OP0105

ZCCHC6 DELETION DOWNREGULATES IL-6 AND REDUCES THE SEVERITY OF EXPERIMENTAL OSTEOARTHRITIS IN MICEM.Y. Ansari, M.N. Khan, I. Ahmad, T.M. Haqqi. *Anatomy and Neurobiology, Northeast Ohio Medical University, Rootstown, USA*

Background: Osteoarthritis (OA) is the most common joint disease in elderly and is a major cause of disability. Currently no disease modifying agents exist to treat OA. ZCCHC6 (zinc-finger CCHC-domain containing protein 6) is a member of family of terminal uridylyltransferases (TUTs) and is known to carry out template independent addition of Uridine at the 3' ends of miRNAs. ZCCHC6 has been implicated in miRNA-mediated regulation of cytokine gene expression; however, the role of ZCCHC6 in the pathogenesis of OA is unknown.

Objectives: The aim of this study was to investigate the effect of ZCCHC6 deletion on proinflammatory cytokine, IL-6, expression in human and mouse chondrocytes and to study the role of ZCCHC6 in OA pathogenesis *in vivo* using Zcchc6^{-/-} mice.

Methods: Human or mouse chondrocytes were prepared by sequential enzymatic digestion and treated with recombinant human or mouse IL-1 β to mimic OA pathogenic conditions. Cytokine profiling was done using qPCR array and multiplex assay. IL-6 expression in chondrocytes was analysed by qPCR and immunoblotting/ELISA. IL-6 mRNA stability was determined by Actinomycin-D chase experiments. The 3'-uridylation of miRNAs was analysed by deep sequencing of small RNAs using Illumina MiSeq. ZCCHC6 and IL-6 expression in OA cartilage was analysed by immunohistochemistry. For *in vivo* studies, OA was induced by surgical destabilisation of medial meniscus (DMM) in the knee joints of mice. The severity of OA was assessed by safranin O/fast green staining followed by OARSI scoring.

Results: ZCCHC6 expression was upregulated in OA cartilage. Cytokine expression profiling in ZCCHC6 depleted human and Zcchc6^{-/-} mouse chondrocytes revealed IL-6 as a major target of ZCCHC6. Depletion of ZCCHC6 expression in human chondrocytes resulted in decreased expression of IL-6 at mRNA and protein levels. ZCCHC6 depletion suppressed IL-1 β induced expression of IL-6. Overexpression of ZCCHC6 in human chondrocytes resulted in increased expression of IL-6 in the presence or absence of IL-1 β . Chondrocytes from Zcchc6^{-/-} mice also showed decreased levels of IL-6 expression compared to Zcchc6^{+/+}. Furthermore, overexpression of mouse Zcchc6 in Zcchc6^{-/-} chondrocytes rescued IL-6 expression. IL-6 mRNA half-life was significantly reduced in Zcchc6^{-/-} mouse chondrocytes and ZCCHC6 depleted human chondrocytes. Deep sequencing of small RNAs in ZCCHC6 depleted human chondrocytes showed reduced 3'-uridylation of IL-6 targeting miRNAs miR-26a/26b. Human chondrocytes transfected with miR-26a/26b mimic suppressed IL-6 expression, however, miR-26b mimic with additional 'UU' failed to suppress IL-6 expression. Zcchc6^{-/-} mice expressed low levels of MMP13 and showed lesser matrix degradation in the joints with DMM surgery. Zcchc6^{-/-} mice developed less severe OA as determined by safranin O/fast green staining followed by OARSI scoring. Synovitis was also decreased in the Zcchc6^{-/-} mice DMM joints in comparison to Zcchc6^{+/+} +DMM joints.

Conclusions: Our data demonstrate that ZCCHC6 is upregulated in OA cartilage and regulates IL-6 expression via miR-26b 3'-uridylation. These data identify a previously unknown function of ZCCHC6 in OA pathogenesis and identifies a potential therapeutic target for the management of OA.

