In the PDT experiment on human RA synovial biopsies, the groups incubated with 28 H1–700DX and exposed to light showed apparent cell death in the synovial tissue as evidenced by the positive staining of both the gH2AX and caspase 3 markers (figure J and K). Staining of these markers co-localised with areas of high FAP staining (figure L). This was not the case in the control samples that were not exposed to either 28 H1–700DX and/or light (figure A – I). All biopsies did show FAP staining indicating that the cell death was only achieved when the biopsies were exposed to both the antibody and the light.

Conclusions: We have demonstrated fibroblast-specific cell death by targeted PDT using 700DX-conjugated 28 H1. Furthermore, we demonstrated that PDT also induces cell death of FAP-positive cells in synovial tissue from RA patients, suggesting FAP-targeted PDT as a promising new tool in treating RA.

Disclosure of Interest: None declared

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SAT0062

METABOLOMICS AND METABOLIC FUNCTION ANALYSIS OF THE SECRETOME OF ARTICULAR CARTILAGE AND CHONDROCYTES IN RESPONSE TO PRO-INFLAMMATORY CYTOKINES

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Background: Chondrocytes rely primarily on glycolysis to meet their energy requirements, but can support cell survival and matrix synthesis during periods of nutrient stress by enhancing glycolysis with mitochondrial respiration. Accessing this 'spare respiratory capacity' requires optimal mitochondrial function. Impaired mitochondrial function is implicated in osteoarthritis (OA). Metabolic adaptation is evident in early-stage OA, however cartilage from late-stage disease does not seem to have this flexibility. A deeper understanding of these complex metabolic pathways may identify new markers of disease stage, and support therapeutic strategies for treating OA.

Objectives: Metabolomics has the potential to reveal pathological pathways and identify novel biomarkers. The aim was to identify metabolic processes involved in early stage disease by analysis of metabolites and metabolic function in pro-inflammatory models of cartilage degradation.

Methods: Macroscopically normal articular cartilage was obtained from equine and bovine metacarpophalangeal joints. Equine cartilage explants (n=6), and primary chondrocytes seeded at 105,000/cm² (n=4), were cultured for 7 days in serum-free DMEM (Gibco) with or without 10 ng/ml equine interleukin-1 β (IL-1 β) and 10 ng/ml tumour necrosis factor- α (TNF- α). Secretome metabolite levels were measured using AbsoluteIDQ p180 targeted metabolomics kit (Biocrates), with Waters Xevo TQ-S mass spectrometer coupled to an Acquity UPLC system. PCA and OPLS-DA were performed using SIMCA-P v12.0 software. Metabolic function of primary equine (n=9) and bovine chondrocytes (n=3) was determined using Seahorse XFp and XF24 analyzers. Cells were treated with species-specific 10 ng/ml IL-1 β and/or 10 ng/ml TNF- α for 18 hour, and metabolically challenged with the Mito Stress Test. Metabolite levels, and oxygen consumption rates, were normalised to total cell protein, and values analysed by ANOVA with Tukey's multiple comparison post-tests.

Results: Cytokine treatment decreased proline, ornithine and alpha-aminoadipic acid (p<0.0001) in explant secretome. Citrulline increased with cytokine treatment (p<0.0001) and glutamate, present in DMEM, was also elevated (p<0.0001). Metabolomic analysis of chondrocyte secretome showed that glutamine decreased (p<0.02) with cytokine treatment whereas citrulline was elevated (p<0.003). Metabolic analysis showed that cytokine treatment reduced basal respiration and negated spare respiratory capacity in chondrocytes (p<0.01), and the effect was due to IL-1 β alone.

Conclusions: Explant metabolites which decreased with cytokine treatment are all downstream of glutamate. With elevated glutamate, this suggests that cytokines inhibit glutamate uptake and metabolism. Elevated citrulline in cell and explant models may be attributed to disruption of the urea cycle via induction of nitric oxide synthase. IL-1 β alone negated spare respiratory capacity, and chondrocytes remained glycolytic. In conclusion, cytokines disrupt glutamate and citrulline metabolism, normally tightly regulated mitochondrial pathways, and IL-1 β alone is responsible for the metabolic switch. These metabolic pathways could provide markers of early-stage inflammatory disease.

Disclosure of Interest: None declared

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SAT0063

EFFECTS OF INTRA-ARTICULAR INJECTED DIACEREIN-LOADED NANOPARTICLES ON JOINT IN RAT MODEL OF OSTEOARTHRITIS

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Background: Osteoarthritis (OA) is a major health problem in recent years, but the current medical treatment is mainly symptom control and joint disability improvement. Diacerein (DIA) reduces the level of interleukin (IL)–1 receptor on the surface of chondrocytes, alleviates the pain, and prevents the structural degradation of the joint tissue. However, DIA has the side effects such as diarrhoea and urine discoloration when taken orally. To increase bioavailability and reduce systemic side effects, it is preferable to inject DIA directly into the joints. Nanoparticulate drug carriers have been attempted with the advances in drug delivery systems.

Objectives: We investigated that DIA-loaded nanoparticles (DIA/NPs) can efficiently inhibit the inflammatory reaction in synoviocytes stimulated by lipopolysaccharide *in vitro* and alleviate both inflammation and cartilage degeneration in monosodium iodoacetate (MIA)-induced OA rat model *in vivo*.

Methods: DIA/NPs were fabricated by water/oil/water emulsion method. *In vitro*, the mRNA levels of pro-inflammatory cytokines (IL-1, IL-6, MMP-3, MMP-13, COX-2, ADAMTS-5, and TNF- α) were measured at 1 st and 3rd day after the administration of NPs only and DIA/NPs to synoviocytes using real-time PCR. MIA was intra-articular injected through the infrapatellar ligament of the rats' knee to induce OA. The rats were randomly divided into the six treatment groups: ¹ control, ² MIA, ³ MIA and NPs, ⁴ MIA and DIA(1%)/NPs, ⁵ MIA and DIA(5%)/NPs, and ⁶ MIA and DIA(5%) solution injection. After NPs, DIA(1%)/NPs, DIA(5%)/NPs, and DIA(5%) solution were injected, at 8th week, the rats were sacrificed to evaluate the plain radiographic and micro-computed tomography (micro-CT), histological study, and pro-inflammatory cytokines expression.

Results: The mRNA expression levels for pro-inflammatory cytokines in cells seeded with DIA(5%)/NPs and DIA(5%) solution were significantly lower than those in cells seeded with NPs at 1 st and 3rd day. Moreover, the mRNA levels of pro-inflammatory cytokines in cells injected with DIA(5%) solution decreased much greater than in cells injected with DIA(5%)/NPs. The rats injected DIA(5%)/NPs showed the least amount of cartilage and bone damage on plain radiography and micro-CT and had the less cartilage loss and the bony erosions on microscopic observation. The pro-inflammatory cytokines expression was lowest in the rats injected DIA(5%)/NPs, followed by NPs, DIA(1%)/NPs, and DIA(5%) solution.

Abstract SAT0063 – Figure 1. The macroscopic observations for 9 weeks after the MIA injection and for 8 weeks after treated with NPs, DIA (1%)/NPs, DIA (5%)/NPs, or DIA (5%) solution injections (arrows indicate erosions).

Conclusions: DIA(5%)/NPs are a promising therapeutic material to control the symptoms and prevent the progression of OA.