

# Semaphorin 3a: a potential target for low back pain

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## Introduction

Low back pain (LBP) is a common disorder. Around 60% of the adult population suffers from back discomfort at some point in their lifetime ( [Hoy et al., 2012](#) ; [Campbell and Colvin, 2013](#) ). However, a definite pathological cause to this sickness is still unknown. Prior research has reported various potential factors, which may be associated with back pain, such as mechanical changes, low pH throughout the disc, disc degeneration, cytokines etc. Anatomically, it has been proposed that degenerative joint disease and intervertebral disc degeneration are the most common factors. In addition, pathological innervation into the degenerative intervertebral disc is said to be closely related with pain of intervertebral disc origin ( [Luoma et al., 2000](#) ; [Cheung et al., 2009](#) ; [García-Cosamalón et al., 2010](#) ; [Miyagi et al., 2014](#) ). Thus, most therapeutic research on low back pain focuses on inhibiting neural invasion and delaying disc degradation ( [Mantyh, 2014](#) ; [Vasiliadis et al., 2014](#) ; [Sakai and Grad, 2015](#) ).

Semaphorin 3A, originally known for its potent inhibition of axonal outgrowth, has been found to play pivotal roles in several other systems ( [Luo et al., 1993](#) ; [Barresi et al., 2009](#) ; [Shim et al., 2013](#) ; [van Gils et al., 2013](#) ). Notably, several recent studies have suggested that the expression of semaphorin 3A and its receptors (neuropilins) correlates with disease activity and histological features in some skeletal disorders ( [Hayashi et al., 2012](#) ; [Negishi-Koga and Takayanagi, 2012](#) ; [Fukuda et al., 2013](#) ; [Takagawa et al., 2013](#) ). Previous research has demonstrated that semaphorin 3A is associated with innervation and vascularization, enzyme secretion, and cartilage development in skeletal tissues ( [Gomez et al., 2005](#) ; [Okubo et al.,](#) <https://assignbuster.com/semaphorin-3a-a-potential-target-for-low-back-pain/>

[2011](#) ; [Fukuda et al., 2013](#) ). These effects contribute to physiological and pathological alteration of the skeletal system. Further research also indicates the important role of enzyme secretion in disc degradation ( [Canbay et al., 2013](#) ; [Xu et al., 2014](#) ). Since semaphorin 3A has been proven to be involved in both processes, we question that if there is any correlation between semaphorin 3A and low back pain.

## **Hypothesis**

Based on the effects of semaphorin 3A on innervation and vascularization, as well as on enzyme secretion in the skeletal system, coupled with the understanding of pathophysiology of low back pain, we hypothesize that semaphorin 3A may be a potential therapeutic target for low back pain.

## **Evaluation of the Hypothesis**

It has been observed in both animal and human studies that with the progression of degeneration, sensory nerve fibers—which require a low level of chemical and mechanical stimuli to trigger pain—begin to innervate normally anural and avascular areas ( [Freemont et al., 1997](#) ; [Miyagi et al., 2014](#) ). Research by Mantyh et al. showed that the administration of anti-nerve growth factors dramatically block the sprouting of these fibers, therefore significantly inhibited pain in mice ( [Mantyh et al., 2010](#) ). Therefore, an approach to inhibit pathological neural and vascular innervation in degenerative vertebral discs represents a new potential for pain management and treatment.

The mechanisms underlying the degeneration of intervertebral discs along with aging are complex, though MMP has been shown to play an important

role. Research showed that the expression of MMPs is positively related to the severity of degeneration ( [Rutges et al., 2008](#) ; [Xu et al., 2014](#) ). Based on their catabolic biological activities, the function of these enzymes is to maintain the integrity of the matrix by cooperating with other factors that perform anabolic activities ( [Le Maitre et al., 2007](#) ). However, in a pathological condition the balance disrupts and can lead to excessive degradation of disc components ( [Vo et al., 2013](#) ).

