

Macrophage migration inhibitory factor may contribute to hypertrophy of lumbar ligamentum flavum in type 2 diabetes mellitus

Qi-Lin Lu, Xiao-Zhen Wang, Wei Xie, Xiong-Wei Chen, Yi-Liang Zhu, Xu-Gui Li

Department of Orthopedics, Hubei 672 Orthopaedics Hospital of Integrated Chinese & Western Medicine, Hubei University of Chinese Medicine, Wuhan, Hubei 430065, China.

To the Editor: Lumbar spinal canal stenosis (LSCS) is a common disease among older individuals. Hypertrophic lumbar ligamentum flavum (LLF) plays a vital role in the pathogenesis of LSCS. The physiological LLF is a kind of dense connective tissue with thickness of 2 to 4 mm, which is mainly composed of fibroblasts and extracellular matrix (ECM). ECM contains elastic, collagen fibers and ground substances. The distribution characteristics of fibers show that a large number of elastic fibers are mixed with a small amount of the collagen fibers; mainly type I and type III collagen fibers. These fibers are arranged tightly and regularly along the direction of column's axis. The LLF is located in the dorsal part of the dura mater of the spinal canal, and it attaches to the upper border and lower parts of anterior surfaces of the laminae. The hypotrophy of LLF is the consequence of several factors such as aging, inflammatory process, stress loading and genetic predisposition. Once the hypertrophy of LLF occurs, it can cause the stenosis for the central spinal canal, nerve root canal and intervertebral foramen. This pathology can lead to low back pain, sciatica, and even urinary and bowel disorders.

Fibrosis is the main cause of the LLF hypertrophy. The micro cosmic morphology study has found obviously increased thickness and brittleness in the hypertrophic LLF. Proinflammatory reaction plays an important role in the LLF's fibrosis. Increased matrix metalloproteinase (MMP) expression in LLF is accompanied by degradation of elastic fibers and increased quantity of the collagen fibers. Inflammatory stimulus leads to the proliferation of fibroblasts, and collagen fibers that are secreted by those fibroblasts becomes disordered in arrangement. The proliferation of fibroblasts and these increased and disorganized collagen fibers mainly contribute to the hypertrophy of LLF.

Previous studies have implicated the proinflammatory factors including interleukin (IL)-1 α , IL-6, tumor necrosis factor (TNF)- α , prostaglandin E2 (PGE2), nitric oxide (NO), MMP13 and transforming growth factor (TGF)- β 1 as a potential contributor in the pathogenesis of LLF hypertrophy.^[1] Among them, IL-1 α , IL-6, TNF- α , PGE2, and NO can lead to the excessive expression of collagen fibers: type I collagen by IL-1 α and IL-6, whereas type III collagen by TNF- α , PGE2, and NO. Studies have shown that MMP-13 plays a crucial role in the degeneration of elastic fibers.^[1] In addition, TGF- β 1, as a multifunctional growth factor, not only participates in the synthesis of ECM proteins, but also promotes the proliferation and differentiation of the fibroblasts. Therefore, these inflammatory mediators constitute a complicated regulation networks and get involved in the morphological changes of LLF.

Previous studies have demonstrated that the mechanical degeneration of spine causes micro-injury to LLF and induces inflammatory reaction. However, more and more scholars have started paying attention to the role of metabolic factors in the inflammatory reaction for LLF hypertrophy. Researchers have shown a definite relationship between LSCS and systemic diseases; especially, type 2 diabetes mellitus (T2DM).^[2] They have shown that the LLFs in T2DM patients have more obvious infiltration of macrophages and its thickness is more than those in non-diabetic group. T2DM was always associated with decreased expression of elastin fiber loss in LLF caused by higher expression of MMP-13. However, the potential pathogenesis underlying LLF hypertrophy remains to be fully elucidated.

