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Abstract

Background: Intervertebral disc degeneration (IVDD) is a major pathological process leading to low back pain, closely associated with the functional decline of nucleus pulposus progenitor cell (NPPC). The role of the cGAS-STING pathway in mediating DNA-sensing-associated inflammation and senescence in IVDD has not been fully elucidated.

Methods: This study integrated genetics, computational biology, cellular experiments, and animal models to systematically investigate whether taurine (TAU) exerts protective effects by modulating this pathway.

Results: Mendelian randomization analysis suggested a causal relationship between higher TAU levels and reduced risk of IVDD. Molecular docking and dynamics simulations demonstrated that TAU stably binds to cGAS and STING. In both degenerated human nucleus pulposus (NP) tissues and an H₂O₂-induced NPPC senescence model, the cGAS-STING pathway was significantly activated. TAU intervention maintained mitochondrial function, reduced cytosolic mtDNA leakage, and enhanced autophagic degradation of STING, thereby suppressing downstream TBK1-IRF3/NLRP3 inflammatory signaling and subsequently alleviating cellular senescence, inflammatory responses, and apoptosis. TAU treatment effectively delayed intervertebral disc height loss, histopathological progression, and pain sensitivity in a rat IVDD model.

Conclusion: This study is the first to reveal that TAU mitigates IVDD through multi-targeted modulation of the “mitochondria-cGAS-STING” axis, providing a theoretical foundation for its translational application as a disease-modifying agent.

Keywords: taurine, intervertebral disc degeneration, STING, mitochondria, nucleus pulposus progenitor cell

Introduction

Intervertebral disc degeneration (IVDD) is a common chronic musculoskeletal disorder and a leading cause of low back pain, drawing significant attention due to its high prevalence and substantial disability burden [1]. The IVD is composed of the endplates, annulus fibrosus (AF), and nucleus pulposus (NP) [2]. IVDD is characterized by excessive degradation of the extracellular matrix and a marked reduction in cellularity within NP tissue [3]. The etiology of IVDD is multifactorial, involving a combination of risk factors such as aging, oxidative stress, osteoporosis, mechanical stress, inflammation, and metabolic dysregulation [4]. Within the NP, nucleus pulposus progenitor cell (NPPC) exhibits multilineage differentiation potential and plays a crucial role in maintaining the functional integrity of NP tissue [5]. However, the avascular nature of the NP

results in a harsh microenvironment characterized by chronic hypoxia and nutrient deficiency [6]. Accumulating evidence indicates that the depletion or dysfunction of NPPC is a major contributor to NP degeneration, further exacerbating IVDD and increasing the risk of disc herniation [7]. To date, the specific molecular mechanisms underlying IVDD progression remain incompletely elucidated, underscoring the need for in-depth investigation into its pathogenesis and the identification of novel therapeutic targets.

Notably, genomic instability is a hallmark of aging-related diseases. Accumulated DNA damage not only induces cellular senescence but also promotes aberrant secretion of inflammatory cytokines, a phenotype known as the senescence-associated secretory phenotype (SASP) [8]. Persistent DNA damage and hyperactivation of DNA damage signaling pathways are considered central mechanisms driving the initiation and maintenance

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of cellular senescence [3]. The cyclic GMP-AMP synthase (cGAS)-stimulator of interferon genes (STING) signaling pathway is a critical mediator of innate immune responses, primarily responsible for sensing and responding to cytosolic DNA [9]. Upon binding cytosolic DNA, cGAS activates STING (also known as STING1), initiating downstream signaling cascades that contribute to various pathological processes, including DNA damage-associated senescence, NOD-like receptor thermal protein domain associated protein 3 (NLRP3) inflammasome-mediated pyroptosis, increased reactive oxygen species (ROS) levels, accelerated extracellular matrix degradation, and enhanced apoptosis of NPPCs [10–12]. These mechanisms suggest that the cGAS-STING pathway may play a pivotal role in IVDD progression.

Therefore, enhancing autophagy-mediated clearance of damaged mitochondria, reducing cytosolic accumulation of mitochondrial DNA (mtDNA), or directly blocking downstream signaling may represent effective strategies for delaying the progression of IVDD. However, clinically effective pharmacological interventions targeting this signaling axis are currently lacking. In the search for potential therapeutic strategies, TAU, a free amino acid abundantly distributed in intracellular fluids of various tissues such as the brain, heart, and skeletal muscle, has garnered increasing interest. It supports essential physiological functions in these tissues [13]. However, plasma TAU levels decline with age in both humans and rats, a change closely associated with cellular senescence [14]. TAU exhibits strong antioxidant properties, mitigating oxidative stress by neutralizing free radicals and ROS [15]. Furthermore, studies indicated that TAU can modulate aging processes through mechanisms involving endoplasmic reticulum stress and mitochondrial function, highlighting its potential value in delaying cellular senescence and maintaining tissue homeostasis [16].

Based on this background, although previous studies have established the critical roles of the cGAS-STING axis, cell death (apoptosis and pyroptosis), and inflammatory responses in IVDD [3], the role of TAU in retarding senescence remains controversial [17], and its regulatory effects on STING signaling and IVDD progression in senescent NPPCs are still unclear. In particular, the interrelationship among TAU, STING signaling, and IVDD has not been systematically elucidated. Therefore, this study aims to innovatively investigate the interaction between TAU intervention and cGAS-STING pathway activation during NPPC senescence, providing new insights into the molecular mechanisms of IVDD and potential therapeutic targets.

Materials and methods

Intervertebral disc specimens

NP tissue specimens were collected from 12 patients who underwent unilateral biportal endoscopic lumbar discectomy (UBE). The patients had a mean age of 55.71 ± 4.63 years, and all presented with chronic IVDD accompanied by progressive neurological symptoms. As conservative management had failed, surgical intervention via UBE was indicated. The degree of IVDD was evaluated using the Pfirrmann classification system based on T2-weighted magnetic resonance imaging (MRI) [18]. The samples were classified as follows: three samples were graded as Pfirrmann II, three as Pfirrmann III, three as Pfirrmann IV, and three as Pfirrmann V. Furthermore, tissue samples graded as Pfirrmann

II and V were subjected to Hematoxylin and Eosin (HE) staining and were histologically scored according to the relevant pathological scoring system. The use of human tissue samples in this study was approved by the Ethics Committee of Northern Jiangsu People's Hospital Affiliated to Yangzhou University (Approval No. 202103427, 2 March 2021).

Molecular docking

The two-dimensional structure of the small molecule ligand was acquired from the PubChem database, and its three-dimensional conformation was constructed using ChemOffice software. A protein crystal structure with high resolution was selected from the RCSB PDB database to serve as the molecular docking receptor. The protein structure was preprocessed with PyMOL software, including the removal of non-protein components such as water molecules and phosphate ions. Subsequently, molecular docking was performed using AutoDock Vina 1.5.6 to investigate the interaction patterns between the protein and the ligand. Finally, the docking results were visualized with PyMOL and Discovery Studio 2019 software, generating two-dimensional and three-dimensional interaction diagrams illustrating the binding between the test compound and key amino acid residues.

Molecular dynamics simulation

Molecular dynamics (MD) simulations were performed for 100 ns using Gromacs 2022. The CHARMM36 force field was applied for the protein, while the ligand topology was generated using the General AMBER Force Field 2 (GAFF2) [19]. The protein-ligand complex was solvated in a cubic box under periodic boundary conditions [20]. Electrostatic interactions were treated using the Particle Mesh Ewald method, and the Verlet cutoff scheme was employed. The system was subsequently energy-minimized and equilibrated under canonical (NVT) and isothermal-isobaric (NPT) ensembles. Finally, a production MD simulation was carried out for 100 ns under constant temperature (310 K) and pressure (1 bar) using Gromacs 2022.

Mendelian randomization

Mendelian randomization (MR) employs genetic variants as instrumental variables to infer causal relationships between exposures and disease outcomes [21, 22]. The alleles of exposure-associated genetic variants are randomly allocated and thus not subject to reverse causation bias [23–25]. In this study, a two-sample MR analysis was conducted to examine the causal link between TAU and IVDD. Publicly available expression quantitative trait loci and protein quantitative trait loci related to IVDD susceptibility were utilized. Summary-level eQTL data were retrieved from the IEU OpenGWAS database (<https://gwas.mrcieu.ac.uk/>). Genome-wide association study (GWAS) summary data for IVDD outcomes were obtained from the FinnGen database (<https://www.finnngen.fi/>). Causal estimates were derived using the inverse variance weighted (IVW) method.

NPPC isolation

All Sprague-Dawley (SD) experimental rats used in this study were obtained from the Animal Experimental Center of Yangzhou Uni-

versity (License No. SYXK (SU) 2021–0027). Primary NPPCs were obtained from SD rats aged 8–12 weeks with a body weight of 250–300 g. The isolation method of NP tissue was the same as our previous research [26–28]. Briefly, after euthanasia of SD rats using an overdose of pentobarbital, the rat tail was obtained. After removing the skin and thoroughly disinfecting, the nucleus pulposus tissue was carefully separated and appropriately minced. The nucleus pulposus tissue was digested in a 0.2% type II collagenase solution at 37°C in a 5% CO₂ incubator overnight. The cell suspension was then centrifuged at 1000 rpm for 4 min to collect the cells. After adding 5 ml of complete medium to the centrifuge tube and thoroughly pipetting, it was transferred to a cell culture dish and placed in a 37°C, 5% CO₂ cell incubator. The medium was changed every 2 days, and the cell status was observed. When the cells reached 80% confluence, they were passaged at a ratio of 1:3, and cells were observed and photographed under a microscope. The third generation of cells was used for subsequent experiments. All procedures involving animal tissue samples in this study were approved by the Animal Ethics Committee of Yangzhou University on 3 March 2025 (Approval No. 202502889).

Cell culture and STING overexpression

NPPCs were cultured in Dulbecco's Modified Eagle Medium (DMEM; Gibco, Thermo Fisher Scientific, Waltham, MA, USA) supplemented with 15% fetal bovine serum and 1% penicillin-streptomycin, under conditions of 37°C, 21% O₂, and 5% CO₂. To simulate STING overexpression, the cells were treated with the STING receptor agonist DMXAA.

