has been associated with IL-17A-mediated inflammatory diseases, including PsA and AS.^{3,4} IL-17F production in MAIT cells remains largely unexplored.

Objectives: To explore the importance of IL-23 signalling in MAIT cell-derived IL-17A and IL-17F production, examine the presence of MAIT cells in psoriatic lesional skin and assess the contribution of MAIT cell-derived IL-17A and IL-17F using *in vitro* models of skin inflammation.

Methods: IL-17A and IL-17F production by MAIT cells was assessed by flow cytometry, ELISA, qPCR and CyTOF upon activation by anti-CD3/CD28 or fixed *E. coli* via MR1-presented riboflavin metabolites, with or without disease-relevant recombinant cytokines or an IL-23-neutralising antibody. RNAscope was utilised to observe MAIT cells in psoriatic lesional skin. MAIT cell supernatant, generated from FACS sorted activated MAIT cells, was cultured with normal human dermal fibroblasts (NHDFs) in the presence of IL-17-isoform-specific antibodies, including bimekizumab, a monoclonal antibody that potently and selectively neutralises both IL-17A and IL-17F.

Results: Optimal MAIT cell IL-17A and IL-17F production occurred upon T cell receptor triggering with IL-12 and IL-18, independently of IL-23. IL-17F expression was greater at both gene and protein levels than IL-17A. The kinetics and threshold of activation for IL-17A and IL-17F suggest tighter regulation compared with other inflammatory cytokines, including IFN γ and TNF. Optimal MAIT cell IL-17A and IL-17F production requires monocytes, which contribute to IL-12 production upon IL-18 stimulation. MAIT cells were abundant in psoriatic lesional skin. NHDFs cultured with supernatant generated from activated MAIT cells produced inflammatory mediators IL-6, IL-8 and CCL2, which were reduced upon inhibition of either IL-17A or IL-17F, with optimal suppression achieved following dual neutralisation with bimekizumab.

Conclusion: IL-17A and IL-17F can be produced from MAIT cells independently of IL-23, and contribute to inflammatory responses in NHDFs. These results support dual neutralisation of IL-17A and IL-17F as a complete and targeted approach to suppress IL-17-driven inflammatory responses.

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OP0303

MONOSODIUM URATE AND CALCIUM PYROPHOSPHATE CRYSTAL-INDUCED INTERLEUKIN 1 PRODUCTION DEPENDS ON GLUCOSE UPTAKE THROUGH GLUT1 TRANSPORTER

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Background: Monosodium urate (MSU) and monocalcium pyrophosphate dihydrate (mCPPD) crystals are responsible for relapsing acute arthritis which is driven by interleukin 1 β (IL-1 β). IL-1 β production relies on NLRP3 inflammasome activation leading to ASC and caspase-1 recruitment. In tumor cells and in LPS-stimulated macrophages a switch of cell metabolisms toward glycolysis favors IL-1 β production.

Objectives: The aims of this study were to assess 1/whether crystal-induced NLRP3 activation and IL-1 β production involved glucose metabolism and 2/how MSU and mCPPD crystals induced glucose uptake focusing on the role of glucose transporter Glut1.

Methods: Synthetic and pyrogen-free MSU and mCPPD crystals were used to stimulate THP-1 cells and mouse bone marrow-derived macrophages (BMDM). Cells were stimulated in presence or absence of glucose (2g/L) and pyruvate (10mM). Glycolysis was inhibited by 2-deoxy-glucose (2DG) and the role of

glucose transporter 1 (Glut1) was assessed by pharmacological inhibitor (STF-31) and siRNA. IL-1 β production was quantified by ELISA. Metabolomic analysis was performed by mass spectrometry. Glucose uptake was determined using ¹⁸F-DG (Fluor18 labeled-2DG) and positron emission tomography (PET). Glut1 membrane localization was assessed by flux cytometry and confocal microscopy. ASC speck formation by confocal microscopy. *In vivo*, we used murine air pouch model to assess the effects of 2DG and Glut1 inhibition in crystal-mediated inflammation. Glut1 membrane localization of circulating neutrophils was compared to synovial fluid neutrophils harvested during gout flare.

Results: *In vitro*, both MSU and mCPPD crystal-induced IL-1 β secretion and ASC speck formation were inhibited when cells were cultured in glucose-free medium or in presence of 2DG. Similarly, MSU and mCPPD crystal-induced inflammation was abrogated in mice treated with 2DG. In THP-1 cells stimulated by MSU and mCPPD crystals, metabolomic analysis displayed alteration of glycolysis pathway and Krebs cycle and decrease of intracellular ATP production. Interestingly, MSU and mCPPD crystals increased glucose uptake *in vitro*, *ex vivo* and *in vivo*. Crystal-induced IL-1 β secretion was decreased by STF-31 and in THP-1 cells transfected with Glut1 siRNA. Next, we observed that MSU and mCPPD crystals increased membrane localization of Glut1 in THP-1, BMDM and neutrophils infiltrated in air pouch lavages and membranes. Glut1 membrane localization was positively correlated with IL-1 β production. Moreover, during gout flare, the proportion of Glut1 positive neutrophils was higher in synovial fluid neutrophils than in circulating neutrophils. Finally, STF-31 treatment decreased, *in vitro*, glucose uptake induced by MSU and mCPPD crystals, and *in vivo* MSU and mCPPD crystal-induced inflammation.

Conclusion: Glucose uptake through Glut1 transporter enhanced IL-1 β production induced by MSU and mCPPD crystals. Studies to decipher how these crystals induced Glut1 membrane localization are ongoing. Similarly, we investigate how glycolysis regulates NLRP3 and ASC activation. Decreasing Glut1 membrane localization might be a potential target to dampen crystal-induced inflammation.

References: **Disclosure of Interests:** Félix Renaudin: None declared, Laure Campillo-Gimenez: None declared, Florence Castelli: None declared, François Fenaille: None declared, Aurélie Prignon: None declared, Christèle Combes: None declared, Martine Cohen Solal Speakers bureau: Amgen and Lilly, Frederic Lioté Grant/research support from: institutional grants from Grunenthal, Ipsen Pharma/Menarini, Novartis, SOBI for the European Crystal Network Workshops, Consultant for: Grunenthal, Novartis, Hang Korng Ea: None declared

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OP0304

GENETIC AND FUNCTIONAL STUDY OF OMENTIN REGARDING CARDIOVASCULAR RISK IN AXIAL SPONDYLOARTHRITIS

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Background: Cardiovascular (CV) disease is one of the main causes of mortality in axial spondyloarthritis (axSpA). The higher incidence of CV risk factors and systemic chronic inflammation increase CV risk in axSpA.¹ This is enhanced by a dysregulation of adipokines. Low levels of omentin, an anti-inflammatory adipokine, have been associated with metabolic dysfunction and CV disease in general population and conditions different from axSpA.^{2,3}

Objectives: To evaluate the implication of omentin in CV risk and subclinical atherosclerosis in axSpA at the genetic and functional (mRNA and protein) level.

Methods: 382 patients fulfilling the ASAS classification criteria for axSpA⁴ and 84 controls were included. Carotid ultrasound was performed to evaluate the presence of subclinical atherosclerosis. Serum omentin levels were assessed by ELISA. mRNA expression of *ITLN1*, coding omentin, was evaluated by RT-qPCR. *ITLN1* rs12409609 (C/T), in complete linkage disequilibrium with a polymorphism