Semaphorin 3A, a prototypical class 3 secreted semaphorin, is a potent inhibitor of axonal outgrowth in a specific subset of sensory and sympathetic neurons and induces collapse of their growth cones. Research by Sotonye et al. showed that semaphorin 3A is highly expressed by healthy disc cells and decreased significantly in degenerate samples ( [Tolofari et al., 2010](#) ).

Considering its inhibition of axonal outgrowth, semaphorin 3A may act as a biological barrier against neuronal ingrowth within healthy intervertebral disc. In addition, mRNA for semaphorin 3A receptors (neuropilins) was identified in healthy and degenerate tissues ( [Tolofari et al., 2010](#) ).

Neuropilins have also been confirmed to bind to vascular endothelial growth factor (VEGF), which is a key regulator of normal and pathologic angiogenesis ( [Dai and Rabie, 2007](#) ). As VEGF and class 3 semaphorins compete for binding to neuropilins, reduction of semaphorin 3A may lead to increased binding of VEGF. Furthermore, binding of neuropilins to VEGF has been shown to result in promotion of the migration, proliferation, and tube formation of endothelial cells ( [Bates et al., 2003](#) ; [Dai and Rabie, 2007](#) ; [Roskoski, 2007](#) ; [Staton et al., 2007](#) ). This process provides chemoattractive cues for vascular innervation, which may be associated with vascularization

in degenerated intervertebral disc. All in all, semaphorin 3A is a potent inhibitor of both pathological innervation and vascular proliferation.

Research on lung cancer has further shown a negative correlation between protein expression levels of semaphorin 3A and MMP-14 ( [Zhou et al., 2014](#) ). In neurons, semaphorin 3A was also shown to consistently reduce MMP-3 expression and activity ( [Gonthier et al., 2009](#) ). Recent research on osteoarthritic cartilage has also shown that semaphorin 3A inhibited VEGF165-induced overexpression of MMPs ( [Okubo et al., 2011](#) ). These findings demonstrate the potential role of semaphorin 3A in negatively regulating MMP secretion. Although there is no direct evidence showing a relationship between the expression of MMPs and semaphorin 3A in patients with low back pain, the observations in other tissues provide some clues on the effects of semaphorin 3A on degenerative intervertebral discs.

Therefore, based on the potent effects of semaphorin 3A on repelling nerve ingrowth and vascular proliferation, as well as its negative regulation of MMPs, we hypothesize that semaphorin 3A may be a potential therapeutic target for low back pain.

## **Author Contributions**

All of the authors meet all 4 of the requirements as stipulated in the Guide for Authors. Substantial contribution to the concept and design of this study: Pengbin Yin, Peifu Tang, and Licheng Zhang; literature retrieval: Licheng Zhang, Houchen Lv; and manuscript drafting: Pengbin Yin.

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## Conflict of Interest Statement

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

## References

Barresi, V., Vitarelli, E., and Cerasoli, S. (2009). Semaphorin3A immunohistochemical expression in human meningiomas: correlation with the microvessel density. *Virch. Arch.* 454, 563–571. doi: 10. 1007/s00428-009-0757-3

[PubMed Abstract](#) | [CrossRef Full Text](#) | [Google Scholar](#)

Bates, D., Taylor, G. I., Minichiello, J., Farlie, P., Cichowitz, A., Watson, N., et al. (2003). Neurovascular congruence results from a shared patterning mechanism that utilizes Semaphorin3A and Neuropilin-1. *Dev. Biol.* 255, 77–98. doi: 10. 1016/S0012-1606(02)00045-3

[PubMed Abstract](#) | [CrossRef Full Text](#) | [Google Scholar](#)

Campbell, J., and Colvin, L. A. (2013). Management of low back pain. *BMJ* 347: f3148. doi: 10. 1136/bmj. f3148

[PubMed Abstract](#) | [CrossRef Full Text](#) | [Google Scholar](#)

Canbay, S., Turhan, N., Bozkurt, M., Arda, K., and Caglar, S. (2013). Correlation of matrix metalloproteinase-3 expression with patient age, magnetic resonance imaging and histopathological grade in lumbar disc degeneration. *Turk. Neurosurg.* 23, 427–433. doi: 10. 5137/1019-5149. JTN. 7459-12. 0