Cell viability assay

Cytotoxicity of TAU on NPPC was assessed using the Cell Counting Kit-8 (CCK-8; Beyotime, China). Briefly, NPPCs were seeded into 96-well plates at a density of 5×10^3 cells per well and cultured at 37°C under 5% CO₂. After 24 h of treatment under respective conditions, 10 μ l of CCK-8 solution was added to each well, followed by incubation for 2 h. The optical density was then measured at 450 nm using a microplate reader (Bio-Rad, Hercules, USA). The cell viability was calculated using the following formula: (the absorbance value of the experimental group—the absorbance value of the blank group)/(the absorbance value of the control group—the absorbance value of the blank group) $\times$ 100%.

RNA isolation and qRT-PCR

The total RNA of NPPCs was extracted using TRIzol reagent (Invitrogen, USA). Then, according to the manufacturer's instructions, the entire RNA was reverse transcribed into complementary DNA (cDNA) by Prime Script-RT reagent kit (Vazyme Biotech, China), and cDNA amplification was performed using SYBR Premix Ex Taq (Vazyme Biotech, China). The expression levels of target genes in different groups were calculated by the comparative Ct method to obtain the cycle threshold (Ct) value, and the relative gene expression level was standardized by the expression level of the internal reference gene GAPDH. According to the sequence in GenBank, the primers were designed by Prime 5.0 software.

Detection of mtDNA

mtDNA isolation was performed as described in the previous section. Briefly, NPPCs were subjected to the following treatments: no intervention; 100 μ M H₂O₂ for 12 h; TAU for 12 h; or DMXAA for 12 h. Cells were subsequently lysed in normal DMEM for 3 days, and dsDNA was isolated from the cytosolic fraction. mtDNA in the cytoplasm was quantified by quantitative real-time PCR. To accurately assess cytoplasmic mtDNA levels, the following mitochondrial genes were examined: mtND1, mtCYTB, and mtCOX1.

Protein extraction and western blot analyses

Total protein was extracted using a whole cell lysis assay kit (Key-Gen, China). The supernatant was collected as the total protein extract, and protein concentration was quantified using the bicinchoninic acid assay. Equal amounts of protein (~25 μ g) were separated by 4%–20% SDS-PAGE and transferred onto 0.22 μ m PVDF membranes. The membranes were washed with TBST and then blocked with rapid blocking buffer for 30 min. Subsequently, they were incubated overnight at 4°C with primary antibodies diluted according to the manufacturer's instructions. After three washes with TBST, the membranes were incubated with species-appropriate secondary antibodies, also diluted as recommended, for 1 h at room temperature on a shaker. Following another three TBST washes, the blots were visualized and captured using a Bio-Rad imaging system and then analyzed with ImageJ software.

5-Ethynyl-2'-deoxyuridine (EdU) incorporation assay

Cell proliferation was assessed using the EdU Cell Proliferation Detection Kit (Beyotime, China). NPPCs were seeded into 6-well plates and treated with respective compounds at 37°C under 5% CO₂ until reaching appropriate confluency. Pre-warmed 2 $\times$ EdU working solution was mixed 1:1 with pre-warmed complete medium and added to the cells for 2 h. Subsequently, the cells were fixed with 4% paraformaldehyde for 15 min, permeabilized with 1 ml immunostaining permeabilization solution per well for 10–15 min at room temperature, and incubated with Click reaction mixture for 30 min. After washing three times with washing buffer, the cells were stained with 1 ml of 1x Hoechst solution for 10 min at room temperature protected from light. Images were acquired using an inverted fluorescence microscope, and the number of EdU-positive nuclei was quantified and analyzed with ImageJ software (NIH, USA).

Senescence assays

Cellular senescence was assessed using the Senescence β -Galactosidase Staining Kit (Cell Signaling Technology) according to the manufacturer's instructions. NPPCs were seeded into 6-well plates at an appropriate density and treated with compounds after cell attachment. Following treatment, cells were fixed with 1 ml of β -Gal staining fixative for 15 min at room temperature, washed three times with PBS, and incubated overnight at 37°C without CO₂ in SA- β -Gal working solution. Senescent cells were subse-

quently examined under a microscope and analyzed using ImageJ software.

Assessment of apoptosis by flow cytometry

To clarify the effect of STING activation, cell apoptosis was detected using Annexin V-FITC/PI Cell Apoptosis Detection Kit (KeyGen, China) according to the manufacturer's protocol. After adding the cells to the drug for intervention and washing with PBS, NPPCs in each group were collected by trypsin digestion and resuspended in 500 μ l 1x binding buffer. Then, 5 μ l PI and 5 μ l annexin-v were added to the cell suspension and incubated at room temperature for 15 min. The percentage of annexin V-FITC and PI positive labeled cells was analyzed by flow cytometry (BD, USA).

JC-1 assay for mitochondrial membrane potential

MMP of NPPCs was evaluated using the JC-1 Assay Kit (KeyGen, China). In healthy mitochondria, JC-1 forms aggregates in the matrix, emitting intense red fluorescence (indicating polarization), whereas in impaired mitochondria, it remains monomeric in the cytoplasm and produces green fluorescence due to MMP loss (depolarization). After treatment according to the manufacturer's protocol, NPPCs from each group were observed and imaged under a fluorescence microscope. The ratio of green to red fluorescence intensity was analyzed using ImageJ software.

Mitochondrial electron microscopy

For transmission electron microscopic observation of mitochondria in NPPC, the cells were first chemically fixed to preserve their ultrastructure. This was followed by a series of dehydration steps to replace cellular water with resin. The samples were then embedded to form rigid blocks. Subsequently, these blocks were sectioned into ultrathin slices using an ultramicrotome and stained to enhance contrast. Finally, the sections were observed and imaged under the electron microscope to visualize the detailed morphology of the mitochondria.

ROS assay

Intracellular reactive ROS generation in NPPC was detected using the fluorescent probe dihydroethidium (DHE) assay kit (KeyGen, China). NPPCs were seeded into 6-well plates and treated as described above. After treatment, the cells were washed twice with PBS and incubated with 10 μ M DHE at 37°C for 30 min. ROS-associated fluorescence was visualized and analyzed using a fluorescence microscope and ImageJ software.

Apoptosis staining

TUNEL staining was performed using a One Step TUNEL Apoptosis Assay Kit. Briefly, cells were fixed with immunostaining fixative (P0098) or 4% paraformaldehyde for 30 min. After permeabilization with immunostaining strong permeabilization buffer (P0097) or PBS containing 0.3% Triton X-100 for 5 min at room temperature, 50 μ l of prepared TUNEL detection solution was added and

incubated at 37°C for 60 min in the dark. The cells were washed three times with PBS and then visualized under a fluorescence microscope using an excitation wavelength of 450–500 nm and an emission wavelength of 515–565 nm.

Immunofluorescence assay

Immunofluorescence staining was performed to detect the expression of target proteins within cells. Briefly, NPPCs were seeded onto poly-L-lysine-coated cell slides (25 mm in diameter). The cells were fixed with 4% paraformaldehyde for 15 min and washed twice with PBS containing 0.5% Triton X-100 for 15 min each at room temperature. Subsequently, the cells were blocked with QuickBlock™ Blocking Buffer for Immunol Staining (Beyotime, China) for 1 h. Primary antibody incubation was carried out overnight at 4°C in the dark. The cells were then washed twice with TBST and incubated with a fluorophore-conjugated goat anti-rabbit IgG secondary antibody at 37°C for 2 h. After counterstaining with DAPI for 10 min, the stained NPPC samples were visualized using either a fluorescence microscope or a laser scanning confocal microscope (Zeiss LSM 710, Germany) and analyzed with ImageJ software.

Comet single-cell gel electrophoresis assay

The comet assay was performed following the instructions provided with the single-cell electrophoresis assay kit (ENZO Life Sciences, USA). NPPCs were treated with vehicle control, 50 ng/ml IL-1 β , 50 ng/ml hydroxyurea, or 100 μ M H₂O₂ for 24 h, followed by incubation in normal DMEM for an additional 3 days. The cells were then trypsinized, centrifuged, and resuspended in 1 $\times$ PBS at a density of 1 $\times$ 10⁵ cells/ml. A 50 μ l aliquot of the cell suspension was mixed with 500 μ l of 1% low-melting-point agarose, and 75 μ l of the mixture was layered onto a slide pre-coated with 1% normal-melting-point agarose. The slide was allowed to solidify at 4°C in the dark for 10 min. After incubation in pre-chilled lysis buffer for 1 h, the slide was placed in a horizontal electrophoresis unit containing alkaline electrophoresis buffer and kept at room temperature in the dark for 60 min to allow DNA unwinding. Electrophoresis was conducted at 25 V and 300 mA (0.73 V/cm) for 10 min. Subsequently, the slide was rinsed with distilled water, treated with neutralization buffer (pH 7.5), dehydrated in 70% ethanol for 5 min, and air-dried. Prior to analysis, the slide was stained with 100 μ l of CYGREEN® dye for 30 min in the dark at room temperature. After complete drying at 37°C, the samples were visualized using a fluorescence microscope (OLYMPUS CKX41) with excitation/emission wavelengths of 489/515 nm.

Single-cell sequencing database

Comprehensive sample information for the single-cell sequencing data presented in this study is available from the GEO database under accession number GSE205535. Violin plots were used to compare the expression distribution of DNA marker genes between degenerative and normal NPPC. A statistical significance of $P < 0.05$ indicated a statistically significant difference between the degenerative group and the normal control group.

Rat model of IVDD

A total of 18 male SD rats aged 8–12 weeks and weighing 250–300 g were selected for this study. All experimental rats were procured from the Comparative Medicine Center of Yangzhou University. A rat model of IVDD was established using a fine-needle puncture method [29]. After body weight measurement, rats in the IVDD and TAU groups were anesthetized by intraperitoneal injection of 1% pentobarbital at a dose of 40 mg/kg. Following adequate anesthesia, the target caudal intervertebral discs were located and marked. The surgical area was disinfected three times with povidone-iodine. A 21-gauge needle was inserted perpendicular to the longitudinal axis of the tail at the marked site to a depth of 5 mm—a needle holder was fixed 5 mm from the tip to control the penetration depth. The needle was rotated 360° and maintained in situ for 30 s before withdrawal. The puncture site was disinfected again with povidone-iodine and compressed with sterile gauze for 1 min to achieve hemostasis. Two weeks after puncture, rats in the TAU group received daily oral gavage of TAU (100 mg/kg) for 8 consecutive weeks. The severity of IVDD at the puncture level was evaluated using radiographic and pathological methods at 4 and 8 weeks after treatment. IVDD was assessed based on the Pfirrmann grading system [18] and histological scoring criteria with reference to established literature [30].

