Background: Short chain fatty acids are generated in the colon by bacterial fermentation of dietary fibres and serve as natural agonists for the free fatty acid receptor 2 (FFA2R) without any assembly/activation of the superoxide generating NADPH-oxidase (1). Allosteric modulators bind to receptors at sites topographically distinct from the agonist/antagonist binding site and can regulate receptor functions positively or negatively.

Objectives: We undertook this study to determine whether an FFA2R selective modulator affects the neutrophil response induced by natural FFA2R agonists.

Methods: Neutrophils were collected from healthy blood donors. Release of superoxide anions generated by the assembled/activated NADPH-oxidase was recorded by sensitive isoluminol/HRP amplified chemiluminescence method. Intracellular Ca²⁺transients were measured with FURA 2-AM labelled neutrophils.

Results: The allosteric modulator lacked a direct activating effect on neutrophils, but turned natural FFA2R agonists into potent activating agonists that triggered not only a transient rise in the cytosolic concentration of free Ca²⁺ ions but also an assembly of the NADPH-oxidase. The NADPH-oxidase activity induced by the combined effect of the allosteric modulator and the natural agonist acetate could be further increased in neutrophils treated with the pro-inflammatory cytokine TNF-α. The receptor selectivity was demonstrated through the inhibition of the neutrophil activity by the novel FFA2R antagonist CATPB. In addition, the allosteric modulator lacked effect on neutrophil responses triggered by a novel and selective agonist for the closely related GPR84, a receptor that recognises medium chain fatty acids.

Conclusions: Allosteric modulators that positively co-operate with natural FFA2R agonists and prime neutrophils in their response to such agonists may serve as good tools for further unravelling the physiological functions of the FFA2R and its involvement in various diseases. In this study, allosteric modulation of FFA2R is introduced as a receptor selective mechanism to prime neutrophils to increase amounts of reactive oxygen species.

REFERENCE:

Disclosure of Interest: None declared

AB0069 INCREASED EXPRESSION OF SOLUBLE MIC-A IN THE SYNOVIAL FLUID OF RHEUMATOID ARTHRITIS PATIENTS

L. Bernardi1,2, A. Mariotte1, A. Scardu2, D. Noël3, L. Punzi2, S. Bahram4, P. George1, J. Sibilia1, 1INSERM UMR_S 1109, Fédération de Médecine Translationnelle de Strasbourg, Université de Strasbourg, Strasbourg, France; 2Rheumatology Unit, Department of Medicine-DIMED, University of Padova, Padova, Italy; 3INSERM UMR_S 1183, Montpellier University, Montpellier, France

Background: MIC-A (Major histocompatibility complex class I chain-related gene A)1 is a transmembrane or soluble protein that interacts with the activating NKG2D receptor. MIC-A stimulates effector responses mediated by NK and CD8+ T cells under cellular stress conditions, like cancer or infections.2 MIC-A is also associated with autoimmune diseases (such as rheumatic disorders) characterised by immune dysregulation triggered by environmental factors, and plays important roles in immune activation and surveillance.3 In mice, various NKG2D ligands were discovered: Rae-1, H60 and MULT1 families.4

Objectives: This study aims at investigating the potential pathological relevance of soluble MIC-A (sMIC-A) protein in inflammatory rheumatic diseases involving articular structures in humans. The expression of orthologous NKG2D ligands in mouse models of experimental joint inflammation is also quantified.

Methods: We collected synovial fluid (SF) from 118 subjects: 22 Rheumatoid Arthritis (RA), 13 Psoriatic Arthritis (PSOA), 12 Gout Disease (GOUT), 18 Calcium

Disclosure of Interest: None declared