

NALP3/CIAS1 are associated with other autoinflammatory diseases: Muckle-Wells syndrome, familial cold urticaria and chronic infantile neurological cutaneous and articular syndrome (CINCA/NOMID). These share some clinical characteristics with Blau syndrome. NALP3 regulates IL-1 β production which in turn mediates NALP3-associated autoinflammatory diseases. We recently described a mouse model of MDP-induced uveitis, in which mice treated with an intravitreal injection of MDP develop ocular inflammation. MDP-induced uveitis is dependent on NOD2, as NOD2 knockout mice fail to show an ocular inflammatory response to MDP. IL-1 β production as assessed by ELISA was significantly increased in the eye in response to MDP in a NOD2-dependent manner. MDP-induced IL-1 β production in the eye was impaired in caspase-1 knockout mice. This indicates that MDP-induced IL-1 β production requires both NOD2 as well as caspase-1, a component of the NALP3 inflammasome. Unexpectedly, IL-1 β does not appear to be a predominant mediator of MDP-induced uveitis, as deletion of either IL-1-receptor-1 or caspase-1 had no impact on the intravascular inflammatory response to MDP as measured by intravitreal microscopic quantification of leukocyte rolling and sticking. In contrast, deletion of interferon gamma does reduce the ocular inflammatory response induced by MDP. Our studies shed light onto the role of NOD2 as a key regulator of IL-1 β production. Despite clinical similarities of NLR-associated autoinflammatory diseases, NOD2 may contribute to inflammation in an IL-1 β -independent mechanism.

doi:10.1016/j.cyto.2007.07.134

130 MAGUK Family Member Dlg1 Coordinates TCR-dependent p38 Activation, Specifically Linking TCR Engagement to Activation of NFAT but not NF- κ B

J.L. Round¹, L.A. Humphries¹, T. Tommasian², P. Mittelstadt³, M. Zhang¹, M.C. Miceli^{1,2,3}, ¹ Microbiology, Immunology, and Molecular Genetics, University of California, Los Angeles, CA 90066, USA, ² Molecular Biology Institute, University of California, Los Angeles, CA 90066, USA, ³ Laboratory of Immune Cell Biology, Center for Cancer Research, National Cancer Institute, Bethesda, MD 20892, USA

Proximal kinase activation couples TCR engagement to discrete signaling cascades capable of differentially contributing to T cell function. However, mechanisms of channeling TCR signals toward specific targets remain undefined. Previously, we established a role for Dlg1 in TCR/CD28 NFAT activation and lymphokine production. Here, we show that alternatively activated p38 associates with the MAGUK family member Dlg1 and identify a novel Dlg1/p38/Zap70 signaling complex. TCR stimulation utilizes a unique “alternative” p38 activation whereby Lck and ZAP70 cooperate to directly phosphorylate and activate p38. Our data suggest that Dlg1 may act to coordinate T cell-specific p38 activation and begin to define downstream effectors of this pathway. By manipulating Dlg1 levels in T cells we demonstrate that Dlg1 facilitates alternative p38 and NFAT, but not JNK or NF- κ B, activation. Further, expression of a p38-binding-deficient-Dlg1 inhibits TCR-induced p38 and NFAT activation and pharmacologic inhibition of p38 ablates Dlg1-mediated NFAT upregulation. Taken together, our findings elucidate a novel signaling mechanism whereby TCR proximal kinase activity is selectively channeled toward p38-mediated NFAT activation through Dlg1. In combination with reports that the MAGUK family member CARMA1 regulates JNK and NF- κ B, but not p38 or NFAT activity, these data suggest independent roles for MAGUKs in orchestrating TCR signal specificity. Lisa A Humphries is a recipient of the Arthritis Foundation Postdoctoral Fellowship. E-mail address: cmiceli@ucla.edu (M.C. Miceli).

doi:10.1016/j.cyto.2007.07.135

131 Ultra Small Doses of Antibodies to Human Gamma Interferon in the Treatment of Patients with Allergy and Viral Infections

M. Rudenko¹, N. Markin¹, A. Zabelev¹, I. Rudenko², A. Shemshura³, ¹ Clinical Center EuroDon, Rostov-on-Don, Russian Federation, ² 629 Outpatients' Clinic, Rostov-on-Don, Russian Federation, ³ Rostov Research Institute of Microbiology and Parasitology, Rostov-on-Don, Russian Federation

Recent studies showed that immune changes caused by viral infections can lead to decrease of the number of T cells with the prevalence of Th2 response. [Luss L, Russian Immunology Journal 2006;1:17; Fedoskova T, Allergology 2007;2:265; Markova T, Cytokines and Inflammation 2005;3:129]. The aim of our study was to detect the peculiar changes in immune system and to try to influence on them. Twenty-six allergic patients 25–32 years with persistent HSV, EBV, CMV infections were carefully examined. We used following methods: microscopy of nasal smears, PCR, ELISA, blood and urine tests, immunologic examination and tests (CD3, CD4, CD8, CD16, CD20, CD3; CD95, CD3; HLADR, NST, IgA, IgM IgG IgE, Th1 and Th2). The patients were divided randomly into two groups. In the first one we used ultra small doses of antibodies to human gamma interferon (C12, C30 and C200) 3 times per day during 20 days, in the second-placebo. After the treatment we compared results in two groups and revealed improvement of allergy symptoms, decreased quantity of eosinophils in nasal smears in the first group. The immune parameters also improved Th1 was increased (first group $8.07 \pm 0.09\%$; second group $6.06 \pm 1.01\%$; $p < 0.05$) Th2 was decreased (first group $0.8 \pm 0.19\%$; second group $3.56 \pm 0.67\%$; $p < 0.05$), the number of T cells NK cells normalized. We can conclude that stimulation of gamma interferon production leads to positive changes in immune system and though that to clinical improvement.

doi:10.1016/j.cyto.2007.07.136

132 Toll-like Receptors (TLRS) Contribute in the Inflammation and Pathogenesis of RA

Sandra Sacre, Alexandra Lo, Mino Medghalchi, Bernard Gregory, Lynn Williams, Fionula Brennan, Richard Williams, Brian Foxwell, Kennedy Institute of Rheumatology Division, Faculty of Medicine, Imperial College of Science, Technology and Medicine, London, UK

TLRs are a family of innate immune receptors that have been shown to respond to both exogenous as well as endogenous ligands. They are attractive candidates for a more targeted therapy in autoimmune diseases where many endogenous TLR ligands could be present. Recently, we demonstrated that the TLR signaling molecules MyD88 and Mal both have a role in pro-inflammatory cytokine production from human rheumatoid arthritis (RA) synovial membrane cell cultures. RA is one of the most common autoimmune diseases affecting 1:100 people and causes inflammation and damage to the joints. Further studies have identified inhibitors of TLR induced cytokine production. These inhibitors were able to significantly inhibit disease progression in the murine collagen induced arthritis (CIA) model as measured by an improvement in clinical score, decreased cell infiltration and reduced histology scoring. We also examined the effects of the inhibitors in human RA synovial membrane cultures. These cultures spontaneously release inflammatory cytokines, three of which, TNF, IL-6 and IL-1 are targets for biological therapies in human RA. We observed that the spontaneous release of these cytokines from human RA cell cultures was significantly decreased in the presence of the TLR inhibitors, suggesting that inhibition of the relevant TLRs may be beneficial in RA.

doi:10.1016/j.cyto.2007.07.137