Histology, immunofluorescence, and immunohistochemistry

IVD tissues harvested from rats were fixed in 4% paraformaldehyde (PFA), decalcified with 10% ethylene diamine tetraacetic acid solution, embedded in paraffin blocks, and tissue-sectioned. The specimens were cut into 5 μ m histological sections and stained with haematoxylin–eosin (HE), safranin-o/fast green (S-O). The degree of IVDD was evaluated using the histological grading scale of Norcross et al. for histological images [30].

For the immunohistochemical analysis, the IVD tissue was fixed in 4% paraformaldehyde. The tissue was dehydrated, embedded, and made into paraffin blocks. A microtome was used to slice the paraffin block into thin sections, which were then placed in a buffer solution. A diluted primary antibody (anti-Collagen II, anti-MMP-9, anti-ACAN, anti-STING, anti-cGAS, anti-IL-6, anti-IL-1 β antibody) solution was applied to the sections, which were then placed in a wet box and incubated overnight in a 4°C refrigerator. The sections were rinsed several times with PBS buffer. The secondary antibody was applied to the sections for incubation, followed by rinsing with PBS buffer. Finally, the staining results were observed under a light microscope and photographed for records.

Immunofluorescence staining was finally performed, and the sections were washed with PBS. Bovine serum albumin was used to incubate the sections at room temperature for 30–60 min. The diluted primary antibody (anti-Collagen II, anti-Bax, anti-Bcl-2, anti-MMP-9, anti-dsDNA, anti-STING, anti-cGAS, anti-LC3 antibody) was dropped on the sections, placed in a wet box, and incubated in a 4°C refrigerator overnight. The next day, the sections were washed with PBS solution for several times, 5 min each time, and the fluorescently labeled secondary antibody was dropped on the sections and incubated for 60 min without light. It was also washed with PBS solution for several times, 5 min each time. DAPI was counterstained in the dark at RT for 3 min. Fluorescence

microscope (OLYMPUS CKX41) was used to obtain digital images. They were observed under a fluorescence microscope. According to the fluorophore used, the appropriate excitation filter block was selected to observe fluorescent signals of different colors, respectively, and take photos with a high-resolution camera.

Radiographic and MRI analyses

Radiographic and MRI scans were performed before puncture and at 6 and 10 weeks post-puncture. Disc height index (DHI) was measured from X-ray images. A 7.0 T MRI system (Philips Intera Achieva 7.0, the Netherlands) was used to acquire sagittal T2-weighted images. The degree of IVDD was evaluated using the Pfirrmann grading system based on signal intensity and disc height. Both DHI and Pfirrmann grading were assessed independently by three spine surgeons who were blinded to the treatment groups. DHI was calculated as the ratio of the disc height to the height of the adjacent vertebral body.

Statistical analysis

The experimental data are expressed as mean $\pm$ standard deviation ($X \pm S$). The obtained experimental data are statistically analyzed on SPSS 25.0 software, and then the statistical graphs are drawn using GraphPad Prism 9.5 software. The comparison between groups is conducted using unpaired t-test or one-way analysis of variance, and $P < 0.05$ is considered statistically significant difference.

Results

MR, molecular docking, and MD simulations

Employing a two-sample MR approach, we identified significant evidence supporting a causal association between TAU and IVDD risk (IVW: OR = 0.85, 95% CI: 0.77–0.94, $P = 0.001$). Cochran's Q-test revealed no substantial heterogeneity ($Q_P > 0.05$). Both MR-Egger regression ($P > 0.05$) and funnel plot symmetry indicated the absence of significant horizontal pleiotropy. These findings were visualized via a scatter plot. In addition, leave-one-out sensitivity analysis confirmed that the overall causal estimate was not driven by any single nucleotide polymorphism (Fig. 1A–D).

Next, we proceed to the next analysis through molecular docking simulation and MD simulation. Molecular docking simulation is a convenient and effective method for exploring the interaction between small molecules and their target proteins. This study uses AutoDock Vina1.5.6 software for molecular docking to explore protein-ligand interactions. In general, when the binding energy is less than -5.0 kcal/mol, it indicates that the two have good binding activity, less than -7.0 kcal/mol indicates strong binding activity, the lower the binding energy, the stronger the binding activity between the two, the higher the affinity, and the more stable the conformation. In this study, the binding energies of TAU with cGAS and STING proteins were -4.3 kcal/mol and -3.6 kcal/mol, respectively, indicating that TAU has affinity for both cGAS and STING. The residues GLY304, HIS363, and LYS362 on the cGAS receptor form hydrogen bond interactions with TAU, while the residues ALA364, GLU366, SER274, GLU372, GLU373, THR374, ALA273, and LEU277

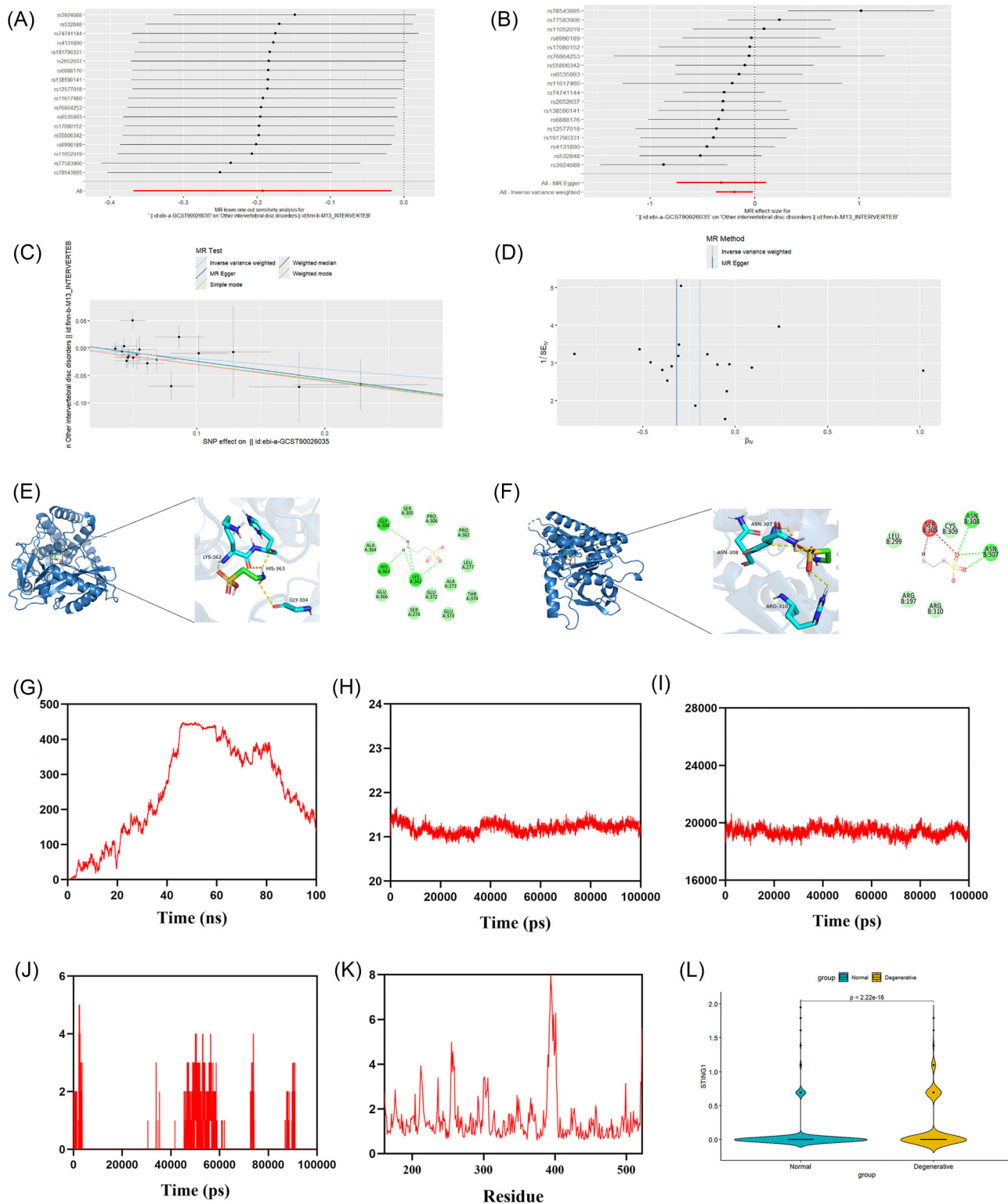


Figure 1 (A–D) TAU targeting of cGAS/STING is causally associated with IVDD. MR determines the relationship between TAU and IVDD. (E) Molecular docking simulates the binding force of TAU with cGAS protein. (F) Molecular docking simulates the binding force of TAU with STING protein. (G–K) MD simulations examine the stability of the complex system formed by the binding of cGAS and TAU. (L) Single-cell sequencing reveals changes in STING in human degenerative NPPCs. Data are expressed as mean $\pm$ SD. (* $P < 0.05$, ** $P < 0.01$, *** $P < 0.001$, **** $P < 0.0001$).

on the cGAS receptor form van der Waals forces with TAU (Fig. 1E). The residues LEU299, ARG197, ARG310, and CYS309 on the STING receptor form van der Waals forces with TAU. The residues ASN307 and ASN308 on the STING receptor form hydrogen bond interactions with TAU (Fig. 1F). These docking results suggested that TAU may interact directly with cGAS and STING and may play a biological role in IVDD through these proteins.

The root mean square deviation (RMSD) is a good indicator for measuring the conformational stability of proteins and ligands, and it also measures the degree of deviation of atomic positions from their starting positions. The smaller the deviation, the better the conformational stability. During the simulation process of the cGAS protein, the complex system showed an upward trend, reaching equilibrium after 98 ns, and eventually fluctuating below 4.2Å. There were no significant RMSD fluctuations, indicating that the protein structure was not damaged in any way (Fig. 1G). Further analysis revealed that the radius of gyration and solvent accessible surface area of the complex system exhibited slight fluctuations during the movement process, indicating conformational changes in the complex system (Fig. 1H, I). Hydrogen bonds play an important role in the binding between ligands and proteins, and the number of hydrogen bonds between the complex systems ranged from 0 to 5. In most cases, the complex had about 2 hydrogen bonds, indicating that the complex has good hydrogen bond interactions (Fig. 1J). The root mean square fluctuation (RMSF) can represent the flexibility of amino acid residues in proteins, and the RMSF value of the complex is relatively low (mostly below 4Å), so its flexibility is low and its stability is high (Fig. 1K). The results showed that cGAS, as the core protein of pathway activation, forms a complex system with TAU that has high stability.