[PubMed Abstract](#) | [CrossRef Full Text](#) | [Google Scholar](#)

Cheung, K. M., Karppinen, J., Chan, D., Ho, D. W., Song, Y. Q., Sham, P., et al. (2009). Prevalence and pattern of lumbar magnetic resonance imaging changes in a population study of one thousand forty-three individuals. *Spine (Phila Pa 1976)* 34, 934–940. doi: 10. 1097/BRS. 0b013e3181a01b3f

[PubMed Abstract](#) | [CrossRef Full Text](#) | [Google Scholar](#)

Dai, J., and Rabie, A. B. (2007). VEGF: an essential mediator of both angiogenesis and endochondral ossification. *J. Dent. Res.* 86, 937–950. doi: 10. 1177/154405910708601006

[PubMed Abstract](#) | [CrossRef Full Text](#) | [Google Scholar](#)

Freemont, A. J., Peacock, T. E., Goupille, P., Hoyland, J. A., O'Brien, J., and Jayson, M. I. (1997). Nerve ingrowth into diseased intervertebral disc in chronic back pain. *Lancet* 350, 178–181. doi: 10. 1016/S0140-6736(97)02135-1

[PubMed Abstract](#) | [CrossRef Full Text](#) | [Google Scholar](#)

Fukuda, T., Takeda, S., Xu, R., Ochi, H., Sunamura, S., Sato, T., et al. (2013). Sema3A regulates bone-mass accrual through sensory innervations. *Nature* 497, 490–493. doi: 10. 1038/nature12115

[PubMed Abstract](#) | [CrossRef Full Text](#) | [Google Scholar](#)

García-Cosamalón, J., del Valle, M. E., Calavia, M. G., García-Suárez, O., López-Muñiz, A., Otero, J., et al. (2010). Intervertebral disc, sensory nerves and neurotrophins: who is who in discogenic pain? *J. Anat.* 217, 1–15. doi: 10. 1111/j. 1469-7580. 2010. 01227. x

[PubMed Abstract](#) | [CrossRef Full Text](#) | [Google Scholar](#)

Gomez, C., Burt-Pichat, B., Mallein-Gerin, F., Merle, B., Delmas, P. D., Skerry, T. M., et al. (2005). Expression of Semaphorin-3A and its receptors in endochondral ossification: potential role in skeletal development and innervation. *Dev. Dynam.* 234, 393–403. doi: 10. 1002/dvdy. 20512

[PubMed Abstract](#) | [CrossRef Full Text](#) | [Google Scholar](#)

Gonthier, B., Koncina, E., Satkauskas, S., Perraut, M., Roussel, G., Aunis, D., et al. (2009). A PKC-dependent recruitment of MMP-2 controls semaphorin-3A growth-promoting effect in cortical dendrites. *PLoS ONE* 4: e5099. doi: 10. 1371/journal. pone. 0005099

[PubMed Abstract](#) | [CrossRef Full Text](#) | [Google Scholar](#)

Hayashi, M., Nakashima, T., and Takayanagi, H. (2012). The regulatory mechanisms of bone metabolism by semaphorin. *Clin. Calcium.* 22, 1693–1699. doi: CliCa121116931699

<https://assignbuster.com/semaphorin-3a-a-potential-target-for-low-back-pain/>



[PubMed Abstract](#) | [CrossRef Full Text](#) | [Google Scholar](#)

Hoy, D., Bain, C., Williams, G., March, L., Brooks, P., Blyth, F., et al. (2012). A systematic review of the global prevalence of low back pain. *Arthritis Rheum.* 64, 2028–2037. doi: 10. 1002/art. 34347

[PubMed Abstract](#) | [CrossRef Full Text](#) | [Google Scholar](#)

Le Maitre, C. L., Pockert, A., Buttle, D. J., Freemont, A. J., and Hoyland, J. A. (2007). Matrix synthesis and degradation in human intervertebral disc degeneration. *Biochem. Soc. Trans.* 35(Pt 4), 652–655. doi: 10. 1042/BST0350652

