Molecular Biology Reports (2025) 52:533
https://doi.org/10.1007/s11033-025-10653-6

REVIEW

Exploring kartogenin: advances in therapeutics and signaling mechanisms for musculoskeletal regeneration

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Received: 19 March 2025 / Accepted: 27 May 2025

Abstract

Kartogenin (KGN) is a small synthetic heterocyclic molecule with chondrogenic and chondroprotective effects. Since its discovery, there has been a focus on regenerating cartilage damage and treating Osteoarthritis) OA(. In the treatment of OA, it's important to target both cartilage and subchondral bone. KGN appears to reduce cartilage degradation and changes in subchondral trabecular bone. It can also reduce inflammation and pain behavior in vitro and in vivo. Additionally, KGN promotes chondrocyte differentiation and proliferation. It has been applied in many regenerative research fields including aesthetic procedures, limb skeletal growth, wound healing, tendon and bone regeneration and disc regeneration. KGN is similar to the natural ligands involved in cell signaling and differentiation. The master regulator of cartilage genes, Sex-determining region-box 9 protein (SOX9), is upregulated by KGN, making it an ideal drug to promote cartilage repair. Advantages of KGN include demonstrated low toxicity across various cell types and no apparent adverse effects in animals. It is highly stable, easily stored at room temperature, and can be synthesized inexpensively and efficiently. Analogues of KGN have entered clinical trials.

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Published online: 02 June 2025

KGN and MiRNAs

MicroRNAs (miRNAs) are small molecules (18–25 nucleotides) that can regulate cartilage degeneration through post-transcriptional modulation [64]. EV-based strategies can be used as a novel therapeutic approach to stimulate chondrogenic differentiation of native MSCs. It has been shown that sEVs released from KGN-preconditioned hUCMSCs was enriched with miR-381-3p. MiR-381-3p in KGN-sEVs can promote chondrogenic differentiation by upregulating the expression of SOX9, COL II, and ACAN. MiR-381-3p exerts prochondrogenic effects by targeting TAOK1 and suppressed the Hippo signaling pathway (Fig. 4). TAOK1/3 are direct kinases for LATS1/2, which are upstream regulators of YAP/TAZ. When miR-381-3p inhibits TAOK1/3, phosphorylation of YAP/TAZ is suppressed. As a result, the Hippo signaling pathway is suppressed [61]. KGN upregulates NRF2 expression in OA chondrocytes by downregulating miR-146a. Previous investigations revealed that miR-146a suppresses the expression of GAGs and COL II in mice. It has been demonstrated that miR-146a inhibits NRF2 expression by binding to its mRNA 3′-UTRs. Overexpression of miR-146a downregulates NRF2 and diminishes the protective effect of KGN. It seems that KGN regulates miR-146a-NRF2 via the MAPK signaling pathway [28]. Studies have shown that miR-145-5p expression is increased in patients with OA. MiR-145-5p is a target for SOX9 and inhibits MSC differentiation into cartilage. Liu and his colleagues showed that when BMSCs treated with KGN were injected into a rat OA model, the expression of miR-145-5p decreased, and chondrogenic differentiation was promoted by targeting the Samd4 pathway. Additionally, intra-articular injection of KGN-pretreated BMSCs alleviated OA-related pain [64].

Conclusion, perspectives, and challenges

OA is marked by gradual cartilage breakdown, rising incidence, and limited effectiveness of current treatments. Patients worldwide suffer from a heavy socio-economic burden due to the disease. Since KGN is a chondrogenic and chondroprotective agent, it is expected to serve as a novel therapy for OA. It has been demonstrated that KGN can be applied across various regenerative research fields, including aesthetic procedure, limb skeletal growth, wound healing, tendon and bone regeneration, and disc regeneration. Although the potential of KGN in cartilage regeneration has been widely recognized, several scientific challenges remain. More animal and clinical studies are needed to determine optimal timing, dosage, administration methods, and delivery systems for KGN. The clinical use of KGN continues to face obstacles, such as concerns about metabolic pathways, long-term safety, and potential interactions with other medications. KGN might influence the effectiveness of other drugs or lead to negative side effects. There is presently a gap in long-term toxicological evaluation of KGN, with limited investigation into potential side effects, including impacts on hepatic and renal function following prolonged treatment. There are still many challenges in developing of chemical leads into drugs for regenerative medicine.

Acknowledgements The authors would like to thank Shiraz University of Medical Sciences, Shiraz, Iran and also Center for Development of Clinical Research of Nemazee Hospital and Dr. Nasrin Shokrpour for editorial assistance.

Author contributions SK conducted the comprehensive literature search, assisted in the collection and organization of data, contributed to write the initial draft of manuscript and integrate finding from various study. SK and VR led the conceptual development of the study, perform the critical reviews of the manuscript, edited the final manuscript. SK contributed to write the initial draft of manuscript, too. JF assist in integrating findings from various study and edited final manuscript. NT edited the final manuscript and checked the formatting consistency. All author reviewed and approved the final version of the manuscript before submission.

Funding The authors have received no funding for this maunscript.

Data availability No datasets were generated or analysed during the current study.

Declarations

Competing interests The authors declare no competing interests.

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