Although absent from healthy adult articular cartilage, our initial studies identified high expression levels of ROR2 in chondrocytes from patients with OA, suggesting a role in the disease process

Objectives: To test the potential of ROR2 blockade as a disease-modifying treatment for OA.

Methods: Human cartilage organoid model in nude mice, menisco-ligament injury (MLI) model of OA in mice, behavioural studies, *in vitro* studies in cells.

Results: ROR2/WNT5A signaling was increased in osteoarthritic cartilage. Blocking ROR2 was sufficient to induce articular chondrogenesis and suppress expression of aggrecanases in a mesenchymal stem cell line, and to support cartilage formation in a human cartilage organoid model in nude mice using primary chondrocytes from patients with OA.

In the MLI model of OA, blocking ROR2 in therapeutic regime using atelocollagen-conjugated siRNA resulted in reduced cartilage destruction and in rapid and sustained pain relief. Due to the limited expression pattern of ROR2 in adulthood, no systemic or local toxicity were expected, nor were any observed⁴.

With the current technology, ROR2 blockade requires intra-articular (IA) injections of siRNA conjugated to atelocollagen every 5 days. Preliminary efficacy data of potentially longer-acting ROR2 blockers are promising.

The mechanism of action of ROR2 blockade was independent of modulation of canonical WNT signaling.

ROR2/WNT5A promoted nuclear localization of YAP, which required both Rho and G-proteins. YAP signaling downstream of ROR2 also required Rho, but not G-proteins. YAP and TEAD inhibition was required, but not sufficient, for the chondrogenic effect of blocking ROR2. Therefore, additional, yet unknown mechanisms must be involved downstream of ROR2.

Conclusion: ROR2 blockade has potential as a disease-modifying treatment for OA, resulting in cartilage protection and rapid and sustained pain relief in a murine model. This will be crucial for clinical success of any treatment for OA and promote patient compliance.

Our current siRNA-atelocollagen based technology requires IA injections too frequently to be acceptable for patients. We are developing ROR2 blockade which can be administered systemically or IA not more often than every 3 months - work funded by FOREUM.

REFERENCES:

- [1] DeChiara, T. M. *et al.* Ror2, encoding a receptor-like tyrosine kinase, is required for cartilage and growth plate development. *Nat. Genet.* **24**, 271–4 (2000).
- [2] Bokhoven, H. Van, Celli, J. & Kayserili, H. Mutation of the gene encoding the ROR2 tyrosine kinase causes autosomal recessive Robinow syndrome. *Nature* **25**, 423–426 (2000).
- [3] Afzal, A., Rajab, A., Fenske, C. & Oldridge, M. Recessive Robinow syndrome, allelic to dominant brachydactyly type B, is caused by mutation of ROR2. *Nature* **25**, 419–422 (2000).
- [4] Thorup, A.-S. *et al.* ROR2 blockade as a therapy for osteoarthritis. *Sci. Transl. Med.* **12**, eaax3063 (2020).

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Origin and role of myeloid cells during homeostasis and inflammation

OP0201

DYNAMIC CHANGES IN O-GLCNAcylation REGULATE OSTEOCLAST DIFFERENTIATION AND BONE LOSS IN ARTHRITIS

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Background: Bone remodeling is a constant process maintained by the balance between osteoclast-triggered bone resorption and osteoblast-mediated bone formation. In inflammatory arthritis, such as rheumatoid arthritis (RA), the pro-inflammatory environment favors osteoclast differentiation and skews the balance towards resorption, leading to progressive bone erosion and bone loss. O-GlcNAcylation is a post-translational modification, which transfers a single N-acetylglucosamine molecule to the serine or threonine of the target protein. The modification is accomplished by a single pair of enzymes, O-GlcNAc transferase (OGT) and O-GlcNAcase (OGA). Unlike other glycosylation, O-GlcNAcylation occurs in multiple cellular compartments, including the nucleus. Although O-GlcNAcylation is one of the most common modifications, its role in bone homeostasis is still poorly understood.

Objectives: We aimed to investigate the role of O-GlcNAcylation in osteoclastogenesis under pro-inflammatory milieu. We also focused on dissecting the signaling pathways affected by O-GlcNAcylation during osteoclast differentiation.

Methods: We examined the levels of O-GlcNAc during *in vitro* osteoclastogenesis by western blotting. The levels of O-GlcNAc in tissue from RA patients and experimental arthritis were detected by immunofluorescence. Pharmacological inhibition and genetic knockout were used to manipulate O-GlcNAcylation during osteoclastogenesis. RNA sequencing was performed to study O-GlcNAc-mediated pathways.

