

circPDE4B prevents articular cartilage degeneration and promotes repair by acting as a scaffold for RIC8A and MID1

Xiangqian Fang

Zhejiang University, China



Abstract

Objectives: Circular RNAs (circRNAs) have emerged as significant biological regulators. Herein, we aimed to elucidate the role of an unidentified circRNA (circPDE4B) that is reportedly downregulated in osteoarthritis (OA) tissues.

Methods: The effects of circPDE4B were explored in human and mouse chondrocytes in vitro. Specifically, RNA pull-down (RPD)-mass spectrometry analysis (MS), immunoprecipitation, glutathione-S-transferase (GST) pull-down, RNA immunoprecipitation and RPD assays were performed to verify the interactions between circPDE4B and the RIC8 guanine nucleotide exchange factor A (RIC8A)/midline 1 (MID1) complex. A mouse model of OA was also employed to confirm the role of circPDE4B in OA pathogenesis in vivo.

Results: circPDE4B regulates chondrocyte cell viability and extracellular matrix metabolism. Mechanistically, FUS RNA binding protein (FUS) was found to promote the splicing of circPDE4B, while downregulation of circPDE4B in OA is partially caused by upstream inhibition of FUS. Moreover, circPDE4B facilitates the association between RIC8A and MID1 by acting as a scaffold to promote RIC8A degradation through proteasomal degradation. Furthermore, ubiquitination of RIC8A at K415 abrogates RIC8A degradation. The circPDE4B–RIC8A axis was observed to play an important role in regulating downstream p38 mitogen-activated protein kinase (MAPK) signaling. Furthermore, delivery of a circPDE4B adeno-associated virus (AAV) abrogates the breakdown of cartilage matrix by medial meniscus destabilization in mice, whereas a RIC8A AAV induces the opposite effect.

Conclusion: This work highlights the function of the circPDE4B–RIC8A axis in OA joints, as well as its regulation of MAPK-p38, suggesting this axis as a potential therapeutic target for OA.

Biography

Xiangqian Fang is a doctor/professor of Sir Run Run Shaw Hospital, China. He is the director of Zhejiang University and Key Laboratory of Musculoskeletal System Degeneration and Regeneration Translational Research. He has been published in internationally renowned journals like Spine, Ann Rheum Dis, and Molecular Cancer et al.



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