Macrophage migration inhibitory factor (MIF) is a multipotent soluble protein with obvious pro-inflammatory and chemotactic function. In addition to the

Access this article online

Quick Response Code:



Website:
www.cmj.org

DOI:
10.1097/CM9.0000000000000680

Correspondence to: Prof. Xu-Gui Li, Department of Orthopedics, Hubei 672 Orthopaedics Hospital of Integrated Chinese & Western Medicine, Hubei University of Chinese Medicine, Wuhan, Hubei 430065, China
E-Mail: bxjarlene@aliyun.com

Copyright © 2020 The Chinese Medical Association, produced by Wolters Kluwer, Inc. under the CC-BY-NC-ND license. This is an open access article distributed under the terms of the Creative Commons Attribution-Non Commercial-No Derivatives License 4.0 (CCBY-NC-ND), where it is permissible to download and share the work provided it is properly cited. The work cannot be changed in any way or used commercially without permission from the journal.

Chinese Medical Journal 2020;133(5)

Received: 04-11-2019 Edited by: Ning-Ning Wang

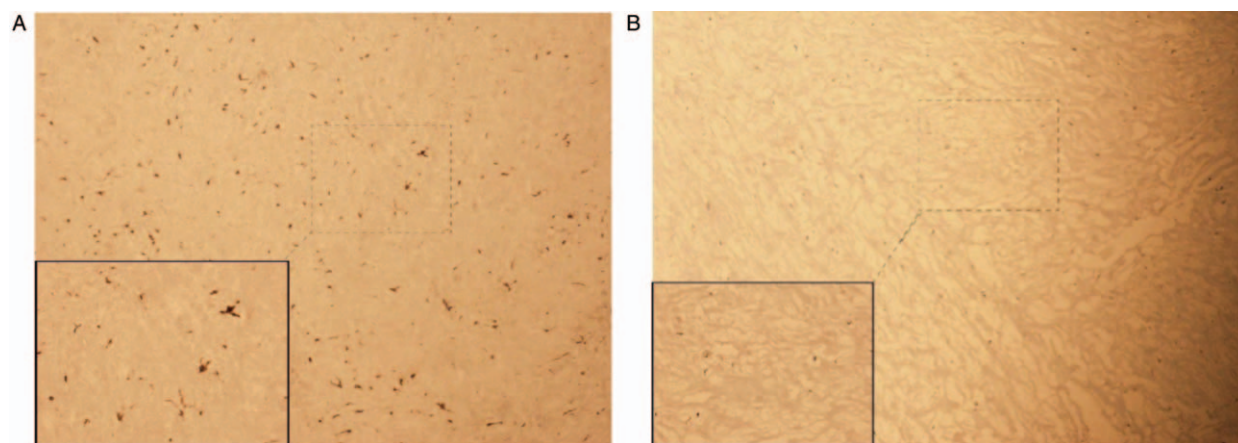


Figure 1: Immunohistochemistry result of LLF from T2DM+ showed more fibroblasts proliferation and obvious MIF positive staining which was distributed both in fibroblasts and ECM (A); immunohistochemistry result of LLF from T2DM- showed less MIF positive staining and less fibroblasts proliferation (B) (original magnification $\times 100$, original magnification $\times 400$ at left bottom of each picture). ECM: Extracellular matrix; MIF: Macrophage migration inhibitory factor; LLF: Lumbar ligamentum flavum; T2DM: Type 2 diabetes mellitus.

activated T cells, human islet beta cells, macrophages, eosinophils, basophils, and adipocytes can also secrete this multipotent protein. Previous studies have identified some polymorphisms in the gene promoter region of MIF which are associated with T2DM. A study revealed that the concentration of MIF in serum of T2DM patients was significantly higher than that in the normal people.^[3] MIF was an important mediator in the development of T2DM itself and its complications. Some scholars have proposed that MIF could be a new predictor of metabolic disturbances and complications in T2DM. In 2018, Mokshagundam^[4] has proposed that MIF could be applied as a potential target for T2DM prevention. As mentioned above, IL-6, IL-1 α , TNF- α , TGF- β 1, and MMP-13 played a vital role in the fibrosis of LLF, and it has been proven that MIF could promote the expression of these factors. Moreover, scholars have found that MIF could promote myocardial fibrosis and fibroblast proliferation through Src kinase signaling pathway.^[5] However, the relationship between MIF and ligamentum flavum matrix and fibroblasts in T2DM patients has not been established yet after thorough literature review.