Results: We demonstrate the dynamic changes in O-GlcNAcylation during osteoclastogenesis. The elevated O-GlcNAcylation was found in the early differentiation stages, whereas its downregulation was detected in the maturation process. TNF α elaborates the dynamic changes in O-GlcNAcylation, which further intensifies osteoclast differentiation.

Targeting OGT by selective inhibitor and genetic knockout restrain O-GlcNAcylation and hinder the expression of the early differentiation marker *Nfatc1*. Inhibition of OGA, which forces high levels of O-GlcNAcylation throughout the differentiation, reduces the formation of multinucleated mature osteoclasts. Consistent with our *in vitro* data, suppressing OGT and OGA both ameliorate bone loss in experimental arthritis. We detected a reduced number of TRAP-expressing precursors and mature osteoclasts in the mice subjected to OGT inhibition. While inhibiting OGA only lowers the number of TRAP⁺F4/80⁺ mature osteoclasts without affecting the number of TRAP⁺F4/80⁺ precursors.

Transcriptome profiling reveals that O-GlcNAcylation regulates several biological processes. Increased O-GlcNAcylation promotes cytokine signaling and oxidative phosphorylation. The downregulation of O-GlcNAcylation is essential for cytoskeleton organization and cell fusion.

Conclusion: We demonstrate that the dynamic changes of O-GlcNAcylation are essential for osteoclast differentiation. These findings reveal the therapeutic potential of targeting O-GlcNAcylation in pathologic bone resorption.

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Crystal diseases

OP0202

DOES EXCESS WEIGHT AFFECT GOUT RISK DIFFERENTLY AMONG GENETICALLY PREDISPOSED INDIVIDUALS? – SEX-SPECIFIC PROSPECTIVE COHORT FINDINGS OVER >26 YEARS

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Background: Global burden of gout has increased substantially, particularly among women.^{1,2} Addressing obesity, a major modifiable risk factor for gout, may alleviate this burden; however, there is also a significant genetic contribution to gout risk according to the genome-wide association studies (GWAS).^{3,4} Genetic predisposition may modify the excess weight effect on gout risk.

Objectives: To investigate the potential role of genetic predisposition on the association between excess weight (i.e., BMI ≥ 25 kg/m²) and gout risk in two US prospective longitudinal cohorts over >26 years, stratified by sex.

Methods: We examined the association between excess weight and risk of incident gout meeting the ACR survey criteria,⁵ according to genetic risk, in 18,512 women from the Nurses' Health Study (NHS) over 32 years, and 10,917 men from Health Professionals Follow-Up Study (HPFS) over 26 years. We derived a genetic risk score (GRS) using 114 serum urate single nucleotide polymorphisms from the latest GWAS.³ We also calculated the population attributable risk (PAR) for excess weight according to GRS stratum.

Results: We ascertained 530 incident gout cases in NHS and 983 in HPFS. While the relative risks (RRs) due to excess weight (overweight or obesity) appeared larger among women above the mean than below the mean, the RRs among men appeared similar according to genetic predisposition (Table 1). The RRs among women for excess weight compared to normal were 1.66 (95% CI, 1.17 to 2.37) and 2.55 (1.95 to 3.34) below and above the mean GRS, respectively (P for multiplicative interaction = 0.06), whereas corresponding RRs among men were 1.68 (95% CI, 1.31 to 2.16) and 1.76 (1.47 to 2.10) (P for multiplicative interaction = 0.8). The risk differences (RD) among women for excess weight were 0.69 and 2.38 with GRS below and above the mean, respectively, resulting in the relative excess risk due to interaction (RERI) of 1.69 (95% CI, 1.03 to 2.35, P for additive interaction = 5.4x10⁻⁷); for men, the corresponding RDs were 0.70 and 1.46, with RERI = 0.76 (0.26, 1.25; P for additive interaction = 2.6x10⁻³). Excess weight accounted for a larger proportion of incident gout cases among women with GRS above the mean (PAR, 48.5% [95% CI, 38.8 to 55.9]) compared to those with GRS below the mean (PAR, 29.0% [95% CI, 10.5 to 42.1]), whereas the PARs among men were similar (31.6% vs 29.7%, respectively).

Conclusion: These large scale longitudinal prospective cohorts suggest maintaining healthy weight is an important gout prevention strategy, regardless of underlying genetic risk. In genetically predisposed individuals, addressing excess weight may prevent a large proportion of gout cases, especially among women.