[PubMed Abstract](#) | [CrossRef Full Text](#)

Luo, Y., Raible, D., and Raper, J. A. (1993). Collapsin: a protein in brain that induces the collapse and paralysis of neuronal growth cones. *Cell* 75, 217–227. doi: 10. 1016/0092-8674(93)80064-L

[PubMed Abstract](#) | [CrossRef Full Text](#) | [Google Scholar](#)

Luoma, K., Riihimäki, H., Luukkonen, R., Raininko, R., Viikari-Juntura, E., and Lamminen, A. (2000). Low back pain in relation to lumbar disc degeneration. *Spine (Phila Pa 1976)* 25, 487–492. doi: 10. 1097/00007632-200002150-00016

[PubMed Abstract](#) | [CrossRef Full Text](#) | [Google Scholar](#)

Mantyh, P. W. (2014). The neurobiology of skeletal pain. *Eur. J. Neurosci.* 39, 508–519. doi: 10. 1111/ejn. 12462

<https://assignbuster.com/semaphorin-3a-a-potential-target-for-low-back-pain/>

[PubMed Abstract](#) | [CrossRef Full Text](#) | [Google Scholar](#)

Mantyh, W. G., Jimenez-Andrade, J. M., Stake, J. I., Bloom, A. P., Kaczmarska, M. J., Taylor, R. N., et al. (2010). Blockade of nerve sprouting and neuroma formation markedly attenuates the development of late stage cancer pain. *Neuroscience* 171, 588–598. doi: 10.1016/j.neuroscience.2010.08.056

[PubMed Abstract](#) | [CrossRef Full Text](#) | [Google Scholar](#)

Miyagi, M., Millecamps, M., Danco, A. T., Ohtori, S., Takahashi, K., and Stone, L. S. (2014). Increased innervation and sensory nervous system plasticity in a mouse model of low back pain due to intervertebral disc degeneration. *Spine (Phila Pa 1976)* . 39, 1345–1354. doi: 10.1097/BRS.

0000000000000334

[PubMed Abstract](#) | [CrossRef Full Text](#) | [Google Scholar](#)

Negishi-Koga, T., and Takayanagi, H. (2012). Bone cell communication factors and Semaphorins. *Bonekey Rep* . 1: 183. doi: 10.1038/bonekey.2012.183

[PubMed Abstract](#) | [CrossRef Full Text](#) | [Google Scholar](#)

Okubo, M., Kimura, T., Fujita, Y., Mochizuki, S., Niki, Y., Enomoto, H., et al. (2011). Semaphorin 3A is expressed in human osteoarthritic cartilage and antagonizes vascular endothelial growth factor 165-promoted chondrocyte migration: an implication for chondrocyte cloning. *Arthritis Rheum* . 63, 3000–3009. doi: 10.1002/art.30482

[PubMed Abstract](#) | [CrossRef Full Text](#) | [Google Scholar](#)

<https://assignbuster.com/semaphorin-3a-a-potential-target-for-low-back-pain/>

Roskoski, R. Jr. (2007). Vascular endothelial growth factor (VEGF) signaling in tumor progression. *Crit. Rev. Oncol. Hematol.* 62, 179–213. doi: 10. 1016/j. critrevonc. 2007. 01. 006

[PubMed Abstract](#) | [CrossRef Full Text](#) | [Google Scholar](#)

Rutges, J. P., Kummer, J. A., Oner, F. C., Verbout, A. J., Castelein, R. J., Roestenburg, H. J., et al. (2008). Increased MMP-2 activity during intervertebral disc degeneration is correlated to MMP-14 levels. *J. Pathol.* 214, 523–530. doi: 10. 1002/path. 2317

[PubMed Abstract](#) | [CrossRef Full Text](#) | [Google Scholar](#)

Sakai, D., and Grad, S. (2015). Advancing the cellular and molecular therapy for intervertebral disc disease. *Adv. Drug Deliv. Rev.* 84, 159–171. doi: 10. 1016/j. addr. 2014. 06. 009

