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THU0052

RELATIONSHIP BETWEEN INTERFERON- γ -PRODUCING IMMUNOCOMPETENT CELLS AND DISEASE ACTIVITY IN ADULT-ONSET STILL'S DISEASE

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Background: In the acute phase of adult-onset Still's disease (AOSD), elevated levels of proinflammatory cytokines including interferon- γ (IFN- γ) are shown. Moreover, IFN- γ impacts on activating macrophages which play a crucial role in the pathogenesis of AOSD. Natural killer (NK) cells and T helper cells are in charge of secreting IFN- γ in the innate and adaptive immune systems of disease, respectively. However, the features of their IFN- γ -producing variation depending on disease activity are still uncertain in AOSD.

Objectives: We investigated characteristics of IFN- γ -producing CD4⁺ T cells and NK cells in patients with AOSD.

Methods: Twenty-four patients in the acute phase of AOSD (active AOSD), 8 of them after treatment (remission), and 12 healthy controls (HC) were recruited in this study. Peripheral blood mononuclear cells and serum samples were provided from them for the experimental analysis. Flow cytometry was used for analyzing CD4⁺ T cells, CD4⁺ regulatory T cells (Tregs), NK cells, and their intracellular IFN- γ expression levels as well as suppression assay of Tregs. The serum concentration of interleukin-18 (IL-18) was measured using commercially available ELISA kit. Relationship between the analyzed data and clinical findings related to disease activity were statistically evaluated.

Results: IFN- γ expression in CD4⁺ T cells was significantly higher in active AOSD than in HC ($p < 0.05$). Tregs also significantly indicated higher expression of IFN- γ in active AOSD than in HC ($p < 0.0001$); and moreover, Tregs were significantly impaired in their suppression ability ($p < 0.05$). In both CD4⁺ T cells and Tregs, expression of IFN- γ was significantly correlated with serum ferritin levels in active AOSD ($p < 0.05$). IFN- γ expression in CD4⁺ T cells was significantly higher in patients with splenomegaly than those without that ($p < 0.05$). The proportion of NK cells was significantly lower in active AOSD than in HC ($p < 0.005$), whereas IFN- γ expression in NK cells was significantly higher in active AOSD than in HC ($p < 0.0005$). The number of NK cells and IFN- γ -expressing NK cells had inverse relationship with serum ferritin levels in active AOSD ($p < 0.05$ and $p < 0.005$, respectively). Increased number of NK cells and their decreased expression of IFN- γ were significantly demonstrated in remission ($p < 0.05$). In the analyses of NK cell subsets, lower expression of IFN- γ in CD56^{bright} NK cells and higher than in CD56^{dim} NK cells were significantly indicated in active AOSD than HC ($p < 0.05$). In remission, IFN- γ expression was significantly decreased in CD56^{dim} NK cells ($p < 0.05$) despite no significant recovery of that in CD56^{bright} NK cells ($p = 0.311$). Meanwhile, increased expression of IFN- γ in CD56^{bright} NK cells was demonstrated in only patients who were treated with biologics. Although serum levels of IL-18 were significantly higher in active AOSD than in remission and HC; however, they had no significant correlations with any analyzed data.

Conclusion: CD4⁺ T cells and NK cells promote IFN- γ expression in the acute phase of AOSD. Meanwhile, increased expression of IFN- γ in CD4⁺ T cells and decreased number of NK cells were correlated with serum ferritin levels, suggesting that they are indicators of disease activity. Furthermore, high disease activity may impact on the alteration of IFN- γ -producing balance in two distinct population of NK cells, and the plasticity of Tregs leading to defect in suppression ability.

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THU0053

CONTRIBUTION OF DEFECTIVE NON-APOPTOTIC FAS SIGNALING TO IMMUNE DYSREGULATION IN AUTOIMMUNE LYMPHOPROLIFERATIVE SYNDROME (ALPS)

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Background: ALPS patients show impaired generation of humoral memory for T independent antigens whereas they generate memory for self-antigens due to impaired FAS-dependent removal of autoreactive germinal center B cells. It is known that FAS signaling via caspase activation results in cell apoptosis. However, FAS ligation may also initiate or modulate non-apoptotic signaling as shown for example by its ability to activate NF- κ B. Recent data implicate a regulatory role of FAS in the modulation of mTOR signaling in ALPS double-negative T cells. Moreover, a recently described C194V FAS mutation disturbs its post-translational modification leading to impaired apoptosis induction while non-apoptotic signalling is still intact. Consequently, C194V FAS protects from the autoimmune phenotype in the murine ALPS system. This supports the view that FAS may prevent autoimmunity with other mechanisms than inducing apoptosis.