Higher concentration of MIF in the LLF of T2DM patients might be the underlying pathogenesis of LLF hypertrophy. To study the pathological differences between the LSCS patients with or without T2DM, 19 hypertrophic LLF samples from LSCS patients with T2DM (T2DM+; $n = 9$) and without T2DM (T2DM-; $n = 10$) were obtained during their lumbar surgery. LLF thickness was 5.9 ± 0.3 mm in T2DM+ group and 5.1 ± 0.2 mm in T2DM- group ($t = 2.398$; $P = 0.028$) by Jong-Beom Park method. The concentration of MIF was 366.7 ± 20.1 pg/mg protein in T2DM+ group and 207.3 ± 19.1 pg/mg protein in T2DM- group ($t = 5.740$; $P < 0.001$) by enzyme-linked immunosorbent assay. Therefore, the differences of LLF thickness and concentration of MIF between two groups were statistically significant. Statistics analysis also revealed that the MIF concentration in LLF had a positive correlation with its thickness ($r = 0.686$, $P = 0.001$). More positive staining

was found both in nucleus of the fibroblasts and matrix of T2DM+ LLF using immunohistochemistry as compared to that from T2DM- patients [Figure 1]. By these results, we reasonably hypothesize that MIF may contribute to the fibrosis and hypertrophy of the LLF in T2DM patients, given the peculiar roles of MIF in promoting inflammation, proliferating fibroblasts, and inducing chemotaxis. However, further studies are needed to understand the precise mechanism of this phenomenon.

Declaration of patient consent

The authors certify that they have obtained all appropriate patients' consent forms. In the form, the patients provided their consent for their tissues, surgery and the research information to be reported in the journal. The patient understands that their names and initials will not be published and efforts will be made to conceal their identity.

Funding

This study was supported by the grants from the Scientific Research Grant of Health and Family Planning Commission of Wuhan Municipality (No. WX19B06) and the Health Commission of Hubei Province Scientific Research Project (No. WJ2019H429).

Conflicts of interest

None.

References

1. Park JO, Lee BH, Kang YM, Kim TH, Yoon JY, Kim H, *et al.* Inflammatory cytokines induce fibrosis and ossification of human ligamentum flavum cells. *J Spinal Disord Tech* 2013;26:E6-E12. doi: 10.1097/BSD.0b013e3182698501.
2. Lotan R, Oron A, Anekstein Y, Shalmon E, Mirovsky Y. Lumbar stenosis and systemic diseases: is there any relevance? *J Spinal Disord Tech* 2008;21:247-251. doi: 10.1097/BSD.0b013e31813707af.

3. Morsi HK, Ismail MM, Gaber HA, Elbasmy AA. Macrophage migration inhibitory factor and malondialdehyde as potential predictors of vascular risk complications in type 2 diabetes mellitus: cross-sectional case control study in Saudi Arabia. *Mediators Inflamm* 2016;2016:5797930. doi: 10.1155/2016/5797930.
 4. Mokshagundam SPL. Macrophage migration inhibitory factor-a potential target for diabetes prevention? *Am J Med Sci* 2018;355:519–520. doi:10.1016/j.amjms.2018.03.007.
 5. Xue YM, Deng CY, Wei W, Liu FZ, Yang H, Liu Y, *et al.* Macrophage migration inhibitory factor promotes cardiac fibroblast proliferation through the Src kinase signaling pathway. *Mol Med Rep* 2018;17:3425–3431. doi: 10.3892/mmr.2017.8261.
-
- How to cite this article:** Lu QL, Wang XZ, Xie W, Chen XW, Zhu YL, Li XG. Macrophage migration inhibitory factor may contribute to hypertrophy of lumbar ligamentum flavum in type 2 diabetes mellitus. *Chin Med J* 2020;133:623–625. doi: 10.1097/CM9.0000000000000680