

*Jugoslav Med Biohem 25: 49–50, 2006*

*Naučna konferencija  
Scientific Conference*

### **SPECIFICITY OF CYTOKINE PROFILE AND OXIDANT STRESS IN PATIENTS WITH BRONCHIAL ASTHMA**

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*Summary:* Since morbidity and mortality of bronchial asthma are nowadays increasing more and more, this issue presents a global challenge despite the significant advance in knowledge about the pathogenetic mechanism of asthma, about the role of inflammatory cells, regulation of inflammatory and immune responses, about many mediators and their corregulation. Cytokines and their modulators are becoming increasingly significant because they are crucial intercellular transmitters which contribute to the development of airways remodelling. The aim of this study is to evaluate Th1/Th2 ratio and to estimate the interdependence between cytokines and pro/antioxidant parameters and nitric oxide system in patients with newly diagnosed bronchial asthma, with different degrees of the disease treated with inhalation corticosteroids, which could open the way for some new possibilities in the prevention and therapeutic approach to this chronic disease. These parameters were determined in the patients' plasma, erythrocytes and cultures of lymphocytes treated with Concanavaline A (Con A) and Phorbol 12-myristate 13-acetate (PMA). Differently from Th1 cytokines, Th2 profile of cytokines shows significant increase ( $p < 0.01$ ) when compared to the control group, with higher level in extrinsic (atopic asthma) vs. intrinsic asthma. The results of oxidant stress markers (increased level of lipid peroxide, xanthine oxidase, NO and NOS in blood of patients with BA) and antioxidant's parameters (decreased activity of SOD, increased activity of GPx, catalase and GSH concentration) suggest that the balance of pro/antioxidants has been disturbed oxidant stress is present in patients with newly diagnosed BA. Investigation of cytokines in lymphocyte cultures of patients with BA showed

### **SPECIFIČNOST CITOKINSKOG PROFILA I OKSIDANTNOG STRESA U BOLESNIKA S BRONHIJALNOM ASTMOM**

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*Kratak sadržaj:* Bronhijalna astma (BA), zbog sve većeg morbiditeta i mortaliteta, danas predstavlja globalni izazov uprkos velikom pomaku koji je napravljen u saznanjima o patogenetskim mehanizmima astme uključujući ulogu inflamatornih ćelija, regulaciju inflamatornih i imunih odgovora, brojne medijatore i njihovu koregulaciju. Sve veći značaj se pridaje citokinima i njihovim modulatorima s obzirom da su to ključni interćelijski transmitteri koji doprinose razvoju remodeliranja disajnih puteva. Cilj ove studije je evaluacija Th1/Th2 odnosa i procena međuzavisnosti citokina sa pro/antioksidantnim parametrima i sistemom azot-monoksida u bolesnika sa novootkrivenom bronhijalnom astmom, sa različitim težinom oboljenja tretiranih inhalacionom kortkosteroidnom terapijom, na osnovu čega bi se mogle naći nove mogućnosti u preventivnom i terapijskom pristupu ovoj hroničnoj bolesti. Navedeni parametri određivani su u plazmi, eritrocitima i u kulturama limfocitima pacijenata tretiranih Konkanavalinom A (Con A) i forbol 12-miristat 13-acetatom (PMA). Za razliku od Th1 citokina Th2 citokinski profil (IL-4, IL-10, IL-13) pokazuje značajan porast ( $p < 0,01$ ) u odnosu na kontrolnu grupu, sa većim nivoom u ekstrinzič (atopijskoj) astmi u odnosu na intrinzič astmu. Rezultati markera oksidantnog stresa (povišeni lipidni peroksidi, ksantin oksidaza, NO i NOS u krvi bolesnika sa BA) i antioksidantnih činioca (smanjena aktivnost SOD, povišena aktivnost GPx, katalaze i koncentracije GSH) sugerišu da je došlo do narušavanja ravnoteže pro/antioksidanta te da je prisutan oksidantni stres u bolesnika sa novootkrivenom astmom. Ispitivanje citokina u kulturama limfocita bolesnika sa BA pokazalo je značajan porast koncentracija TNF- $\alpha$  pre ( $p < 0,05$ ), IL-13 ( $p < 0,05$ ) nakon stimulacije sa

significant increase of TNF- $\alpha$  concentration before ( $p < 0.05$ ), IL-13 ( $p < 0.05$ ) after stimulation with Con A and especially after stimulation with PMA (IL-13, INF- $\gamma$ , TNF- $\alpha$  ( $p < 0.01$ )). Results of this thesis also show that there is an interdependence between the investigated parameters and severity of disease. Studying the subtle cellular mechanisms in the initiation and development of asthma allows the application of some blockators of inflammatory, immune mediators and transducers, or the application of supplements that may compensate for the defects in asthma regulation mechanisms, which may balance disturbance and redirect the pathogenesis of the disease to a desired path.

*Key words:* bronchial asthma, Th1/Th2 cytokines, oxidant stress, antioxidants, nitric oxide

Con A i pogotovu stimulisanih sa PMA (IL-13, INF- $\gamma$ , TNF- $\alpha$  ( $p < 0,01$ )). Rezultati ove teze takođe pokazuju da postoji međuzavisnost ispitivanih parametara i težine kliničke slike pacijenata. Proučavanjem suptilnih ćelijskih mehanizama u inicijaciji i razvoju astme pruža se mogućnost primene određenih blokatora inflamatornih, imunih medijatora i transduktora, ili primene suplemenata koji mogu da kompenzuju nedostatke u regulacionim mehanizmima astme, čime se može uravnotežiti disbalans i preusmeriti patogeneza bolesti u željenom pravcu.

*Ključne reči:* bronhijalna astma, Th1/Th2 citokini, oksidantni stres, antioksidanti, azot-monoksid