Activation of the cGAS-STING pathway in degenerative human NP tissues

To assess the extent of cellular senescence in NP tissue, NP samples and corresponding MRI data were collected from five patients undergoing spinal surgery. The samples were classified according to the Pfirrmann grading system (Grades I-V) (Fig. 2A, B). Western blot analysis revealed a progressive upregulation of cGAS, STING, and NLRP3 protein expression with increasing degeneration grade (Fig. 2D, F-H). HE staining further demonstrated that advanced degeneration was accompanied by structural disruption and fibrosis of the NP tissue (Fig. 2E). Single-cell RNA sequencing data indicated significantly elevated STING expression in degenerative NPPC (Fig. 1L). These results suggested that the cGAS-STING pathway is activated in degenerative human NP tissue and is associated with the formation of a local inflammatory microenvironment.

Optimal incubation concentration of TAU

NPPCs were isolated and cultured using an established protocol, with passaged cells exhibiting a characteristic long-spindle morphology [28, 31, 32] (Supplementary Fig. 1A). Based on previous optimization studies, an oxidative stress-induced senescence model was established by treating cells with 100 μ M H₂O₂ for 6 h [33]. Cytotoxicity assessment using CCK-8 assay confirmed that 40 μ M TAU exhibited no adverse effects on cell viability across various exposure durations (0, 6, 12, 24 h) (Supplementary Fig. 1B).

Consequently, this concentration was selected for all subsequent experimental procedures.

TAU suppresses cytosolic dsDNA release during IVDD progression

The single-cell gel electrophoresis (comet) assay results demonstrated that H₂O₂ treatment induced significant DNA damage in NPPC, which was effectively mitigated by TAU intervention. Notably, DMXAA-induced STING overexpression substantially attenuated the protective effects of TAU (Fig. 3A, B). Immunofluorescence imaging revealed markedly elevated levels of cytosolic dsDNA in H₂O₂-treated NPPC compared to controls (Supplementary Fig. 2A, B). Subsequent analysis confirmed the presence of mtDNA within the cytosolic dsDNA fraction. While H₂O₂ treatment increased cytosolic mtDNA content, TAU administration significantly reduced these levels. Conversely, DMXAA-induced STING overexpression reversed the beneficial effects of TAU (Supplementary Fig. 2C-E). These results indicated that oxidative stress promotes cytosolic dsDNA release in degenerative NPPC, and TAU exerts protective effects through specific inhibition of STING overexpression.

In vivo assessment using immunofluorescence and HE staining at 10 weeks post-injury demonstrated progressive degenerative changes and severe IVDD in the puncture-induced rat model (Supplementary Fig. 2F, G). Analysis of human degenerative IVD tissues (Pfirrmann grades II vs V) revealed more severe structural disruption in advanced degeneration, correlating with increased cytosolic dsDNA leakage in NP tissues (Fig. 2C, I). These data established a positive correlation between dsDNA accumulation and IVDD severity.

Anti-inflammatory effects of TAU via STING suppression in degenerative NP

As the primary sensor for cytosolic dsDNA, cGAS demonstrated significantly elevated expression in Pfirrmann grade V discs compared to grade II specimens (Fig. 2D, F-H). Western blot and Immunofluorescence analysis confirmed that H₂O₂ treatment significantly upregulated cGAS, STING, and NLRP3 expression in NPPC, effects that were reversed by TAU treatment. The protective effects of TAU were notably diminished by DMXAA co-treatment (Fig. 3C-H). Furthermore, evaluation of inflammatory signaling pathways revealed significant upregulation of TBK1, IRF3, IL-1 β , and IL-6 in H₂O₂-treated NPPC ($P < 0.05$). TAU treatment effectively suppressed these inflammatory mediators, while DMXAA compromised the anti-inflammatory efficacy of TAU (Fig. 3I, J) ($P < 0.05$). These results indicated that cGAS and STING expression increase in degenerative NP tissue and suggested that TAU may delay IVDD progression by exerting anti-inflammatory effects, potentially via inhibition of the DNA sensor cGAS.

TAU alleviates STING-related autophagic impairment in senescent NPPC

SA- β -galactosidase staining confirmed that H₂O₂-induced STING upregulation promoted NPPC senescence, which was ameliorated by TAU treatment (Fig. 4A, B). Western blot analysis showed decreased LC3-II and increased p62 expression in H₂O₂-treated cells,

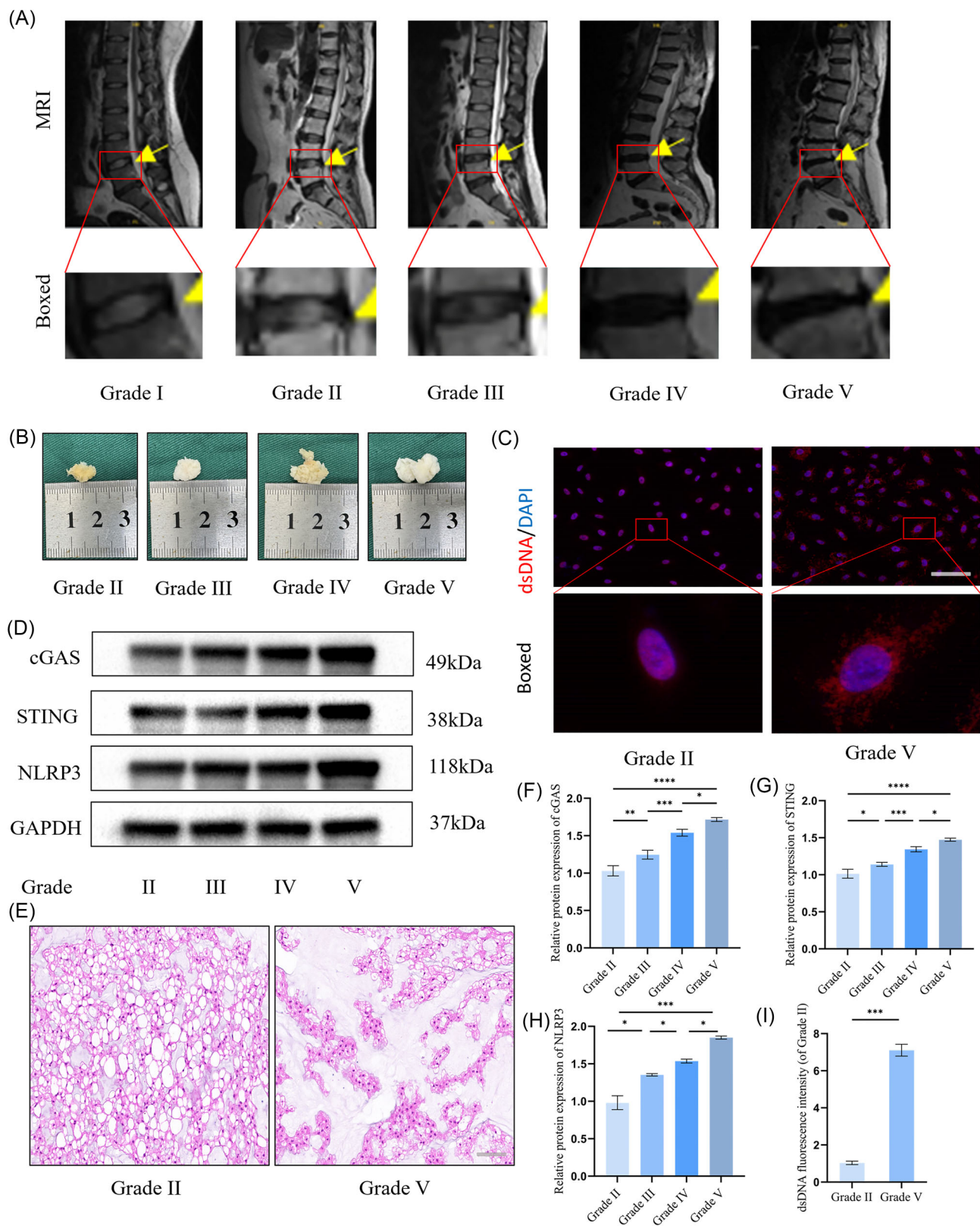


Figure 2 Human IVDD is associated with dsDNA release and pathway activation. (A) MRI data from 5 patients with different degeneration grades undergoing spinal surgery. (B) Nucleus pulposus tissues of varying degeneration grades obtained from 4 surgical cases. (C) Detection of dsDNA release in human NP tissues of Pfirrmann grades II and V by immunofluorescence. Scale bar, 50 μ m. (D) Protein expression and quantitative analysis of cGAS, STING, and NLRP3 in human nucleus pulposus tissues from Pfirrmann grades II to V. (E) Evaluation of degeneration in human nucleus pulposus tissues by H&E staining. Scale bar, 500 μ m. (F–H) Quantitative analysis of cGAS, STING, and NLRP3 proteins in human nucleus pulposus tissues from Pfirrmann grades II to V. (I) Fluorescence quantification of cytoplasmic dsDNA release in human NP tissues. Data are presented as mean $\pm$ SD. (* P < 0.05, ** P < 0.01, *** P < 0.001, **** P < 0.0001).

