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Advances in Animal Models of Lumbar Ligamentum Flavum Hypertrophy

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Commentary

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ABSTRACT

Ligamentum Flavum Hypertrophy (LFH) is a key pathological factor in Lumbar Spinal Stenosis (LSS), driven by mechanisms like mechanical stress and collagen deposition. Although animal models are used to study LFH, they still face limitations in biological authenticity and clinical translation. This commentary reviews the advantages and limitations of surgical and non-surgical modeling approaches, proposing potential optimization strategies. It also explores future research directions to improve LFH models and enhance clinical outcomes.

Keywords: Ligamentum flavum hypertrophy; Animal models; Surgical modeling; Mechanical stress; collagen deposition

INTRODUCTION

LFH is a key factor in LSS, caused by excessive collagen deposition, leading to spinal canal narrowing and nerve compression, resulting in symptoms like leg pain and numbness. The exact mechanisms remain unclear, but LFH is associated with lumbar degeneration and abnormal mechanical loading. Various animal models, both surgical and non-surgical, have been developed to study LFH. Despite providing valuable data, these models face challenges in reproducibility, pathological replication, and clinical translation. This commentary reviews the models, discussing their strengths, weaknesses, and potential optimization directions.

Surgical modeling

Traditional surgical models

In traditional surgical models, ligamentum flavum hypertrophy is induced by disrupting lumbar spine stability. Wang et al. increased mechanical stress by resecting the spinous process, paraspinal muscles, or articular processes in rat models, leading to increased collagen content in the ligamentum flavum [1]. Hayashi et al. used an experimental rabbit model and performed posterior lateral fusion surgery, resulting in increased cartilage matrix deposition and upregulation of TGF-β1 [2].

While these models are cost-effective and replicate pathological features well, they have significant limitations. First, the post-surgical mechanical stress is not accurately quantified, complicating standardization and potentially affecting result reliability. Second, the lack of continuous monitoring of dynamic stress limits the accurate simulation of physiological responses. Future research should focus on improving stress quantification methods and continuous monitoring to enhance model reliability and biological authenticity.

Innovative hybrid modeling methods

In recent years, researchers have combined traditional surgical models with dynamic stress stimulation to enhance biological authenticity and research efficiency. Chen et al. proposed a hybrid approach involving resection of the L5-L6 spinous process, transverse processes, and supraspinous ligament, followed by dynamic loading using a treadmill. This method offers a shorter modeling cycle and greater biological authenticity, especially in simulating dynamic loads similar to human activities [3].

However, despite improving efficiency and accuracy, the model has limitations. The surgical procedure is complex, requiring additional equipment, which increases difficulty and cost. Additionally, while the model yields accurate short-term biological responses, long-term effects and reproducibility still need validation. Future research should focus on simplifying the procedure and reducing costs while maintaining precision and biological relevance.

Non-surgical modeling

Mechanical stress models

Saito et al. designed a mechanical stress s device that flexes the mouse spine to simulate stress [4]. After 12 weeks, the lumbar ligamentum flavum showed increased cross-sectional area and thickness, but lacked hallmark changes seen in human LFH, such as macrophage infiltration and TGF-β1 expression. Zheng et al. forced mice to stand bipedally, which increased ligamentum flavum size and collagen content after 10 weeks. This method is simple, but individual variation in posture limits reproducibility [5].

While mechanical stress models are non-invasive, they fail to replicate key human LFH features, such as inflammation, and show significant variation. Future studies should enhance their biological relevance for better preclinical use.

Chemical induction models

Chemical induction models use agents like LPA or TGF-β1 to activate signaling pathways and promote ligamentum flavum hypertrophy. Zhou et al. used LPA-loaded gelatin sponges to activate the LPAR1-Akt pathway and promote

fibrosis. These models are advantageous in targeting specific molecular pathways, offering precision in studying LFH mechanisms [6].

However, they fail to replicate the true biomechanical environment, limiting their clinical relevance. Therefore, while useful for exploring fibrotic mechanisms, they have limitations in simulating LFH progression. Future research should combine chemical induction with biomechanical loading for more physiologically relevant models.

Future research directions

Current LFH animal models have provided valuable insights but still face challenges in biological authenticity and clinical translation. Future research should focus on dynamic monitoring technologies, such as wearable devices and real-time imaging, to track spinal stress and fibrosis changes. Advances in 3D bioprinting enable the construction of humanized ligamentum flavum organoids, offering new platforms for mechanism studies and drug screening. Multi-omics techniques (e.g., single-cell RNA sequencing) will reveal cellular heterogeneity and molecular networks, guiding targeted therapy. Gene-mechanical signal interactions will deepen understanding of LFH mechanisms.

Despite the potential of these technologies, challenges like technology integration, collaboration, and cost must be addressed for clinical translation. Future research should aim to integrate these technologies to enhance the mechanistic understanding of LFH and enable precision treatment.

AUTHOR CONTRIBUTIONS

Long Chen: Writing – original draft, Writing – review & editing.
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CONFLICT OF INTEREST

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.

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