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Delay in treatment and the role of health professionals

OP0106

WHO IS NOT REACHING REMISSION IN EARLY RA AND WHY? PREDICTORS FOR PERSISTENT DISEASE ACTIVITY IN THE FIRST YEAR DIFFER IN MEN AND WOMEN AND ARE RELATED TO LIFESTYLE AND TREATMENT

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Background: Although early identification and aggressive treatment of RA improves outcomes, we have shown that 45% of early RA participants receiving guideline-based care do not achieve remission in the first year. Moreover, fewer women reached remission than men.

Objectives: To compare predictors of persistent disease activity (LDA/MDA/HAD) in the 1st year of RA treatment in men and women.

Methods: Sample included adults in CATCH (Canadian Early Arthritis Cohort) from 2007–2016 with active disease at baseline and ≥ 12 m F/U. Standardised visits included clinical assessments, questionnaires, and lab tests. Logistic regression with backward selection was used to identify predictors of failing to achieve remission (DAS28 <2.6) by 12 months among baseline sociodemographic and RA characteristics and patient reported outcomes.

Results: The sample included 1628 adults with classifiable RA, who were mostly female (72%) with a mean (SD) age of 55, (15) with 2 (2) comorbidities, and symptom duration of 6 (3) months. At enrollment, 95% had active disease (DAS28 MDA (42%); HDA (53%)), most were initially treated with csDMARDS (any 92%; MTX 75%). 46% of women and 38% of men did not reach remission by 12 months. Among women, multivariable results showed obesity more than doubled the likelihood of not achieving remission; other key predictors were minority status, lower education, and higher TJC and fatigue scores at baseline (table 1). In men, current smoking was associated with a 3.5 greater odds of not achieving remission in the first year; other predictors included older age, and higher pain. Not using MTX increased the likelihood of not achieving remission in women by 28% and men by 45%. Longer symptom duration and higher ESR were associated with not achieving remission in all. Factors not related to persistent disease activity included family history of RA, RF/ACPA status, erosions, SJC, HAQ and depressive symptoms at baseline.

Abstract OP0106 – Table 1

	Women	Men
N	1179	449
Sociodemographics		
Age (each 10 years)	1.04 (0.95, 1.14)	1.48 (1.22, 1.79)
Minority race	1.46 (1.07, 2.00)	Not selected
Education = high school	1.41 (1.09, 1.82)	Not selected
Comorbidities	1.12 (1.05, 1.21)	Not selected
Obese (BMI ≥ 30 kg/m ²)	2.06 (1.49, 2.83)	1.65 (0.95, 2.85)
Current smoking	Not selected	3.45 (2.06, 5.77)
RA Characteristics		
Symptom duration (month)	1.10 (1.05, 1.14)	1.15 (1.07, 1.24)
Family history of RA	Not selected	1.62 (0.95, 2.77)
RF+ or ACPA+	1.23 (0.87, 1.75)	Not selected
Erosions	Not selected	Not selected
MTX Use	0.72 (0.54, 0.95)	0.55 (0.33, 0.90)
Oral Steroids (Y vs N)	0.80 (0.60, 1.07)	1.45 (0.92, 2.27)
Parenteral Steroids (Y vs N)	Not selected	Not selected
ESR (mm/h)	1.01 (1.01, 1.02)	1.02 (1.01, 1.03)
Swollen Joint Count (28)	Not selected	Not selected
Tender Joint Count (28)	1.03 (1.01, 1.06)	Not selected
Patient Reported Outcomes		
High depressive symptoms	Not selected	Not selected
Pain (0-10)	Not selected	1.11 (1.03, 1.20)
HAQ-DI (0-3)	Not selected	Not selected
Fatigue (0-10)	1.05 (1.00, 1.09)	Not selected
Fit Statistics		
AIC	1519	535
BIC	1601	581
Area under the curve	0.69	0.74

Conclusions: In this large pan-Canadian cohort of early RA patients receiving guideline-based arthritis care, obesity in women and current smoking in men were the strongest predictors of not achieving remission in the first 12 months followed by non-use of MTX, higher baseline inflammation and longer symptom duration. Additional poor prognostic indicators in women included minority status, lower