha mimics nucleus pulposus-induced neuropathology. Molecular, histologic, and behavioral comparisons in rats. Spine (Phila Pa 1976). 2000; 25: 2975-2980.
12. Millward-Sadler SJ, Costello PW, Freemont AJ, Hoyland JA. Regulation of catabolic gene expression in normal and degenerate human intervertebral disc cells: implications for the pathogenesis of intervertebral disc degeneration. Arthritis Res Ther. 2009; 11: R65.
13. Hoyland JA, Le Maitre C, Freemont AJ. Investigation of the role of IL-1 and TNF in matrix degradation in the intervertebral disc. Rheumatology (Oxford). 2008; 47: 809-814.
14. Takada T, Nishida K, Maeno K, Kakutani K, Yurube T, Doita M, et al. Intervertebral disc and macrophage interaction induces mechanical hyperalgesia and cytokine production in a herniated disc model in rats. Arthritis Rheum. 2012; 64: 2601-2610.
15. Peng H, Herzog EL. Fibrocytes: emerging effector cells in chronic inflammation. Curr Opin Pharmacol. 2012; 12: 491-496.
16. Reilkoff RA, Bucala R, Herzog EL. Fibrocytes: emerging effector cells in chronic inflammation. Nat Rev Immunol. 2011; 11: 427-435.
17. Antoniou J, Steffen T, Nelson F, Winterbottom N, Hollander AP, Poole RA, et al. The human lumbar intervertebral disc: evidence for changes in the biosynthesis and denaturation of the extracellular matrix with growth, maturation, ageing, and degeneration. J Clin Invest. 1996; 98: 996-1003.
18. Kluba T, Niemeyer T, Gaissmaier C, Gründer T. Human anulus fibrosis and nucleus pulposus cells of the intervertebral disc: effect of degeneration and culture system on cell phenotype. Spine (Phila Pa 1976). 2005; 30: 2743-2748.

19. Cooper RG, Freemont AJ, Hoyland JA, Jenkins JP, West CG, Illingworth KJ, et al. Herniated intervertebral disc-associated periradicular fibrosis and vascular abnormalities occur without inflammatory cell infiltration. Spine (Phila Pa 1976). 1995; 20: 591-598.

20. Peng B, Chen J, Kuang Z, Li D, Pang X, Zhang X. Expression and role of connective tissue growth factor in painful disc fibrosis and degeneration. Spine (Phila Pa 1976). 2009; 34: E178-182.

21. Boos N, Weissbach S, Rohrbach H, Weiler C, Spratt KF, Nerlich AG, et al. Classification of age-related changes in lumbar intervertebral discs: 2002 Volvo Award in basic science. Spine (Phila Pa 1976). 2002; 27: 2631-2644.

22. Yang F, Leung VY, Luk KD, Chan D, Cheung KM. Injury-induced sequential transformation of notochordal nucleus pulposus to chondrogenic and fibrocartilaginous phenotype in the mouse. J Pathol. 2009; 218: 113-121.

23. Ho G, Leung VY, Cheung KM, Chan D. Effect of severity of intervertebral disc injury on mesenchymal stem cell-based regeneration. Connect Tissue Res. 2008; 49: 15-21.

24. Leung VY, Aladin DM, Lv F, Tam V, Sun Y, Lu WW, et al. Mesenchymal stem cells mediate disk regeneration by suppression of fibrosis in nucleus pulposus. Global Spine J. 2012; 2: S4.06.

25. Leung VY, Aladin DM, Lv F, Tam V, Sun Y, Lau RY, et al. Mesenchymal stem cells reduce intervertebral disc fibrosis and facilitate repair. Stem Cells. 2014; 32: 2164-2177.

26. McAnulty RJ. Fibroblasts and myofibroblasts: their source, function and role in disease. Int J Biochem Cell Biol. 2007; 39: 666-671.

27. Hinz B, Phan SH, Thannickal VJ, Galli A, Bochaton-Piallat ML, Gabbiani G. The myofibroblast: one function, multiple origins. Am J Pathol. 2007; 170: 1807-1816.

28. Sarrazy V, Billet F, Micallef L, Coulomb B, Desmoulière A. Mechanisms of pathological scarring: role of myofibroblasts and current developments. Wound Repair Regen. 2011; 19 Suppl 1: s10-15.

