Controllable nitric oxide release material relieves intervertebral disc degeneration through antibacterial effect and inhibiting osteoclast activation

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INTRODUCTION: Low back pain (LBP) is a common health issue and the leading cause of disability. Although the pathogenic mechanism of intervertebral disc degeneration (IVDD) and Modic changes is still controversial, infection is always considered to be one of the pathogenic factors leading to IVDD. In previous study, we found that injecting P.acnes into the intervertebral discs of New Zealand rabbits and rats eventually resulted in IVDD and Modic changes. Nitric oxide (NO) plays an important role in the physiological and pathological processes of many organisms and has shown superior application prospects, especially for antibacterial purposes. In this study, we synthesized a controllable nitric-oxide donor (PEGNO) that can achieve local delivery of NO under red-light irradiation through photoredox catalysis between PdTPTBP and CouN(NO)-NO2 derivatives. We verified that the donor prevented the progress of IVDD and Modic changes through antibacterial effect and inhibited osteoclast differentiation.

METHODS: We covalently incorporated the NO donor and PdTPTBP into the core of micellar nanoparticles. Therefore, the hydroxyl groups of CouN(NO)-NO2 was functionalized with the functional groups of 2-isocyanatoethyl methacrylate to form CouN(NO) and CouN(H) monomers. PdTPTBP and CouN(NO) monomers were polymerized by reversible addition-fragmentation chain transfer (RAFT) polymerization. The copolymers self-assembled into micellar nanoparticles in aqueous solutions. After confirming the antibacterial effect of NO on P.acnes, the donor's biological toxicity and hemolytic activity were tested. Then, in vitro experiments, we confirmed the protective effect of PEGNO with irradiation on intervertebral disc cells which injured by P.acnes, and its inhibitory effect for osteoclast differentiation. We then verified the efficacy of PEGNO in a rat IVDD model.

RESULTS SECTION: The results of the agarose plate show that NO donor can inhibit the proliferation of P.acnes after visible light irradiation. CCK8 and mammalian hemolysis experiments proved that the material has no obvious cytotoxicity up to 0.5g/L. We also found that PEGNO can effectively inhibit the pyroptosis of intervertebral disc cells induced by co-cultivation with P.acnes in vitro. For the rat IVDD model, the PEGNO with irradiation group has better MRI evaluation than the P.acnes injection group and the antibiotic treatment group. HE staining, Safranin Fast Green staining and Immunofluorescence revealed that the disc from the PEGNO with irradiation group had more continuous annulus, less bone destruction, and healthier nucleus pulposus and cartilage endplates.

DISCUSSION: There is currently no ideal treatment for chronic intervertebral disc infection, while traditional antibiotics have limited therapeutic effects on anaerobic infections such as P.acnes. As a potential therapeutic gas molecule, nitric oxide has the characteristics of low toxicity and easily metabolized. In this study, PEGNO was synthesized to achieve efficient NO release in vitro and in vivo. By inhibiting the inflammation of the intervertebral disc and the destruction of the endplate cartilage caused by P.acnes, the progression of IVDD and Modic changes is delayed.

SIGNIFICANCE/CLINICAL RELEVANCE: This study provides strategies for the biological application of NO gas molecules and the treatment of intervertebral disc degeneration.