Objectives: We hypothesize that FAS mutations impair this modulatory signaling, leading to hyper-activation of B cells. Therefore we aim to investigate non apoptotic FAS signaling in B cells derived from healthy individuals and ALPS patients.

Methods: We studied resting and activated B cells in ALPS patients in presence or absence of FAS ligand by flow cytometry analysing relevant molecules to the CD40 signaling pathway. We used mass cytometry to perform functional phenotyping of B cells isolated from secondary lymphoid organs. Proteomic studies were performed to identify potential signaling circuits and RNA sequencing to study the consequences of FAS signaling on B cell fate.

Results: In CD40L activated B cells, FAS signaling results in specific modulation of the mTOR signaling pathway. This modulation is absent in ALPS derived B cells. In line with these data germinal center B cells and plasmablast from secondary lymphoid organs of ALPS patients show hyperactive mTOR signaling pathway. Proteomic studies identify a circuit that links FAS to the phosphatase PTEN via DAXX and the deubiquitinase USP7.

Conclusion: We describe a new role of FAS in the regulation of B cell activation. Defects in FAS signaling in ALPS contribute to dysregulation of the mTOR signaling pathway and disturbed B cell development.

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THU0054

NKTR-358, A NOVEL IL-2 CONJUGATE, STIMULATES HIGH LEVELS OF REGULATORY T CELLS IN PATIENTS WITH SYSTEMIC LUPUS ERYTHEMATOSUS

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Background: Impaired IL-2 production and dysfunction of regulatory T cells (Tregs) have been identified as key immunological defects leading to the breakdown of immune self-tolerance in SLE. Low-dose IL-2 can expand Tregs, but

the effect is limited by a narrow therapeutic window for Treg selectivity. Furthermore, the short half-life of IL-2 necessitates frequent administration. NKTR-358 is a polyethylene glycol (PEG) conjugate of recombinant human IL-2 (aldesleukin sequence) and is differentiated from native IL-2 by its altered binding to the IL-2 receptor and prolonged biological activity. NKTR-358 resulted in marked and selective stimulation of Tregs when administered as a single SC injection to healthy volunteers.

Objectives: This multiple ascending dose study assessed the safety, tolerability, pharmacokinetics (PK), and immune effects of NKTR-358 in patients with SLE after repeated administration of SC doses. The time course and extent of changes in numbers and percentages of Tregs, conventional CD4+ and CD8+ T cells, NK cells, and cytokine levels in peripheral blood were investigated.

Methods: In this double-blind, multiple ascending dose study, patients with mild to moderate SLE received 3 SC doses q2w in 4 cohorts ranging from 3.0 to 24.0 µg/kg (9 active:3 placebo per cohort); patients were followed for a total of 79 days.

Results: There were no dose-limiting toxicities, deaths, or clinically significant abnormalities in either vital signs or electrocardiograms. Adverse events attributed to NKTR-358 were primarily limited to mild (grade 1) injection site reactions. At the highest dose, one subject had transient and mild (grade 1) symptoms of a flu-like syndrome after administration, without associated elevated cytokine levels, and another subject had dosing stopped due to elevated eosinophil levels. No other individual at any dose level had systemic signs or symptoms known to be associated with IL-2 therapy. No anti-drug antibodies were detected. NKTR-358 demonstrated dose-proportional PK with repeated dosing; plasma levels peaked 3-6 days post-dose and declined with a terminal half-life of ~10-13 days.

The primary and consistent effect of NKTR-358 was seen on Tregs. In the four dose cohorts, dose-dependent and sustained increases in absolute numbers and percentages of circulating CD4+FoxP3+CD25^{bright} Tregs were observed. Treg levels remained elevated throughout the dosing period, peaking at Day 10 after the first administration of NKTR-358 and returning to baseline ~20-30 days following last administration. At 24.0 µg/kg, the mean peak increase in numbers of CD25^{bright} Tregs was 11-fold above baseline. In addition, there was an increase in Treg activation markers at doses ≥12.0 µg/kg. In contrast to effects on Tregs, no changes in percentages or numbers of conventional CD4+ or CD8+ T cells were observed at any dose tested. At the highest dose, there were low-level increases in the percentages and numbers of NK cells. Overall, NKTR-358 selectively induced Tregs, evidenced by a 12-fold increase in the mean peak Treg:CD8 ratio over baseline in the 24.0 µg/kg group.