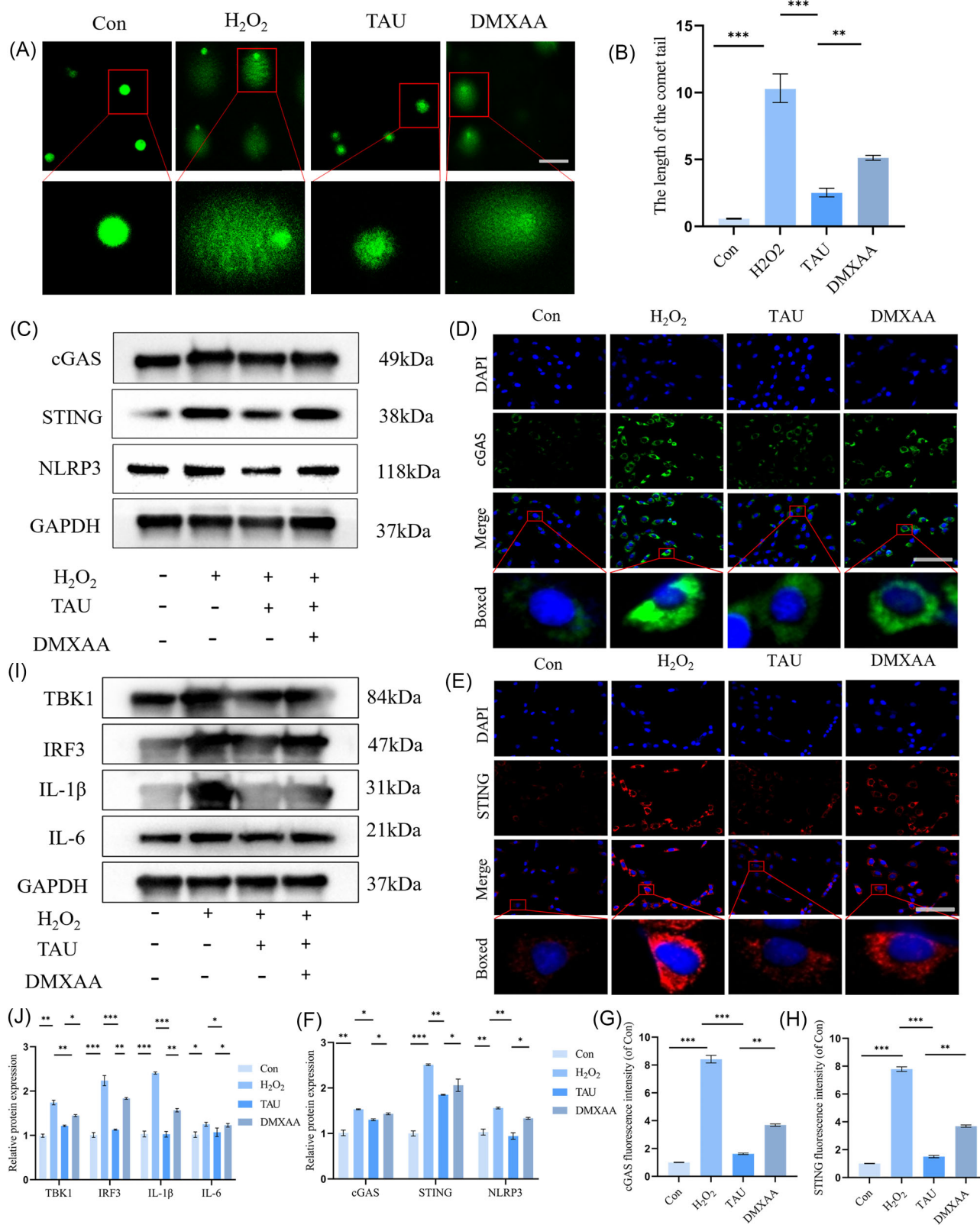


Figure 3 TAU inhibits H_2O_2 -induced DNA damage and cGAS–STING pathway activation in NPPC. (A) Comet assay showing the extent of DNA damage in NPPCs following H_2O_2 and TAU stimulation. Scale bar, 50 μm . (B) Statistical analysis of comet tail moment. (C, F) Protein expression and quantitative analysis of cGAS, STING, and NLRP3 in NPPCs. (D, G) Immunofluorescence detection and quantitative analysis of cGAS changes in NPPCs. Scale bar, 50 μm . (E, H) Immunofluorescence detection and quantitative analysis of STING changes in NPPCs. Scale bar, 50 μm . (I, J) Protein expression and quantitative analysis of TBK1, IRF3, IL-1 β , and IL-6 in NPPCs. Data are expressed as mean $\pm$ SD. (* $P < 0.05$, ** $P < 0.01$, *** $P < 0.001$, **** $P < 0.0001$).

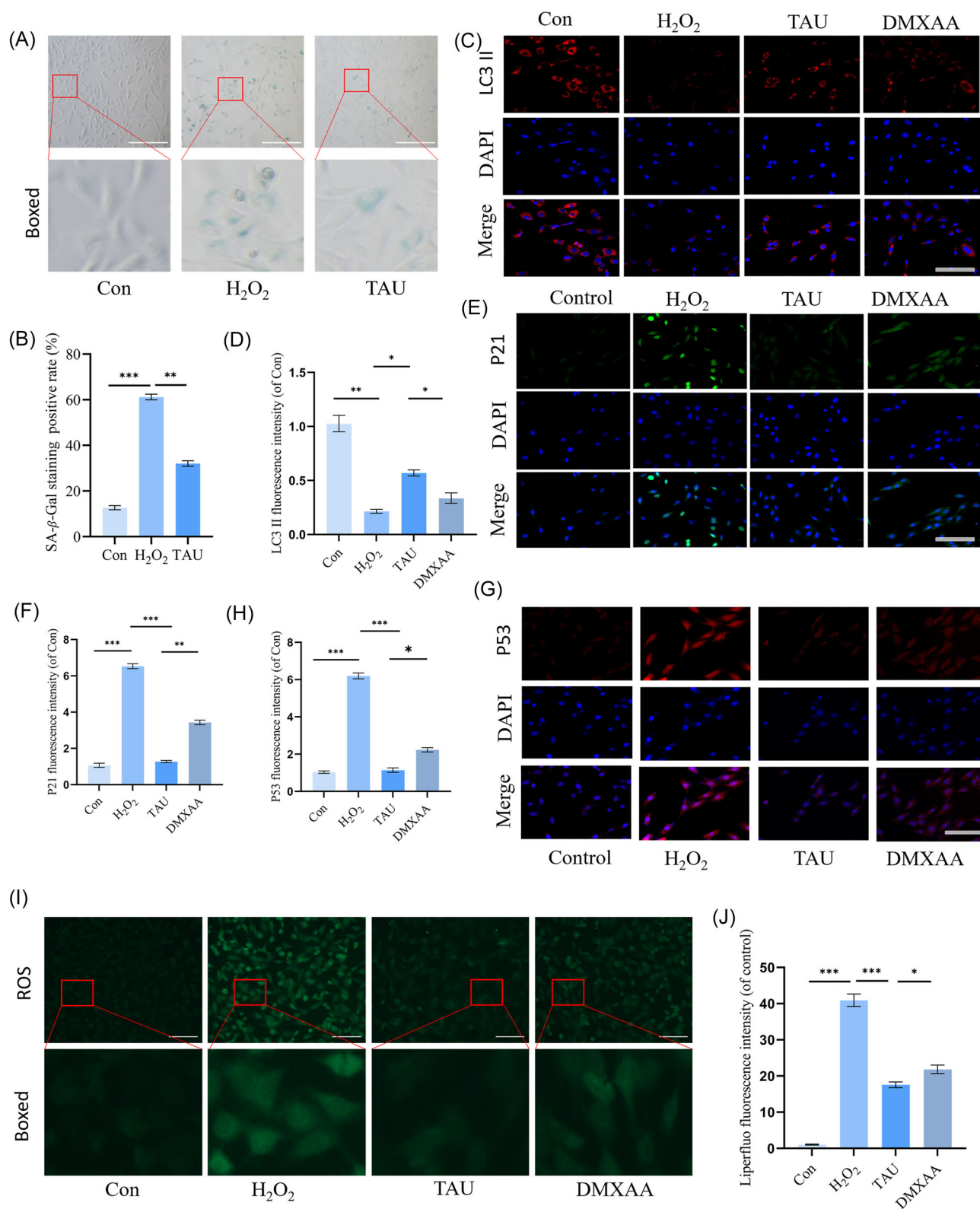


Figure 4 TAU alleviates H₂O₂-induced senescence and enhances autophagy in NPPC. (A) Sa- β -Gal assay showing that H₂O₂ induces senescence in NPPCs. Scale bar, 100 μ m. (B) Proportion of β -Gal-positive NPPCs quantified by statistical analysis. (C) Immunofluorescence detection of LC3 II expression in NPPC. Scale bar, 50 μ m. (D) Quantitative analysis of LC3 II fluorescence intensity. (E, F) Immunofluorescence detection and quantitative analysis of p21 changes in NPPCs. Scale bar, 50 μ m. (G, H) Immunofluorescence detection and quantitative analysis of p53 changes in NPPCs. Scale bar, 50 μ m. (I) Fluorescence results of ROS in different groups. Scale bar, 50 μ m. (J) Quantitative analysis of ROS fluorescence intensity. Data are expressed as mean $\pm$ SD. (* P < 0.05, ** P < 0.01, *** P < 0.001, **** P < 0.0001).

indicating impaired autophagic flux. TAU treatment restored autophagy activity, as evidenced by increased LC3-II and decreased p62 levels (Supplementary Fig. 3A, B). Immunofluorescence microscopy corroborated these findings, demonstrating enhanced LC3 puncta formation following TAU administration (Fig. 4C, D). Molecular analysis revealed that H₂O₂-induced STING overexpression significantly upregulated senescence markers p53, p21, and p16, effects that were counteracted by TAU treatment. DMXAA intervention diminished the beneficial effects of TAU (Fig. 4E–H) (Supplementary Fig. 3C, D). We further examined the protein expression level of MMP-9 by immunofluorescence and Western blotting. The results showed that, compared with the control group, H₂O₂ stimulation significantly upregulated the protein level of MMP-9 in NPPCs, whereas TAU treatment markedly suppressed this increase. Co-treatment with DMXAA attenuated the inhibitory effect of TAU on MMP-9 expression (Supplementary Fig. 3E–J). These findings indicated that senescent NPPCs exhibit impaired autophagic degradation of STING, leading to its accumulation and cellular senescence, while TAU appears to promote STING autophagy, thereby delaying NPPC senescence.

