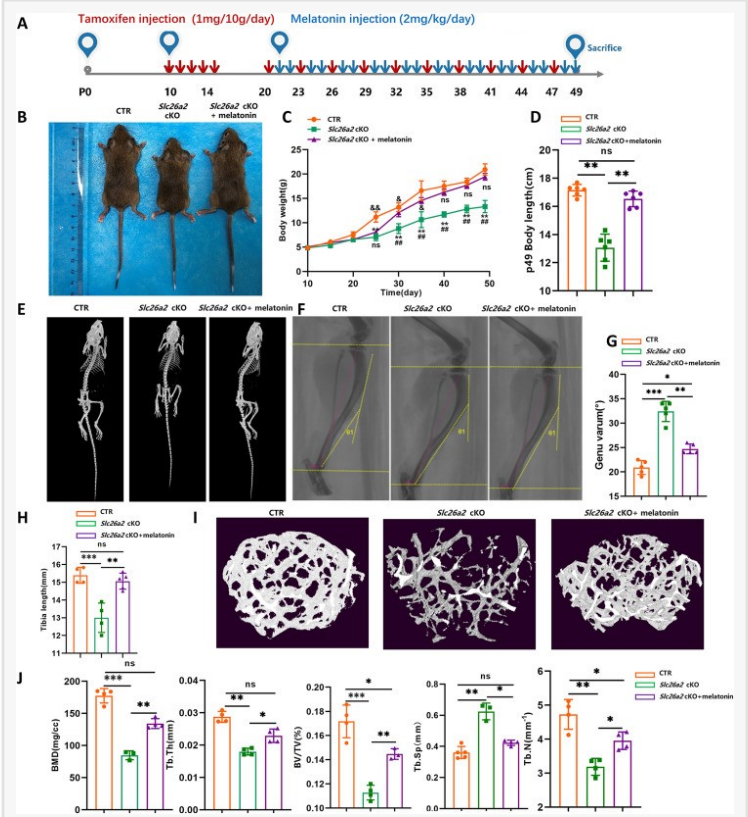
Melatonin Identified as a Potential Therapeutic Agent For SLC26A2-Related Chondrodysplasias

Targeting ER Stress and Calcium Overload to Restore Skeletal Growth in SLC26A2-Deficient Chondrodysplasias

CHINA, March 6, 2025 /EINPresswire.com/ -- Solute carrier family 26 member 2 (SLC26A2) is an SO42− transporter, facilitating the uptake of inorganic sulfate into cells. Mutations in SLC26A2 lead to chondrodysplasia, a rare genetic disorder characterized by abnormal cartilage development that affects bone growth. Unfortunately, the current challenge lies in the absence of effective pharmaceutical interventions for SLC26A2-associated chondrodysplasias.

This research, published in the Genes & Diseases journal by a team from the Fourth Military Medical University, Xi'an Jiaotong University, and Northwestern University, Xi'an, Shaanxi, investigate the therapeutic effects of an indoleamine hormone, melatonin, on SLC26A2-deficient chondrodysplasias.



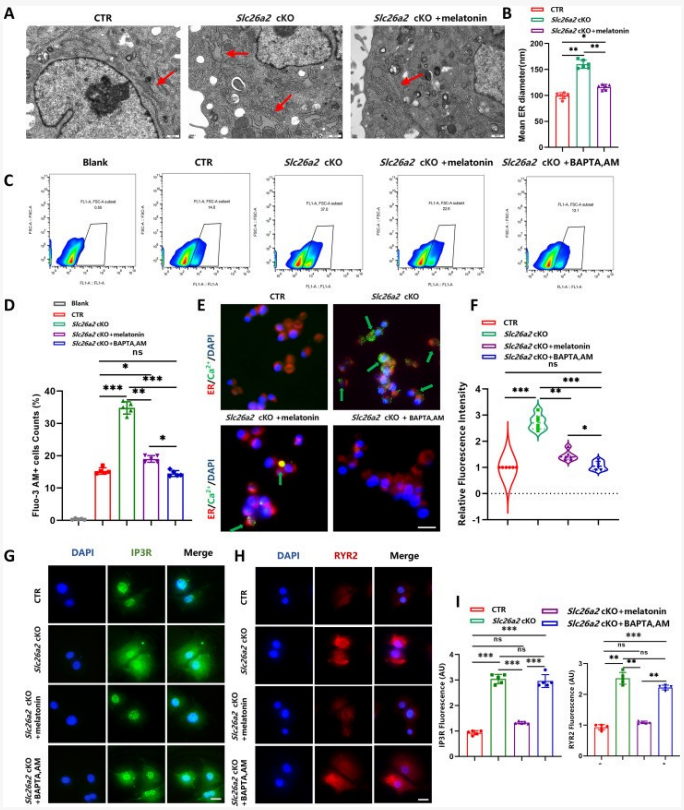
(A) Overview of the drug delivery plan. Tamoxifen was administered to mice at a dosage of 1 mg per 10 g body weight per day, for consecutive 5 days from P10 to P14 and then every three days from P10 to P49. Melatonin was given from P10 to P49. (B) Gross a