29. Iwaisako K, Brenner DA, Kisseleva T. What's new in liver fibrosis? The origin of myofibroblasts in liver fibrosis. J Gastroenterol Hepatol. 2012; 27 Suppl 2: 65-68.

30. Brenner DA, Kisseleva T, Scholten D, Paik YH, Iwaisako K, Inokuchi S, et al. Origin of myofibroblasts in liver fibrosis. Fibrogenesis Tissue Repair. 2012; 5: S17.

31. Gabbiani G, Majno G. Dupuytren's contracture: fibroblast contraction? An ultrastructural study. Am J Pathol. 1972; 66: 131-146.

32. Grönblad M, Virri J, Tolonen J, Seitsalo S, Kääpä E, Kankare J, et al. A controlled immunohistochemical study of inflammatory cells in disc herniation tissue. Spine (Phila Pa 1976). 1994; 19: 2744-2751.

33. Nerlich AG, Weiler C, Zipperer J, Narozny M, Boos N. Immunolocalization of phagocytic cells in normal and degenerated intervertebral discs. Spine (Phila Pa 1976). 2002; 27: 2484-2490.

34. Shamji MF, Setton LA, Jarvis W, So S, Chen J, Jing L, et al. Proinflammatory cytokine expression profile in degenerated and herniated human intervertebral disc tissues. Arthritis Rheum. 2010; 62: 1974-1982.

35. Hastreiter D, Ozuna RM, Spector M. Regional variations in certain cellular characteristics in human lumbar intervertebral discs, including the presence of alpha-smooth muscle actin. J Orthop Res. 2001; 19: 597-604.

36. Ross R, Everett NB, Tyler R. Wound healing and collagen formation. VI. The origin of the wound fibroblast studied in parabiosis. J Cell Biol. 1970; 44: 645-654.

37. Andersson-Sjöland A, Nihlberg K, Eriksson L, Bjermer L, Westergren-Thorsson G. Fibrocytes and the tissue niche in lung repair. Respir Res. 2011; 12: 76.

38. Yamada M, Kubo H, Ota C, Takahashi T, Tando Y, Suzuki T, et al. The increase of microRNA-21 during lung fibrosis and its contribution to epithelial-mesenchymal transition in pulmonary epithelial cells. Respir Res. 2013; 14: 95.

39. Emura M, Ochiai A, Horino M, Arndt W, Kamino K, Hirohashi S, et al. Development of myofibroblasts from human bone marrow mesenchymal stem cells cocultured with human colon carcinoma cells and TGF beta 1. In Vitro Cell Dev Biol Anim. 2000; 36: 77-80.

40. Risbud MV, Guttapalli A, Tsai TT, Lee JY, Danielson KG, Vaccaro AR. Evidence for skeletal progenitor cells in the degenerate human intervertebral disc. Spine (Phila Pa 1976). 2007; 32: 2537-2544.

41. Brisby H, Papadimitriou N, Brantsing C, Bergh P, Lindahl A, Barreto Henriksson H. The presence of local mesenchymal progenitor cells in human degenerated intervertebral discs and possibilities to influence these in vitro: a descriptive study in humans. Stem Cells Dev. 2013; 22: 804-814.

42. Feng G, Yang X, Shang H, Marks IW, Shen FH, Katz A, et al. Multipotential differentiation of human anulus fibrosus cells: an in vitro study. J Bone Joint Surg Am. 2010; 92: 675-685.

43. Liu LT, Huang B, Li CQ, Zhuang Y, Wang J, Zhou Y, et al. Characteristics of stem cells derived from the degenerated human intervertebral disc cartilage endplate. PLoS One. 2011; 6: e26285.

44. Huang B, Liu LT, Li CQ, Zhuang Y, Luo G, Hu SY, et al. Study to determine the presence of progenitor cells in the degenerated human cartilage endplates. Eur Spine J. 2012; 21: 613-622.

Austin J Orthopade & Rheumatol - Volume 1 Issue 1 - 2014
ISSN: 2472-369X | www.austinpublishinggroup.com

Citation: Peng Y and Feng-Juan Lv. Fibrosis in Intervertebral Disc Degeneration: Knowledge and Gaps. Austin J Orthopade & Rheumatol. 2014;1(1): 3.