TAU protects mitochondria by reducing STING expression

Transmission electron microscopy examination revealed mitochondrial ultrastructural abnormalities, including organelle shrinkage and increased cristae density, in H₂O₂-treated NPPC. TAU treatment substantially ameliorated these morphological alterations (Fig. 5A, B). Loss of mitochondrial membrane potential (MMP), an early event in apoptosis, was observed in H₂O₂-treated cells (decreased red JC-1 fluorescence) and was preserved by TAU treatment. DMXAA inhibited this protective effect (Fig. 5C, D). Intracellular ROS levels were significantly elevated in the H₂O₂ group ($P < 0.05$). TAU incubation significantly suppressed ROS overproduction ($P < 0.05$), and DMXAA reduced this inhibitory effect ($P < 0.05$) (Fig. 4I, J). These results demonstrate that TAU alleviates H₂O₂-mediated oxidative stress in NPPCs by reducing ROS levels, an effect attenuated by DMXAA, suggesting STING activation contributes to mitochondrial dysfunction. Thus, TAU can protect NPPC by inhibiting STING expression.

TAU attenuates apoptosis by suppressing STING accumulation

Flow cytometry and TUNEL assays showed significantly increased apoptosis in H₂O₂-stimulated, STING-overexpressing NPPC compared to controls. TAU treatment partially reduced apoptosis, and this effect was diminished by DMXAA (Supplementary Fig. 4A, B) (Fig. 5E, F). EdU staining revealed significantly fewer EdU-labeled NPPC in the H₂O₂ group than in controls ($P < 0.05$); TAU treatment partially increased this number ($P < 0.05$), and DMXAA attenuated TAU's pro-proliferative effect ($P < 0.05$) (Fig. 5G, H). Western blotting, immunofluorescence, and quantitative real-time PCR (qRT-PCR) demonstrated that STING activation upregulated pro-apoptotic proteins (caspase-3, Bax) and downregulated anti-apoptotic Bcl-2, promoting apoptosis. TAU mitigated these changes (Supplementary Fig. 4C–G) (Fig. 5I–K). These results indicated that STING activation promotes NPPC apoptosis, and TAU can mitigate apoptosis by inhibiting STING expression.

Evaluation of TAU's effect on delaying IVDD in an animal model

An IVDD rat model was successfully established and treated with TAU. Radiological and histological evaluations at 6 and 10 weeks post-injury, assessing DHI, Pfirrmann grade, and histological score, showed that TAU treatment delayed IVDD progression (Fig. 6A, B). Immunofluorescence confirmed increased STING expression in the NP tissue of rats with IVDD, which was reduced by TAU treatment (Supplementary Fig. 5A, B and Supplementary Fig. 7A). Immunohistochemistry showed significantly higher expression of cGAS and STING in the degeneration group compared to controls, and TAU treatment decreased their expression (Supplementary Fig. 5C, D). X-ray and MRI analyses indicated that TAU helped maintain IVD height, prevent disc space collapse, and preserve NP tissue integrity (Fig. 6C–F). HE staining of IVD showed intact NP and AF morphology in controls, degeneration-associated changes in the IVDD group, and improvement with TAU treatment (Fig. 6G, H). Safranin O/Fast Green (SO/FG) staining also demonstrated these changes, with strong red staining indicating proteoglycan-rich cartilage endplates (EP) in the control group, while the IVDD group exhibited damaged EP, irregular structure, and loss of hyaline matrix and chondrocytes. TAU treatment helped maintain the morphological structure and matrix composition of the AF and NP (Supplementary Fig. 6A, Supplementary Fig. 7B, Supplementary Fig. 8A and Supplementary Fig. 9B). Masson's trichrome staining, primarily observing mature collagen fibers in the IVD structure, revealed more disorganized AF and increased immature collagen fibers in the degeneration group, which were significantly reversed by TAU treatment (Supplementary Fig. 6B). Furthermore, measurement of the NP area in gross specimens of discs from different groups showed a progressive decrease in the relative NP area over time in the IVDD group; however, TAU treatment reversed these changes (Fig. 6I, J). Immunohistochemical analysis demonstrated that TAU treatment reduced the degradation of aggrecan and collagen II and suppressed the expression of MMP-9 (Fig. 7A–D, Supplementary Fig. 6C, D, Supplementary Fig. 7B, Supplementary Fig. 8A and Supplementary Fig. 9B). Immunohistochemical analysis of IL-1 β and IL-6 in different IVD groups showed that the expression of these two inflammatory markers was higher in the degeneration group than in the control group ($P < 0.05$); however, at 6 and 10 weeks, respectively, the expression of IL-1 β and IL-6 in the TAU group was significantly lower than in the degeneration group ($P < 0.05$) (Fig. 7E–H, Supplementary Fig. 8B and Supplementary Fig. 9A). These results collectively demonstrated that TAU intervention can mitigate both age-dependent and injury-induced IVDD initiation and progression.

Discussion

IVDD is a complex degenerative condition driven by multiple factors, characterized by the progressive deterioration of the NP tissue, ultimately leading to low back pain and related functional impairments [34, 35]. This study systematically elucidated the novel mechanism of action of TAU in mitigating IVDD by integrating genetic analyses, computational simulations, cellular experiments, human tissue validation, and animal models. Our finding was that TAU exerts its effects through multi-target intervention in the critical inflammatory axis of mitochondrial

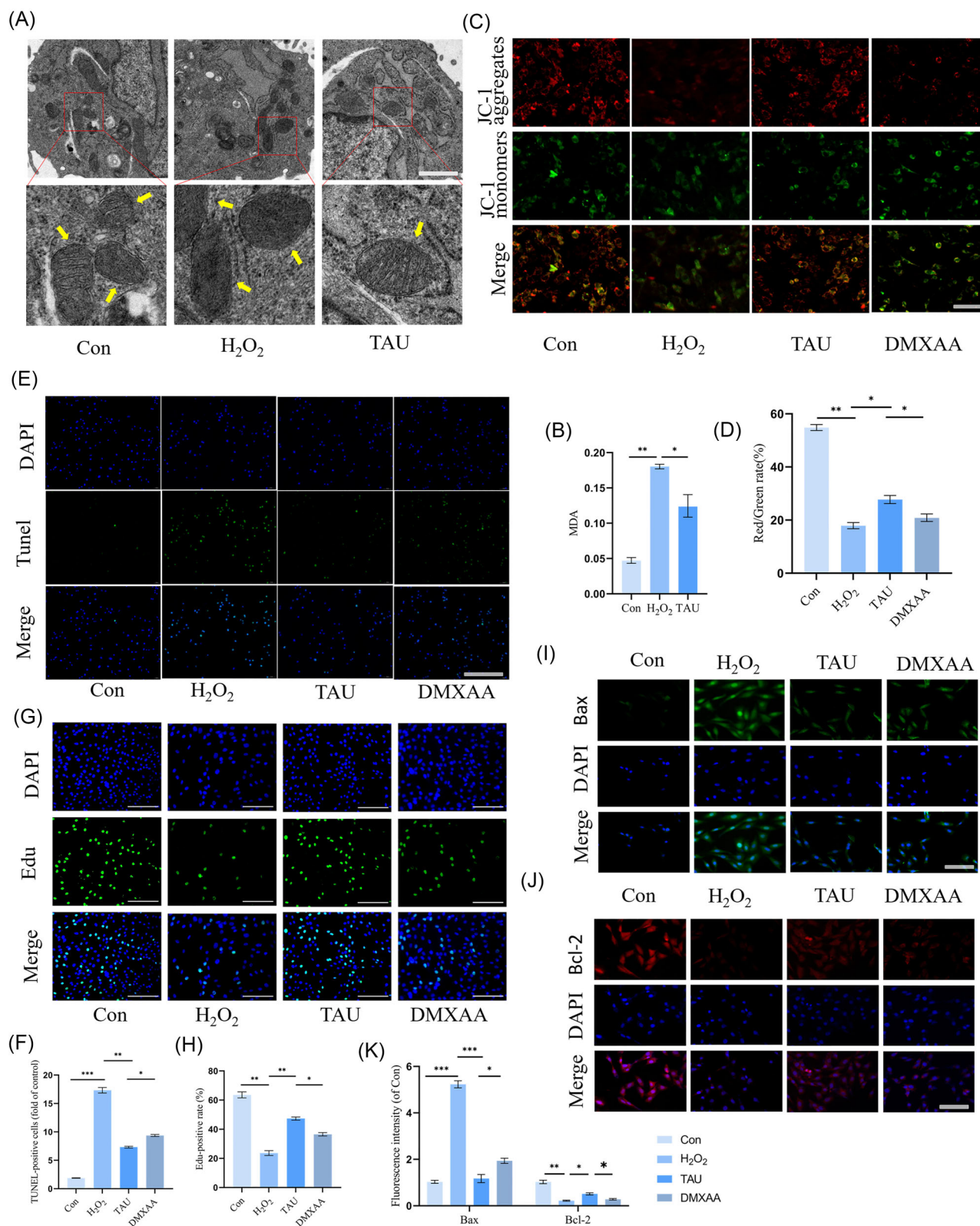


Figure 5 TAU alleviates apoptosis and mitochondrial dysfunction in NPPC. (A, B) Transmission electron microscopy of NPPC mitochondria morphology and quantitative analysis. Scale bar, 100 μ m. (C) Fluorescent results of MMP in different groups. Scale bar, 50 μ m. (D) Quantitative analysis of MMP fluorescence intensity. (E) TUNEL assay results in NPPC. Scale bar, 100 μ m. (F) Quantitative analysis of TUNEL-positive cells. (G) EdU assay results in NPPC of different groups. Scale bar, 100 μ m. (H) Quantitative analysis of EdU-positive cells. (I) Immunofluorescence detection of Bax expression in NPPC. Scale bar, 50 μ m. (J) Immunofluorescence detection of Bcl-2 expression in NPPC. Scale bar, 50 μ m. (K) Quantitative analysis of fluorescence intensity of Bax and Bcl-2. Data are expressed as mean $\pm$ SD. (* P < 0.05, ** P < 0.01, *** P < 0.001, **** P < 0.0001).

