SAT0001 MECHANISM AND SIGNIFICANCE OF COMPLEMENT C3 RECEPTOR IN COLLAGEN-INDUCED RHEUMATOID ARTHRITIS MICE MODEL

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Background: Rheumatoid arthritis (RA) is a kind of chronic autoimmune disease, mainly manifested as small joint synovitis. Disease progression appears joint swelling, bone and cartilage damage, deformity and activity limitation. The etiology of RA is still unclear and is generally considered to be an immune-mediated inflammatory disease. The activation pathway and regulation function of the complement system have become the hotspot of the research of RA pathogenesis. Previous studies have found that C3a/C3b mice had lower levels of antibodies to collagens in the Type II collagen-induced rheumatoid arthritis (CIA model), and the molecular mechanism is unclear. The small fragment C3a and large segment C3b produced by C3 activation are the main effect products, and their biological effects are performed by combining with the specific receptor, C3aR and CD11b respectively.

Objectives: To investigate the mechanism of C3a and C3b, the cleavage products of C3 in rheumatoid arthritis, binding to their corresponding receptors, the signalling pathway of complement activation and the effect on arthritis conditions.

Methods: This study was intended to establish a CIA model on C3aR knockout and CR3 knockout mice (C3aR−/−or CD11b−/−) to investigate the effect of complement C3a-C3aR signalling and C3b-CR3 signalling on rheumatoid arthritis. Methods using C57BL/6 background transgenic mice (Gifted by King’s College London), Mice were divided into 3 groups according to the experimental mouse strains: C3aR−/− group, CD11b−/− group and WT control group. The clinical score of the joints in each group was measured after the establishment of the CIA model through collagen induction. Moreover, joint specimens were collected for pathologic grading. Besides, the level of CD4+ T cell, CD8+ T cell, Th17/Treg ratio and the level of IFN-gamma of NK cell in mouse spleen were detected by flow cytometry.

Results: The clinical score of C3aR−/− group was slightly lower than that of WT group, and the clinical score of CD11b−/− group was significantly higher than that of WT group; 2. Pathological score (12 points): The CIA scores of CD11b-/- group, and the clinical score of CD11b-/- group was significantly higher than that of WT group; 2. Pathological score (12 points): The CIA scores of CD11b-/- group, and the clinical score of CD11b-/- group was significantly higher than that of WT group; 3. Immunological grading: Besides, the level of CD4+ T cell, CD8+ T cell, Th17/Treg ratio and the level of IFN-gamma of NK cell in mouse spleen were detected by flow cytometry.

Conclusions: IC3b as well as C3a could bind to their respective complement receptor, and express different influence in the immune mechanism of RA. The IC3b-CD11b signalling has a protective effect in RA, while the C3a-C3aR signal has an inflammatory aggravation effect. Through this study, it helps us to invent the drug related to complement components and their receptors, and further be used in the clinical treatment of RA.

Disclosure of Interest: None declared


SAT0002 THE INTRACELLULAR ITAM TYROSINES OF FC RECEPTOR GAMMA-CHAIN ARE CRITICAL FOR EXPERIMENTAL AUTOIMMUNE ARTHRITIS

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Background: Activating Fcγ-receptors on neutrophils associated with the Fc-receptor γ-chain (FcγR), an immunoreceptor tyrosine-based activation motif (ITAM) containing transmembrane adapter molecule. Previously, we carried out in vitro experiments that showed not only a chaperon-like function of FcγR, but also a signalling role through its intracellular ITAM-tyrosines.

Objectives: Here, we investigated the participation of these tyrosines in an auto-antibody-induced arthritis model (in the KBxN serum transfer arthritis, for the development of which neutrophils and Fc-receptors are essential) using wild type and ITAM tyrosine mutant (Y65F/Y76F) transgenic mice.

Methods: The experimental animals expressed wild type or ITAM tyrosine mutant (Y65F/Y76F) Fcγ-receptor γ-chain on the FcγR−/− genetic background. The arthritis was initiated by a single intraperitoneal injection of control or arthritic serum. The severity of joint inflammation was followed by clinical scoring, measuring ankle thickness changes and detecting joint dysfunction. Homozygous transgenic mice were identified by quantitative PCR.

Results: Compared to wild type mice, FcγRy knockout animals failed to exhibit a measurable joint inflammation. Surprisingly, the arthritis could not develop in wild type FcγRy transgene heterozygous mice. To enhance the expression level of the wild type transgene (which was approximately one third of the expression of the mutant transgene), we crossed our wild type transgene heterozygous mice with each other. As a consequence, wild type FcγRy transgene homzygous mice on each other. As a consequence, wild type FcγRy transgene heterozygous mice on each other. As a consequence, wild type FcγRy transgene heterozygous mice on each other. As a consequence, wild type FcγRy transgene heterozygous mice on each other. As a consequence, wild type FcγRy transgene heterozygous mice on each other. As a consequence, wild type FcγRy transgene heterozygous mice on each other. As a consequence, wild type FcγRy transgene heterozygous mice on each other. As a consequence, wild type FcγRy transgene heterozygous mice on each other. As a consequence, wild type FcγRy transgene heterozygous mice on each other. As a consequence, wild type FcγRy transgene heterozygous mice on each other. As a consequence, wild type FcγRy transgene heterozygous mice on each other. As a consequence, wild type FcγRy transgene heterozygous mice on each other. As a consequence, wild type FcγRy transgene heterozygous mice on each other. As a consequence, wild type FcγRy transgene heterozygous mice on each other. As a consequence, wild type FcγRy transgene heterozygous mice (both at heterozygous and homzygous forms) were fully protected from the development of arthritis despite of comparable neutrophil cell surface Fcγ receptor expressions.

Conclusions: Our in vivo experiments show that the intracellular Fc receptor γ-chain ITAM tyrosines play a critical role in the initiation and progression of an auto-antibody-induced experimental arthritis model, confirming a signalling, rather than just a chaperon-like function of the molecule.

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