REFERENCES:

- [1] Safiri et al., PMID 32755051
- [2] Xia et al., PMID 31624843
- [3] Tin et al., PMID 31578528
- [4] Tai et al., PMID: 32017447
- [5] Wallace et al., PMID: 856219

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Table 1. Relative Risk of Gout by Body Mass Index, Stratified by Mean Genetic Score

BMI	HPFS (men)							
	Below Mean				Above Mean			
	Overall	<25	25-30	>30	Overall	<25	25-30	>30
No. Cases	333	88	172	73	650	172	349	129
Person-Years	104055	43314	49253	11488	98634	41994	46096	10544
Age-Adjusted RR	-	1.0 (ref)	1.71 (1.32, 2.22)	3.00 (2.18, 4.12)	-	1.0 (ref)	1.80 (1.50, 2.16)	2.87 (2.27, 3.62)
MV Adjusted* RR	-	1.0 (ref)	1.53 (1.18, 1.99)	2.31 (1.66, 2.21)	-	1.0 (ref)	1.63 (1.35, 1.96)	2.38 (1.87, 3.03)

BMI	NHS (women)							
	Below Mean				Above Mean			
	Overall	<25	25-30	>30	Overall	<25	25-30	>30
No. Cases	173	47	40	86	357	72	120	165
Person-Years	244392	123849	76414	44129	239259	120229	76123	42907
Age-Adjusted RR	-	1.0 (ref)	1.23 (0.81, 1.88)	4.46 (3.10, 6.41)	-	1.0 (ref)	2.41 (2.17, 3.23)	5.68 (4.82, 7.52)
MV Adjusted* RR	-	1.0 (ref)	1.00 (0.65, 1.53)	2.84 (1.92, 4.20)	-	1.0 (ref)	1.97 (1.46, 2.65)	3.61 (2.68, 4.87)

*Adjusted for age (continuous), menopause, use of hormone therapy (never, past or current), history of hypertension, and systolic and diastolic blood pressure, alcohol, total energy intake and intake of meat, seafood and dairy foods (all continuous).

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OP0203

GENE-DIET INTERACTION ON THE RISK OF INCIDENT GOUT AMONG WOMEN – PROSPECTIVE COHORT STUDY OVER 32 YEARS

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Background: Although gout is conventionally known as a male condition, the recent Global Burden of Disease (GBD) Study found disproportionate worsening among women.¹ We have found Dietary Approaches to Stop Hypertension (DASH) diet is independently associated with a lower risk of incident gout, while Western diet is associated with increased risk.² Whether these risks vary according to genetic risk remains unknown.

Objectives: To investigate the influence of genetic predisposition on the relation between diets (one protective and another hazardous) and gout risk in a large prospective US cohort of women over 32 years.

Methods: We examined the role of genes on the association between two dietary patterns (DASH and Western) on the risk of incident gout in 18,512 women from the Nurses' Health Study. Using validated food frequency questionnaires, for each participant we derived: 1) DASH score emphasizing fruits, vegetables, nuts, legumes, whole grains, low-fat dairy, and reduced intake of saturated fat and sugar-sweetened beverages (SSBs) and 2) Western diet score characterized by high intake of red and processed meats, SSBs, desserts, French fries, and refined grains. A genetic risk score (GRS) was derived using 114 serum urate single nucleotide polymorphisms from the latest GWAS consortium.³

Results: There were 523 incident gout cases meeting ACR survey criteria⁴ (170 vs. 353 in GRS below and above the mean, respectively) (Table 1). Among women with GRS below and above the mean, the multivariable relative risks (RRs) of gout were 1.0, 1.56, 1.32, 0.89, and 0.61 (0.34 to 1.09) and 1.0, 1.0, 0.85, 0.51, and 0.68 (0.49 to 0.96), for quintiles (Q) 1 through 5 of DASH score, respectively (p for interaction = 0.69) (Table 1). For the Western diet, RRs for Q1 through 5 were 1, 1.34, 1.07, 1.33, and 1.63 (0.91 to 2.93) for those with GRS below the mean and 1.0, 1.17, 0.93, 1.27, and 1.77 (1.19 to 2.61) among those with GRS above the mean, respectively (p for multiplicative interaction = 0.64).

Conclusion: In this prospective female cohort that ascertained gout with standardized criteria over 32 years, regardless of genetic predisposition, DASH diet was similarly associated with lower risk of incident gout while Western diet was associated with a higher risk. The anticipated absolute impact of diet among