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 immunomodulatory cytokines including 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 involved in IFN-γ levels of proinflammatory cytokines including interferon-γ (IFN-γ) are shown.

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 more 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 expression in 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 CD56dim NK cells was higher that in CD56bright NK cells were significantly indicated 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 populations 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 ADULT-ONSET 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 autoactive 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-κB. 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 signaling is still intact. Consequently, C194V FAS protects from the autoimmune phenotype in the murine ALPS system. This supports the hypothesis that FAS may prevent autoimmunity with other mechanisms than inducing apoptosis.

Methods: We studied resting and activated B cells in ALPS patients in presence or absence of FAS ligation in the following FAS dependent signaling pathways: FADD, NFκB, and downstream events.

Results: In CD40L activated B cells, FAS signaling results in specific modulations of the mTOR 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.

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...