[PubMed Abstract](#) | [CrossRef Full Text](#) | [Google Scholar](#)

Shim, E. J., Chun, E., Kang, H. R., Cho, S. H., Min, K. U., and Park, H. W. (2013). Expression of semaphorin 3A and neuropilin 1 in asthma. *J. Korean Med. Sci.* 28, 1435–1442. doi: 10. 3346/jkms. 2013. 28. 10. 1435

[PubMed Abstract](#) | [CrossRef Full Text](#) | [Google Scholar](#)

Staton, C. A., Kumar, I., Reed, M. W., and Brown, N. J. (2007). Neuropilins in physiological and pathological angiogenesis. *J. Pathol.* 212, 237–248. doi: 10. 1002/path. 2182

[PubMed Abstract](#) | [CrossRef Full Text](#) | [Google Scholar](#)

<https://assignbuster.com/semaphorin-3a-a-potential-target-for-low-back-pain/>

Takagawa, S., Nakamura, F., Kumagai, K., Nagashima, Y., Goshima, Y., and Saito, T. (2013). Decreased semaphorin3A expression correlates with disease activity and histological features of rheumatoid arthritis. *BMC Musculoskelet. Disord* . 14: 40. doi: 10. 1186/1471-2474-14-40

[PubMed Abstract](#) | [CrossRef Full Text](#) | [Google Scholar](#)

Tolofari, S. K., Richardson, S. M., Freemont, A. J., and Hoyland, J. A. (2010). Expression of semaphorin 3A and its receptors in the human intervertebral disc: potential role in regulating neural ingrowth in the degenerate intervertebral disc. *Arthritis Res. Ther.* 12: R1. doi: 10. 1186/ar2898

[PubMed Abstract](#) | [CrossRef Full Text](#) | [Google Scholar](#)

van Gils, J. M., Ramkhelawon, B., Fernandes, L., Stewart, M. C., Guo, L., Seibert, T., et al. (2013). Endothelial expression of guidance cues in vessel wall homeostasis dysregulation under proatherosclerotic conditions. *Arterioscler. Thromb. Vasc. Biol* . 33, 911-919. doi: 10. 1161/ATVBAHA. 112. 301155

[PubMed Abstract](#) | [CrossRef Full Text](#) | [Google Scholar](#)

Vasiliadis, E. S., Pneumaticos, S. G., Evangelopoulos, D. S., and Papavassiliou, A. G. (2014). Biologic treatment of mild and moderate intervertebral disc degeneration. *Mol. Med.* 20, 400-409. doi: 10. 2119/molmed. 2014. 00145

[PubMed Abstract](#) | [CrossRef Full Text](#) | [Google Scholar](#)

Vo, N. V., Hartman, R. A., Yurube, T., Jacobs, L. J., Sowa, G. A., and Kang, J. D. (2013). Expression and regulation of metalloproteinases and their inhibitors in intervertebral disc aging and degeneration. *Spine J* . 13, 331–341. doi: 10.1016/j.spinee.2012.02.027

[PubMed Abstract](#) | [CrossRef Full Text](#) | [Google Scholar](#)

Xu, H., Mei, Q., Xu, B., Liu, G., and Zhao, J. (2014). Expression of matrix metalloproteinases is positively related to the severity of disc degeneration and growing age in the East Asian lumbar disc herniation patients. *Cell Biochem. Biophys*. 70, 1219–1225. doi: 10.1007/s12013-014-0045-y

[PubMed Abstract](#) | [CrossRef Full Text](#) | [Google Scholar](#)

Zhou, H., Wu, A., Fu, W., Lv, Z., and Zhang, Z. (2014). Significance of semaphorin-3A and MMP-14 protein expression in non-small cell lung cancer. *Oncol. Lett*. 7, 1395–1400. doi: 10.3892/ol.2014.1920

[PubMed Abstract](#) | [CrossRef Full Text](#) | [Google Scholar](#)