Conclusion: NKTR-358, an IL-2 conjugate Treg stimulator, was well tolerated when repeatedly administered (q2w) at doses up to 24 µg/kg. Its administration led to marked, selective, prolonged, and dose-dependent increases in circulating CD25^{bright} Tregs. This clinical study in SLE patients extends the previous results in healthy volunteers and provides strong support for continued testing of NKTR-358 as a new therapeutic in SLE and other inflammatory diseases.

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OA, aetiology, pathology and animal models

THU0055

ANTI-DEGRADATIVE AND PRO-CHONDROGENIC PROPERTIES OF LIRAGLUTIDE, A GLUCAGON-LIKE-PEPTIDE 1 RECEPTOR AGONIST: EVIDENCE FROM PRECLINICAL STUDIES AND IMPLICATION FOR OSTEOARTHRITIS

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Background: Osteoarthritis (OA) is a degenerative joint disease affecting millions of individuals worldwide. Its development has been reported to be associated with cartilage degradation and inflammatory responses leading to pain, swelling and reduced function. Although OA is a disorder of the whole joint, the progressive destruction of cartilage extracellular matrix is considered as its hallmark. To date, approved OA treatments are only symptomatic. Therefore, there is an urgent need to explore disease-modifying OA drugs (DMOADs) that can mitigate, stop, or even reverse the development of OA.

Objectives: In this context, the objective of this study was to assess the effect of liraglutide, a Glucagon-Like-Peptide 1 Receptor (GLP-1R) agonist approved for type 2 diabetes, on chondrogenesis, catabolism/inflammation and cartilage protection in *in vitro* and *in vivo* preclinical models of OA.

Methods: The capacity of liraglutide to induce chondrogenesis was evaluated using primary human mesenchymal stem cells (hMSCs). Alcian blue staining was used to assess differentiation of hMSC into chondrocyte spheroids. IL-1β-stimulated mouse articular chondrocytes were treated with different concentrations of liraglutide for 24h. Production of matrix metalloproteinase MMP-13, prostaglandin E2 (PGE2) and nitrite was measured by ELISA and Griess reaction, respectively. Exendin 9-39, a GLP-1R antagonist, was used to confirm target engagement in the *in vitro* experiments. Intra-articular (IA) injections of liraglutide or vehicle were performed in the type II collagenase rat model. Histopathological analyses (OARSI scores¹) were conducted blindly by one investigator.

Results: Liraglutide induced the differentiation of hMSCs into chondrocytes. Indeed, 21 days after differentiation initiation, 5/6 and 4/6 alcian-blue positive spheroids were observed for 10 and 100nM liraglutide, respectively, versus 0/6 for vehicle. Liraglutide significantly reduced dose-dependently the IL-1β-induced production of PGE2 (5808±178 for vehicle vs 4560±140, 2933±171 and 2365±85 pg/ml for liraglutide 10, 100 and 500nM, respectively, p≤0.001), nitrite (24.9±0.4 for vehicle vs 20.9±1.5, 19.1±0.9 and 16.5±0.5 µM for liraglutide 10, 100 and 500nM, respectively, p≤0.001) and MMP-13 (686±9 for vehicle vs 553±3, 402±5 and 297±8 pg/ml for liraglutide 10, 100 and 500nM, respectively, p≤0.001) in murine chondrocytes. Effects of liraglutide were GLP-1R dependent since exendin 9-39 significantly counteracted both chondrogenesis and inflammation/catabolism markers expression. Histological assessment of rat collagenase-injected knee joint revealed a significant (p≤0.05) decrease of the total joint score in the IA Liraglutide treated group (8±4) compared to vehicle (11±4).

Conclusion: Liraglutide induced chondrogenesis, decreased metalloproteinase and inflammatory mediators production by chondrocytes and protected cartilage in *in vitro* and *in vivo* preclinical OA models, opening the way for repositioning this drug as a potential DMOAD.

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[1] Osteoarthritis Cartilage. 2010 Oct;18 Suppl 3:S24-34

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THU0056

SM04755, A POTENTIAL DISEASE-MODIFYING TREATMENT FOR TENDINOPATHY, MODULATES THE WNT PATHWAY VIA INHIBITION OF CLKS AND DYRK1A

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Background: Tendinopathy is an inflammatory and degenerative disorder of tendons caused by injuries and/or overuse. Left untreated, tendinopathy can lead to pain and rupture. Current therapeutic options only treat symptoms. Stem cell- and growth factor-based treatments are under investigation but have not