nicely correlated with thickening of the synovial lining layer comprising activated macrophages. When collagenase-induced-osteoarthritis was elicited in S100A9−/− mice, significantly lower synovial activation was observed when compared to WT mice. Synovial activation was 62% lower at day 42. Cartilage destruction was significantly lower in all surfaces and ranged from a 45% reduction in the lateral tibia to 73% reduction in the medial femur. When primary mouse chondrocytes were stimulated with S100A8 or S100A9, a strong upregulation of particularly MMP-3 mRNA level was found indicating a direct role of S100A8/A9 in cartilage destruction.

**Conclusions:** Alarmins S100A8/S100A9 are expressed by phagocytes in biopsies of early OA patients. S100A8/A9 play a crucial role in synovial activation and cartilage destruction in an osteoarthritis model that shows clear synovial involvement. S100A8/A9 expression in the synovium causes pathology probably by stimulating MMP-mediated damage in the cartilage matrix.

### 30 ONCOSTATIN M POTENTIALLY INDUCES IL-6 AND RANKL EXPRESSION IN MOUSE SYNOVIAL FIBROBLASTS AND SIGNIFICANTLY ENHANCES THE EFFECTS OF IL-1 AND TNF

**Purpose:** Oncostatin M (OSM) is a multipotent cytokine that is expressed in synovium from rheumatoid arthritis (RA) and osteoarthritis (OA) patients. OSM alone or in concert with pro-inflammatory cytokines such as IL-1 or TNF, can stimulate synovial fibroblasts (SFs) to express genes that promote inflammation and joint destruction in arthritis. This study determined the acute effects of OSM, IL-1, and TNF and their combination on expression of IL-6 and RANKL in SFs.

**Methods:** SFs were derived from non-arthritic mice deficient in OSM receptor expression (OSMR−/−) and strain-matched wildtype control (OSMR+/+). SFs were stimulated with mouse OSM (2 ng/mL), mouse IL-1 (10 ng/mL), and mouse TNF (7.5 ng/mL) and their combination for 1, 6, and 24 hrs. Gene expression was assessed by quantitative RT-PCR analyses. Flow cytometry and immunohistochemistry were performed to identify protein expression.

**Results:** In OSMR+/+ SFs, OSM and IL-1 increased IL-6 mRNA expression by 80 fold at 6 hrs, with OSM further increasing expression at 24 hrs (135 fold vs. 40-fold, IL-1). TNF treatment resulted in a small transient increase in IL-6 mRNA expression which peaked at 1 hr (9 fold) and returned to baseline by 24 hrs. Profound synergistic upregulation of IL-6 mRNA expression was observed when suboptimal doses of OSM and IL-1 were combined (>1000-fold at 6 and 24 hrs). Combining TNF and OSM enhanced IL-6 mRNA expression compared to each cytokine alone at 1 hr (232-fold) but this combination had no additional effect at 6 and 24 hrs compared to OSM alone. OSM, IL-1 and TNF all increased RANKL mRNA expression at 6 hrs (9 fold, OSM; 4 fold, TNF, and IL-1), with the effects of TNF and IL-1 returning to baseline by 24 hrs. OSM treatment, however, further increased RANKL mRNA expression at 24 hrs (20 fold). Combining suboptimal doses of OSM and IL-1 significantly enhanced RANKL expression at 24 hrs (100-fold) but this interaction was not synergistic. Combining OSM and IL-1 had no additional effect on RANKL expression compared to OSM alone. Importantly, OSMR−/− SFs showed no induction of IL-6 or RANKL mRNA expression in response to OSM treatment, but did respond to IL-1 and TNF treatment in a similar manner to the OSMR+/+ SFs. In OSMR+/+ SFs, OSM stimulated mRNA expression of its co-receptors (OSMR, 6-fold at 6 and 24 hrs, and gp130, 3-fold at 24 hrs). Furthermore, OSM increased IL-1 receptor mRNA and protein expression at 24 hrs. IL-1 did not regulate its own receptor, but induced a 3-fold increase in OSMR mRNA expression at 6 and 24 hrs. OSM had no effect on TNF receptor expression. Finally, immunostaining demonstrated protein expression of OSM and its co-receptors in the synovium in normal mouse knee joints; expression was increased in antigen-induced arthritis and was evident in the mouse surgical model of osteoarthritis (destabilization of the medial meniscus).

