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[S-0009]

[Immunity to Infection: New Trends and Developments]

The associations between a gene polymorphism (IL-2 and IL-4) and cytokines in patients with recurrent pulmonary tuberculosis on standard chemotherapy

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Background and Objective: To study the influence of gene polymorphism (IL-2 and IL-4) and cytokines in patients with recurrent pulmonary tuberculosis (RPTB) on standard chemotherapy.

Methods: The study comprised 130 individuals in Kharkiv region of Ukraine including 100 patients RPTB (group 1) and 30 healthy donors (group 2). Serum levels of cytokines IL-2 and IL-4 were evaluated by ELISA. Measurements on serum samples of patients were conducted prior or during first days after admission to the hospital and after 2 months on standard anti-mycobacterial therapy. Investigations of gene polymorphisms of these cytokines were performed using restriction analysis of the amplification products of specific regions of the genome. Two polymorphic variants were examined: T-330G region of IL-2 gene and promoter region C-589T of IL-4. All patients received standard TB drugs: Isoniazid (0.3 g); Rifampicin (0.6 g); Pyrazinamide (2 g); Ethambutol (1.2 g) and/or Streptomycin (1 g).

Results: In the 1st group the levels of IL-4 and IL-2 were 9.55±0.24 pg/L and 39.44±0.71 pg/L, while in 2nd group these values were 29.99±1.27 pg/L and 21.60±0.80 pg/L respectively ($p<0.05$). Among patients with RPTB the heterozygous genotype was most prevalent; 74% (n=74) for IL-2 and 61%(n=61) for IL-4. The homozygous genotype was accordingly less common: 26% (n=26) and 39% (n=39), of which 18% (n=18) and 21% (n=21) of patients had mutation and remaining had normal homozygote genotype, i.e., 8% (n=8) and 18% (n=18) for IL-2 and IL-4 respectively. In contrast, most of healthy donors had normal homozygous genotype with 60% (n=18) and 56.66% (n=17) with low frequency of mutations; 16.66% (n=5) and 23.34% (n=7) and heterozygous genotype 23.34% (n=7) and 20% (n=6)for IL-2 and IL-4 genes respectively. Following a 2 month treatment, there was a significant reduction of cytokine levels in the IL2 (29.59±0.55) pg/L and increased in the IL4 (16.68±0.44) pg/L, when compared to the beginning of therapy and after 2 months ($p<0.001$).

Conclusion: Compared to healthy controls patients with RPTB had significantly lower levels of serum IL-4 and high-IL-2. This coincided with greater frequency of heterozygous polymorphism C-589T and T-330G genes of IL-4 and IL-2. Further studies are warranted whether higher rate of recurrent TB has a causal immunogenetic relationship to allelic polymorphism of genes encoding for IL-2 and IL-4. Standard 2-month TB therapy results in reversal of inflammation characterized by decrease in IL-2 and increase of IL-4 to the levels comparable to healthy donors. IL-4 and IL-2 are immune correlates of treatment outcome and can help to identify better strategy for TB management. TB chemotherapy may have immunomodulatory effect of anti-inflammatory nature.

Keywords: Tuberculosis; cytokines; interleukin-2; interleukin-4; gene polymorphism; treatment of tuberculosis.

[S-0028]

[Tumor Immunology & Molecular Markers]

ATP-binding cassette transporter G1 (ABCG1) is a novel mediator of tumor immunity

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ATP-binding cassette transporter G1 (ABCG1) is a member of the ABC transporter family that regulates cellular cholesterol homeostasis in the cell. Herein, we report a role of ABCG1 as a novel mediator of tumor immunity. Abcg1-/- mice fed a Western diet showed dramatically reduced subcutaneous MB49-bladder carcinoma and B16-melanoma tumor growth compared to control. Abcg1-/- mice also showed diminished spontaneous tumor metastasis and prolonged survival. Selective deletion of ABCG1 in myeloid cells, but not in T cells, reduced tumor growth *in vivo*, demonstrating that the observed effects were mediated through myeloid cell-intrinsic mechanisms. Abcg1-/- mice on Western diet displayed decreased macrophage frequency due to enhanced apoptosis and a shift of the remaining macrophages from a tumor-promoting M2 to a tumor-fighting M1 phenotype within the tumor. Furthermore, *in vitro* polarization studies revealed that Abcg1-/- macrophages exhibited an intrinsic bias towards M1 polarization with increased production of TNF-α, nitric oxide, MHC class II and CD86 and decreased expression of Arg1, Mrc1 and Fizz1. M1 bias of Abcg1-/- macrophages was associated with enhanced NF-κB activation and direct cytotoxicity for tumor cells *in vitro*. Overall, our results show that absence of ABCG1 inhibits tumor growth through modulation of macrophage survival and phenotype within the tumor. This study identifies the cholesterol transporter ABCG1 as a novel mediator of tumor immunity and provides a novel link between cholesterol homeostasis and cancer.

Keywords: ABCG1; cholesterol; tumor; macrophages.