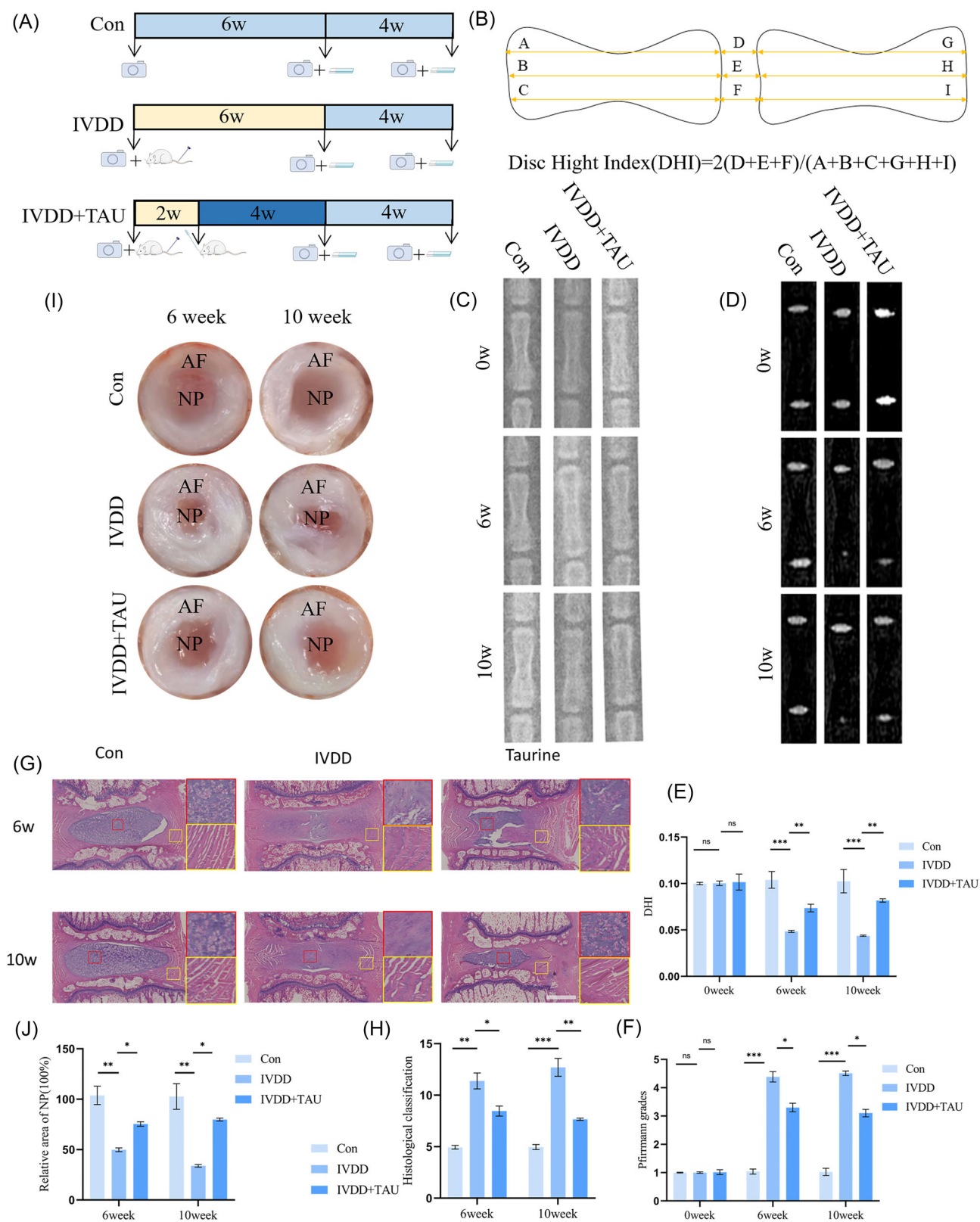


Figure 6 Radiographic and histological results of animal experiments. (A) Schematic of the in vivo experimental procedure. (B) Measurement of IVD height index (DHI). (C) The X-ray images of rats at 0 week, 6 weeks, and 10 weeks after puncture in each group. (D) MRI scans of IVD at 0 week, 6 weeks, and 10 weeks after puncture to evaluate the degree of disc degeneration. (E) Quantitative analysis of DHI. (F) Quantitative analysis of Pfirrmann grading. (G, H) Representative images of HE-stained sections and quantitative histological grade score. Scale bar, 500 μm . (I, J) Gross specimen of NP area measurement and quantitative analysis of different groups. Data are presented as mean $\pm$ SD. (* $P < 0.05$, ** $P < 0.01$, *** $P < 0.001$, **** $P < 0.0001$).

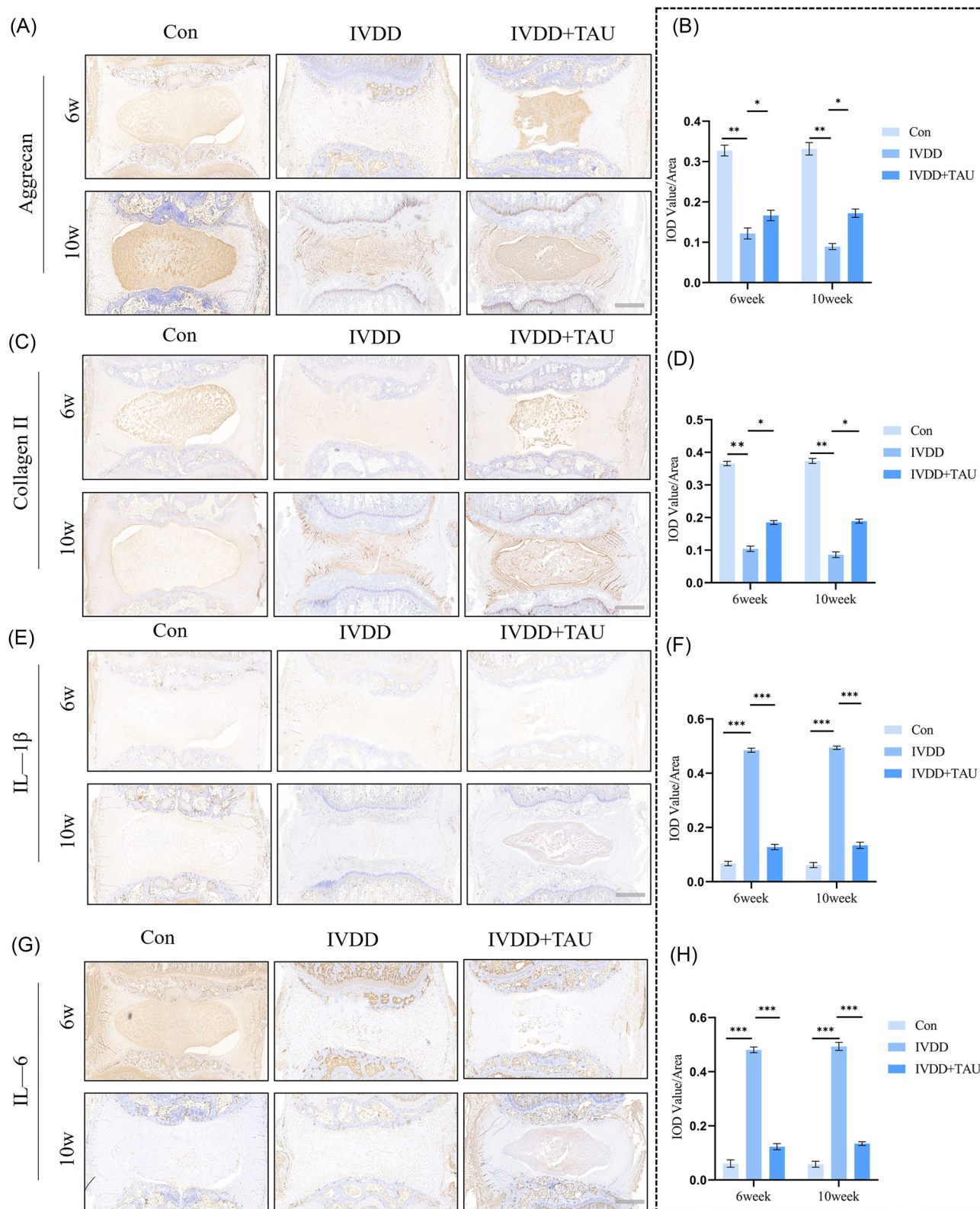


Figure 7 Immunohistochemical results of animal experiments. (A, B) Immunohistochemical detection and quantitative analysis of aggregation protein changes in IVD. (C, D) Immunohistochemical detection and quantitative analysis of Collagenase II changes in IVD. (E, F) Immunohistochemical detection and quantitative analysis of IL-1 β changes in IVD. (G, H) Immunohistochemical detection and quantitative analysis of IL-6 changes in IVD. Scale bar, 500 μ m. Data are expressed as mean $\pm$ SD. (* $P < 0.05$, ** $P < 0.01$, *** $P < 0.001$, **** $P < 0.0001$).