**Conclusions:** Together our data show that OSM, alone or in concert with TNF, is a potent regulator of IL-6 and RANKL expression in SFs. These effects of OSM are dependent on OSMR expression. The ability of OSM and IL-1 to cross-regulate expression of their respective receptors contributes to the synergistic effect of these cytokines in SFs. This study identifies a significant role for OSM, acting through OSMR, in mediating inflammation and bone destruction in arthritic joints.

### 31 SMART, THIN WOMEN WITH HIGHER VITAMIN D INTAKE AND TALL MEN WITH A HAPPY CHILDHOOD ARE PROTECTED FROM ULTRASOUND FEATURES OF HIP OSTEOARTHRITIS: THE NEWCASTLE THOUSAND FAMILIES STUDY

**Purpose:** There has been a paucity of lifestyle research on the risk of osteoarthritis (OA). We performed a lifestyle analysis of potential risk factors for hip OA (defined by osteophytes and femoral head score on ultrasound) acting at different stages of life, among members of the Newcastle Thousand Families birth cohort.

**Methods:** Potential risk factors for hip OA (including birth weight and breast feeding data) have been collected prospectively in this birth cohort and an a priori conceptual framework was developed. Participants from the cohort aged 63 years (born in May-June 1947), had both hips scanned by a trained musculoskeletal sonographer. Ultrasound protocols were derived from EULAR guidelines. Hip OA was considered to be present if an osteophyte or femoral head abnormality was identified. These data were analysed in relation to a range of factors from across the lifetime using logistic regression models.

**Results:** Prevalence of hip OA was 26%, 30% and 40% for right, left and “any” hip, respectively; among 311 participants. There was no significant difference of hip OA prevalence between males and females (p = 0.8). While birth weight, exclusive breast feeding at birth, adverse life events in childhood and height at age 50 showed significant univariate associations with hip OA in men, it was only adverse life events in childhood (OR 3.56 one event vs no event; 95% CI 1.16, 10.9; p = 0.03) and height at age 50 (OR 0.87 per cm; CI 0.79, 0.96; p = 0.004) that showed significant associations in the adjusted model for males. Exclusive breast feeding (OR 0.77 per month; CI 0.58, 1.01; p = 0.06) showed borderline significance in the adjusted model for males. In contrast, higher education level (OR 0.10 graduate vs not completed school; CI 0.01, 0.85; p = 0.03) and dietary intake of vitamin D at age 50 (OR 0.75 per microgram per day; CI 0.59, 0.95; p = 0.02) were found to be protective against hip OA in women, while an increased body fat percentage at age 50 conferred a slightly higher risk of hip OA (OR 1.05; CI 1.0, 1.1; p = 0.03) in the adjusted model for women.

**Conclusions:** This is the first study to perform a lifestyle analysis of hip OA risk using prospectively collected data. Tall men with no adverse life events in childhood were at a significantly decreased risk of hip OA in this study. Increased height might be a function of genetic status, better nutrition (at birth and in childhood), decreased infections and/or better socio-economic status; the factors for the association of hip OA with height require further study to explain this relationship. Adverse life events in childhood might influence their effect on subsequent hip OA through psychological and social pathways, which was beyond the scope of this study. The borderline significance of exclusive breast feeding in men is an interesting finding. While breast feeding is known to decrease risk of adult obesity and therefore of hip OA, this study suggests that exclusive breast feeding might be an independent predictor of hip OA in men. The mechanism for this could be reduced burden of infection and inflammation through the lifestyle – a testable hypothesis.

The protective effect of higher education in women from subsequent hip OA is a novel finding. We hypothesise that this might reflect adoption of healthier lifestyles among educated women or might even be a function of their improved utilisation and uptake of healthcare services. The protective effect of dietary intake of vitamin D in women is in line with results from the Study of Osteoporotic fractures (NE Lane et al, *Arthritis Rheum*;1999) which showed a similar protective effect of dietary Vitamin D intake on incident hip OA in women. This protective effect of vitamin D intake was independent of its effect on BMD at age 50. The findings of this study have potential implications to public health policy especially with regard to dietary vitamin D intake in women.