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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.

Disclosure of Interests: None declared

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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.

Disclosure of Interests: None declared

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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