In the in vitro studies, the researchers found that melatonin ameliorates impaired anabolism and proliferation of Slc26a2-deficient chondrocytes and attenuates activation of unfolded protein response (UPR) induced by Slc26a2 deficiency. Additionally, melatonin also suppressed cytoplasmic calcium overload and significantly inhibited cell death in Slc26a2-deficient chondrocytes.

In the in vivo studies, the research findings indicated that melatonin could effectively rescue

defective formation and abnormal morphology of bone in cartilage-specific Slc26a2 knockout mice (Slc26a2 cKO), which is in line with in vitro mitigating effects. Notably, the histological analysis revealed that melatonin attenuates ER stress and cell death in growth plate cartilage of Slc26a2 cKO mice. Furthermore, melatonin significantly inhibited the expression of proapoptotic proteins, including BAX, cleaved CASP3, and CHOP, while enhancing the expression of the anti-apoptotic protein BCL2. These findings support the effectiveness of melatonin in treating SLC26A2-associated skeletal disorders, highlighting its potential as a therapeutic option.

Although these collective data provide translational insights for drug development, further studies are necessary to fully elucidate melatonin's multifaceted roles in regulating chondrocyte's function and cell fate. In conclusion, the researchers underscore the importance of continued research and development to harness the full therapeutic potential of melatonin for addressing SLC26A2-related skeletal conditions.



(A) Representative transmission electron microscopy images of ER. (B) Statistical analysis of endoplasmic reticulum diameter. (C, D) Flow cytometry analysis of intracellular calcium concentration. (E, F) Co-staining of Fluo-3 AM (green), a fluorescent Ca2

Reference

Title of the original paper: Melatonin ameliorates Slc26a2-associated chondrodysplasias by attenuating endoplasmic reticulum stress and apoptosis of chondrocytes

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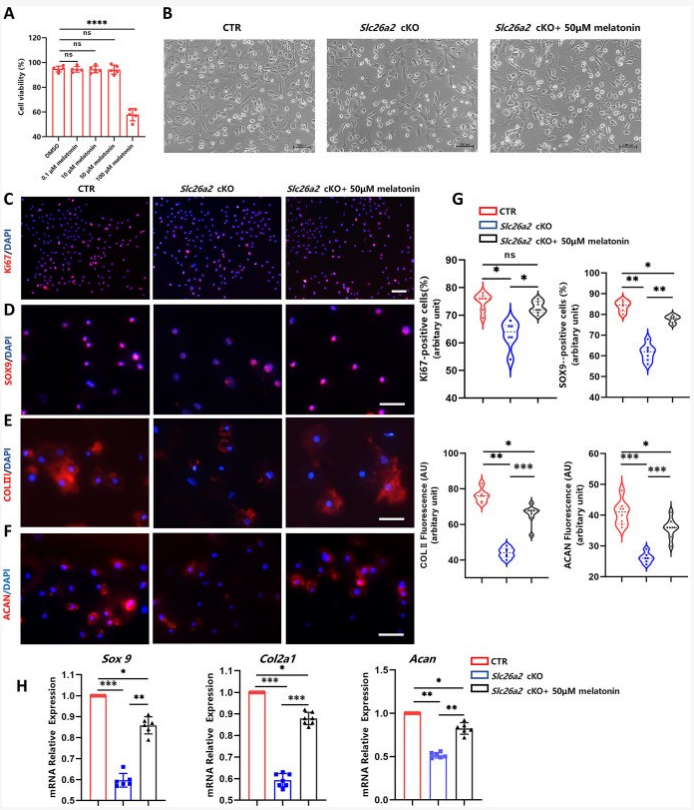

(A) Primary chondrocyte cells were subjected to treatment with different melatonin concentrations, spanning from 0.1 to 100 μM, for 72 h. CCK8 assay revealed that 0.1, 10, and 50 μM melatonin treatments had no impact on cell viability, and the viability o

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