Microbiome Question 1: Can the gut microbiome play a role in causing degenerative spine disease in animal models?

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Response/Recommendation: Unknown. The available preclinical data, at the molecular and histopathological levels, suggest that there is a correlation between an adverse gut microbiota and degenerative spine disease.

Level of Evidence: Weak

Delegate Vote: Agree: %, Disagree: %, Abstain: %

Rationale:

Low back pain is strongly linked to intervertebral disc degeneration (IDD), a multifactorial condition involving microenvironmental changes within the disc [1]. This introduced the concept of the "gut–spine axis," which operates through a complex interplay of systemic inflammation, immune modulation, and metabolic disruption [2, 23].

Preclinical research in rats, mice, and rabbits suggests that the gut microbiome influences the spine through three distinct biological pathways.

First, the gut microbiota is a major regulator of the host immune system. An adverse gut microbiota can cause increased activation of mucosal immune cells and the release of pro-inflammatory cytokines—such as TNF-α, IL-6, and IL-1β—into the bloodstream. These cytokines accumulate near the IVDs, leading to the emergence of nociceptive nerve fibers and the upregulation of pain-related cation channels [7, 8, 21]. Research in germ-free mouse models further supports this, showing that the absence of gut microbiota results in decreased immune signaling, an imbalanced T(H)1/T(H)2 ratio, and systemic T-cell deficiencies compared to mice colonized with species such as *Bacteroides fragilis* [9, 10].

Second, metabolic signaling occurs as gut bacteria produce essential metabolites, including short-chain fatty acids (SCFAs), which regulate energy provision, mucosal protection, and immune modulation [11, 12, 21]. Changes in the abundance of these metabolites can disrupt the homeostasis between osteoblasts and osteoclasts, leading to vertebral bone remodeling, endplate thickening, and IVD calcification [13, 14, 21]. Furthermore, research in New Zealand rabbits has shown that IDD leads to significant changes in gut microbiota—specifically the upregulation of bacterial genera like *Helicobacter* and *Vibrio*—which are closely associated with altered tyrosine and amino sugar metabolism [22].

Third, bacterial translocation can occur when the intestinal epithelial barrier becomes compromised—a condition often termed "leaky gut syndrome." This allows live bacteria or microbial components to enter the systemic circulation and migrate through spinal capillary systems to the intervertebral disc (IVD). Such transport of live microbes through the systemic circulation is believed to occur through the same mechanisms that enable the establishment of the microbiota of tumors and hematogenous seeding of orthopaedic implants that cause infection. Rajasekaran et al. identified several microbial taxa in the gut that were also detected in samples of intervertebral disc [20]. The hypoxic, low-acid and immune privileged environment of the disc provides a niche that anaerobic bacteria such as *Cutibacterium acnes* can colonize. Once present the slow growing organisms can trigger local inflammation and associated tissue damage [3–5, 21]. Conversely, research by Wang Z. indicates that colonizing *Lacticaseibacillus*

paracasei S16 in mice with IDD enhances disc cell proliferation and limits cell death, significantly boosting behavioral recovery and mitigating abnormal inflammatory responses compared to untreated groups [6]. These findings underscore how the hypoxic conditions and lack of immune surveillance within the IVD create an ideal environment for anaerobic bacteria, such as *C. acnes*, to trigger inflammatory cascades [24].

Key animal studies highlight the therapeutic potential of targeting the gut–spine axis. Yao et al. found that fecal microbiota transplant (FMT) from healthy donors was capable of reducing the abundance of inflammatory markers (TNF-α, IL-1β, and IL-6) and matrix-degrading enzymes (MMP-3 and MMP-13), thereby inhibiting cell death pathways involving NLRP3 and Caspase-1 [1, 15]. Central to these immunomodulatory processes is Methyltransferase-like 3 (METTL3), a key protein in the m6A methyltransferase complex that regulates RNA splicing. Research indicates that METTL3 is highly expressed in IDD, and its inhibition via the METTL3/TLR2 pathway can restore healthy gut microbiota and mitigate disc cell senescence [16, 17]. Experimental studies utilizing rat models have demonstrated that the gut–disc axis is a primary pathway through which Traditional Chinese Medicine (TCM) alleviates spinal disease. Song et al. utilized a male Sprague-Dawley rat puncture model to show that Duhuo Jisheng Decoction (DHJSD) restores disc height and reverses histopathological damage by rebalancing the *Firmicutes*/*Bacteroidetes* ratio and normalizing twelve metabolic pathways to suppress nucleus pulposus cell apoptosis [27]. Similarly, Wang et al. identified that Sanbi Decoction (SBD) effectively restores IVD function and hydration by enriching beneficial taxa such as *Patescibacteria* and *Actinobacteriota*, while simultaneously reducing systemic pro-inflammatory markers through the modulation of lipid and amino acid metabolism [18].

Recent human genetic research utilizing bidirectional Mendelian randomization studies has established a causal link between the gut microbiota and IDD. This research identified specific risk factors, such as the phylum *Bacteroidetes* and genus *Marvinbryantia*, as well as protective factors, including the *Eubacterium coprostanoligenes* group and the family *Ruminococcaceae*. These findings provide a theoretical foundation for the "gut–disc axis" and the development of microbial-targeted therapeutic strategies [25, 26].

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