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Nicotinamide riboside chloride (NR), an orally bioavailable nicotinamide adenine dinucleotide (NAD+) precursor, significantly inhibits post-traumatic osteoarthritis (OA) development and associated pain in mice

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Purpose: Nicotinamide adenine dinucleotide (NAD+) is a key metabolite that serves as a cofactor for numerous enzymes involved in cellular energy metabolism and critically regulates multiple cell-signaling pathways. We previously observed that up regulation of expression of CD38, the main NADase (NAD+ consuming enzyme) in mammalian tissues is associated with decline of cellular NAD+ levels in advanced human knee OA chondrocytes/cartilage. In addition, CD38 expression is markedly induced by pro-inflammatory cytokine IL-1beta, correlated with reduced ratio of NAD and NADH. Changes in cellular NAD+ levels are related to the balance between NAD+ biosynthesis and degradation. There is an inhibitor of CD38 activity, apigenin (API), that is believed to achieve increase to NAD+ levels. Thus, we carried out *in vivo* studies using a post-traumatic mouse OA model to examine if oral supplementation of NR or API inhibits OA development and associated pain.

Methods: Male C57BL/6 mice at 3-4 months of age were subjected to the destabilization of medial meniscus (DMM) surgery, randomly divided into 3 groups (n=9/group): NR or API treatments by gavage (500mg and 25 ug/kg/day in water, respectively) and controls. Pain behaviors were evaluated by Von Frey and static weight bearing tests at baseline and every 2 weeks after the surgery. At 10 weeks after the surgery, mice were sacrificed and knee OA pathological changes including cartilage degradation were evaluated using the OARSI score system.

Findings: *In vivo* studies revealed that mice treated with NR or API exhibited significantly reduced cartilage damage after the DMM surgery (Fig 1A). Additionally, they displayed improved pain behaviors (Fig 1B and C). These results suggest NR via oral administration limited post-traumatic OA development and associated pain in mice.

Conclusion: Preventing intracellular NAD+ decline and/or restoration of NAD+ levels through NR supplementation could be a new approach to suppresses cartilage degradation and OA development.

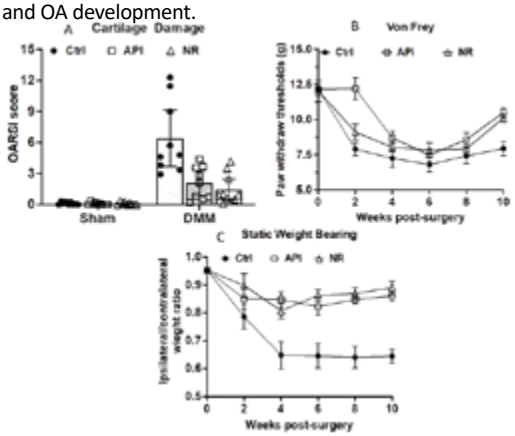

Figure 1: Cartilage damage assessed by OARSI Score (A), pain behavior *in vivo* results from Von Frey (B) and Static Weight Bearing (C) from animals treated with NR or API for ten weeks after DMM.

Recent Publications

1. Correa LB, Pádua TA, Alabarse PVG, et al. Protective effect of methyl gallate on murine antigen-induced arthritis by inhibiting inflammatory process and bone erosion. Inflammopharmacology. 2022.

2. Alabarse PVG, et al. Metabolomic Biomarker Candidates for Skeletal Muscle Loss in the Collagen-Induced Arthritis (CIA) Model. J Pers Med. 2021.

3. Soares MPR, Silva DP, Uehara IA, et al. The use of apocynin inhibits osteoclastogenesis. Cell Biol Int. 2019.

Biography

Paulo V G Alabarse has expertise in rheumatoid arthritis and related muscle loss, as well as osteoarthritis. His research focuses on searching for novel drugs for the treatment of osteoarthritis and search for a metabolic biomarker of muscle loss targeting diagnosis, follow-up and treatment response to improve individual disease progress and treatment response.

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