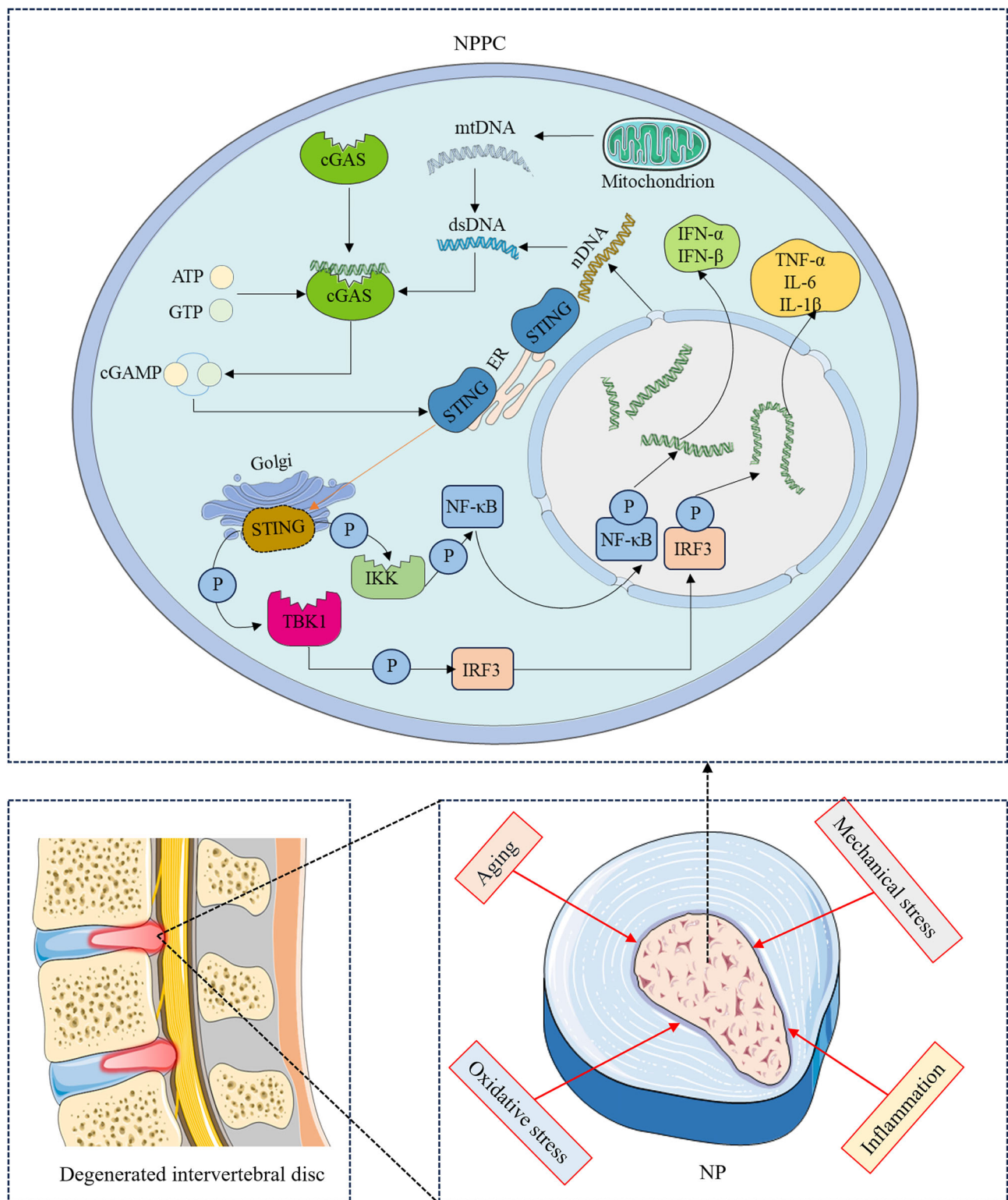


Figure 8 Working model of DNA leakage-triggered cGAS-STING signaling leading to NPPC senescence and apoptosis. Schematic diagram of the working hypothesis: when cells are subjected to external or internal stress, mtDNA leaks from mitochondria into the cytoplasm, where it is recognized by cGAS in the cytoplasm, catalyzing the synthesis of the second messenger 2'3'-cGAMP, and activating STING on the endoplasmic reticulum. The activated STING moves to the Golgi apparatus, recruiting and activating TBK1 and transcription factor IRF3, ultimately inducing the expression of type I interferon (IFN-I) and various inflammatory factors, further leading to adverse outcomes such as senescence and apoptosis of NPPC.

damage-cGAS-STING pathway, thereby alleviating NPPC senescence, inflammatory responses, and mitochondrial dysfunction, and ultimately decelerating IVDD progression. These findings not only revealed a core driver of sterile inflammation in IVDD but also position TAU as a potential disease-modifying agent with translational promise.

Our investigation commenced with a significant causal inference: two-sample MR analysis provided genetic evidence supporting a causal relationship between higher circulating TAU levels and a lower risk of IVDD. This established a solid foundation of clinical relevance for our subsequent experiments, suggesting that elevating TAU levels could be an effective preventive or therapeutic strategy. Subsequently, MD and dynamics simulations suggested that TAU may directly interact with cGAS and STING proteins. Although its binding affinity was relatively moderate compared to high-affinity inhibitors, this likely reflects the characteristic mode of action of TAU—it may function not as a potent inhibitor but rather as a multi-target fine-tuner. This moderate interaction was sufficient to elicit significant biological effects in subsequent functional assays, indicating its regulatory role.

In degenerated human NP tissues, we observed a positive correlation between the expression of key components of the cGAS-STING pathway (cGAS, STING) and the severity of degeneration. This finding aligns with reports by Chen et al., who linked the cGAS-STING pathway to cellular senescence and tissue degeneration [8]. In both human degenerative tissues and a chronic oxidative stress (H_2O_2)-induced NPPC senescence model, we proposed that STING signaling activation is persistent and pathological. Under the chronic, sustained stress typical of IVDD, mitochondrial damage leads to continual leakage of mtDNA, resulting in the chronic overactivation of the cGAS-STING pathway. This exacerbates the local inflammatory microenvironment, ultimately shifting the pathway's role from potentially protective to destructive, driving chronic inflammation and cellular senescence [9]. These events collectively form a vicious cycle of “DNA damage-inflammation-senescence-apoptosis”, accelerating ECM degradation and structural disintegration of the disc. Our study elucidated the therapeutic value of TAU within this pathological context.

TAU's mechanism of action demonstrates multi-layered synergistic effects. Mitochondria serve as central hubs for cellular energy metabolism and apoptotic regulation [36], they also represent a major source of ROS as well as the origin of mtDNA leakage [37]. First, acting upstream, TAU protects mitochondrial integrity and reduces mtDNA leakage, thereby suppressing the aberrant initiation of the cGAS-STING pathway at its source. This indicates that the core benefit of taurine resides in its mitochondrial protective function, which our study specifically attributes to the preservation of mtDNA stability. Second, at the core of the pathway, TAU likely exerts dual negative regulation through direct interaction with cGAS/STING and by promoting the autophagic degradation of STING. Autophagy is a crucial homeostatic process for clearing damaged organelles and proteins within cells [38, 39]. We found that TAU enhances autophagic flux (increased LC3-II, decreased p62), thereby accelerating STING clearance. This finding is significant as it links TAU's action to the cell's intrinsic protein quality control mechanisms [40, 41]. Finally, downstream, TAU effectively inhibits the activation of the TBK1-IRF3 pathway and the production of pro-inflammatory cytokines, halting the inflammatory signaling cascade. This multi-target mode of action enables TAU to effectively mitigate the multiple pathological consequences of sus-

tained STING activation: cellular senescence, ECM degradation, and apoptosis (Fig. 8).

In our animal model, systemic administration of TAU significantly improved disc structure and function in rats and suppressed the intradiscal inflammatory environment, strongly supporting its translational potential. Certainly, this study has limitations. The rat caudal puncture model primarily mimics injury-induced degeneration and does not fully capture the slow, multifactorial, age-related characteristics of human IVDD. The direct binding of TAU to cGAS/STING and its functional consequences require further validation via more precise genetic approaches, such as point mutations. Furthermore, the bioavailability and specific distribution of TAU within the intervertebral disc necessitate optimization through more in-depth pharmacokinetic studies.

In summary, the innovativeness of this study lies in the systematic validation of the cGAS-STING pathway as a key disease driver in IVDD and the revelation that the natural molecule TAU modulates this pathway through a multi-faceted mechanism of “mitochondrial protection-pathway inhibition-autophagy enhancement”. Our work not only provides a new therapeutic target and candidate drug for IVDD but also suggests that restoring communication homeostasis between organelles represents a promising new strategy for treating degenerative diseases.

Conclusion

This study confirms that the persistent activation of the mitochondrial damage-mtDNA leakage-cGAS-STING pathway is a key pathological axis driving sterile inflammation, cellular senescence, and matrix degradation in IVDD. Through a multi-level chain of evidence, we identify the natural small molecule TAU as an effective multi-target modulator of this pathway. TAU exerts protective effects through a coordinated and sequential mechanism. Firstly, at the source, it stabilizes mitochondrial function, significantly reducing the cytosolic leakage of mtDNA, thereby curbing the aberrant initiation of the cGAS-STING pathway. Secondly, at the core of the pathway, TAU directly interacts with cGAS/STING and promotes the autophagic degradation of STING, achieving dual inhibition of signal transduction. Finally, by effectively blocking the downstream TBK1-IRF3/NF- κ B axis, TAU successfully reverses the senescence process in NPPCs and alleviates inflammation-mediated ECM degradation. In the rat IVDD model, TAU treatment effectively delayed the progressive loss of disc height and the disruption of tissue architecture.

In conclusion, our findings position TAU as a potential therapeutic agent capable of intervening in the disease process by reestablishing homeostasis between mitochondria and the cytosol. Targeting the cGAS-STING pathway provides a novel strategy for developing disease-modifying therapies for IVDD, warranting further clinical translation exploration. This work provides a theoretical foundation and experimental basis for developing TAU-based novel interventions or drugs for treating IVDD and associated low back pain.

Ethical statement

The study titled “Calming sterile inflammation in intervertebral disc degeneration: taurine disrupts mitochondria-cGAS-STING signaling via autophagy enhancement” was approved by the

Animal Ethics Committee of Yangzhou University (Approval No. 2025028897) on 3 March 2025. Additionally, the study protocol was approved by the Ethics Committee of the Northern Jiangsu People's Hospital Affiliated to Yangzhou University (Approval No. 2021ky050) on 2 March 2021. All procedures involving human participants and tissues were conducted in accordance with the ethical standards of the institutional research committee and with the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards. Informed consent was obtained from all individual participants included in the study.

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Author contributions

Shuangjia Zai (Conceptualization, Data curation, Formal Analysis, Methodology, Resources, Visualization, Writing – original draft), Huofeng Wu (Conceptualization, Data curation, Investigation, Methodology), Xuan You (Data curation, Validation, Visualization), Chen Liu (Data curation, Investigation, Validation), Zhaoyu Li (Data curation, Validation), Benkui Hua (Data curation, Visualization), Chengyu Hou (Data curation, Validation), Zhengguang Li (Conceptualization, Visualization), Liang Zhang (Conceptualization, Data curation, Formal Analysis, Funding acquisition, Resources, Supervision, Writing – review & editing).

Supplementary material

Supplementary material is available at *PCMDI Journal* online.

Conflicts of interest

The authors have no relevant financial or nonfinancial interests to disclose. The authors declare that there was no outsourced work or data collection conducted by any parties other than the authors themselves.

Data availability

The 2D structures of the small molecule ligands for molecular docking were obtained from the PubChem database. The protein crystal structure was sourced from the RCSB Protein Data Bank (PDB). The summary-level eQTL data for the Mendelian randomization analysis are available from the IEU OpenGWAS project database (<https://gwas.mrcieu.ac.uk/>). The GWAS summary data

for IVDD outcomes were derived from the FinnGen database (<http://www.finnngen.fi/>). Detailed sample information for the single-cell sequencing data is accessible through the GEO database under accession number GSE205535.

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