Volume 43, Issue 3, September 2008 ISSN 1043-4666

ELSEVIER

CYTOKINE

The Official Journal of the International Cytokine Society

Special Issue – Abstracts and Reviews

7th Joint Conference of the International Cytokine Society and the International Society for Interferon and Cytokine Research

Montréal, Québec CANADA

1043-4666(200809)43:3;1-Y

IFN-λ1 and IL-4/13, as well as defines effects on the cytokine production and homing potential of CD4+ T cells.

doi:10.1016/j.cyto.2008.07.351

270

Production of, and response to, IFN-λ1 by plasmacytoid dendritic cells

N. Megjugorac, G.E. Gallagher, G. Gallagher, *Humigen-Genetic Immunology Laboratory*

Type III Interferons (IFN-λ1, 2 and 3) are a recently-discovered family of cytokines with robust antiviral and immunomodulatory effects. Production of IFN-λ1 mimics, in part, that of the Type I IFNs, which are expressed primarily by plasmacytoid dendritic cells (PDC). While epithelial cells and myeloid dendritic cells (MDC) are known to produce of IFN-λ1, there have been no reports on its production by PDC. In these studies, PDC were shown to produce large amounts of IFN-λ1 in response to HSV and CpG ODN, as measured by ELISA and intracellular flow cytometry. High levels of IFN-α are also produced during these stimulations, yet our data show that HSV and CpG directly induce IFN-λ1, with IFN-α acting to enhance production. Not only to PDC produce IFN-λ1, but respond to it as well, and express high levels of IFN-λ receptor (IL-28Rα) mRNA. Stimulation of MDC and PDC by IFN-λ1, in the presence or absence of maturation stimuli, resulted in differential regulation of costimulatory molecules CD80, CD83, CD86 and ICOS-L, as well as the homing molecule CD62L. These studies describe a previously unknown mechanism by which PDC, through the production of IFN-λ1, influence immune responses, as well as identify ways in which this cytokine impacts the activation and maturation of multiple DC subtypes.

doi:10.1016/j.cyto.2008.07.352

271

IFN-λ1 (IL-29) suppresses the differentiation of human naive and memory Th2 cells without inhibiting their proliferation

J. Dai, N. Megjugorac, G. Gallagher, *Humigen-Genetic Immunology Laboratory, 2439 Kuser Road, Hamilton, NJ, USA*

IFN-lambda-1 (IFN-λ1/IL-29), the prototype member of the human interferon lambda family, inhibits the development of human Th2. However, much about the cellular immunology and mechanism of this immunoregulatory property remains unclear. Here, we demonstrate that both naive and memory human CD4+T cells express mRNA for the IFN-λ1 specific receptor IL-28Rα, and are responsive to IFN-λ1. Upon activation in the presence of IFN-λ1, naive CD4+T cells: decrease their IL-5 and IL-13 secretion, diminish their GATA-3 expression and fail to lower CD62L expression. Memory T cells also respond to IFN-λ1 in a similar manner. Proliferation of these cells was not inhibited by IFN-λ1. Our data provide insight to this unique immunomodulatory role of IFN-λ1. The cytokine-responsive suppression of GATA-3 and alteration of migratory capacity by regulating CD62L expression suggests that IFN-λ1 uses a novel mechanism to modulate Th2 responses in peripheral naive and memory human T cells.

doi:10.1016/j.cyto.2008.07.353

272

Antigen-independent proliferation and functional differentiation of CD8 T lymphocytes stimulated by IL-6 in the presence of IL-7 OR IL-15

Subburaj Ilangumaran, Julien Gagnon, Chantal Leblanc, Sheela Ramanathan, *Immunology division, Department of Pediatrics, Faculty of Medicine and Health Sciences, Université de Sherbrooke, Que., Canada*

Signaling via the T-cell antigen receptor (TCR) is a prerequisite for normal activation of CD8 T lymphocytes. We and others have shown that IL-21 can stimulate proliferation of naïve CD8 T cells in the absence of TCR signaling, but only in the presence of IL-7 or IL-15. Here, we show that IL-6, which strongly phosphorylates STAT3 like IL-21, also stimulates proliferation of CD8 T cells in synergy with IL-7 or IL-15. IL-6 displays a stronger synergy with IL-7 than with IL-15 to stimulate naïve CD8 T cells bearing the H–Y transgenic TCR. Proliferation of naïve CD8 T cells induced by cytokines closely correlates with increased phosphorylation and DNA binding activity of STAT5. Importantly, IL-21 and IL-6 reduce the TCR signaling threshold required to stimulate CD8 T cells by antigen. Moreover, cytokine pre-stimulation augments proliferation, cytokine production and cytolytic activity of P14 TCR transgenic CD8 T cells upon subsequent antigen stimulation. Since innate immune cells produce IL-6 and IL-21 abundantly, we propose that these cytokines may play an important role in the transition from innate to adaptive immunity to viral infections by synergizing with IL-7 or IL-15 to induce TCR-independent activation of CD8 T cells.

doi:10.1016/j.cyto.2008.07.354

273

Interlukin-12 enhances the fungicidal activity of neutrophils from gerbils with sporothrix schenckii infection

Aurelio Flores-García [1], Porfirio López-Lugo [1], Pedro Aguiar-García [1,2,3], Nidia K. Castillón-Benavides [1], Omar J. Castillón-Benavides [1], José R. Altamirano-Gallegos [1], Rogelio Sánchez-Gutiérrez [2], Eloy A. Zepeda-Carrillo [2], Martha Barba-Barajas [3], Vicente Garibald [1,2,3], [1] *Unidad Académica de Medicina, Universidad Autónoma de Nayarit.Tepic, Nayarit, México,* [2] *Unidad Académica de Enfermería Universidad Autónoma de Nayarit, Tepic, Nayarit, México,* [3] *Laboratorio de inmunobiología, Centro de Investigación Biomédica de Occidente (CIBO) IMSS, Guadalajara, Jalisco, México*

Background: Sporothrix schenckii is a dimorphic fungus that usually causes localized lymphocutaneous sporotrichosis and systemic infection may occur in immunodeficient patients. Host defense against S. schenckii involves neutrohpil and macrophage phagocytosis. Interleukin-12 (IL-12), is a heterodimeric proinflammatory and immunoregulatory cytokine critical in the host resistance to many infections. Previously we found that recombinant murine IL-12 (rmIL-12) enhanced the fungicidal activity of peritoneal macrophages from gerbils with sporotrichosis. *Objective:* To determine the effect of rmIL-12 on the phagocytic and fungicidal activity, as well as myeloperoxidase activity of neutrophils from gerbils with S. schenckii infection. *Methods:* Twenty gerbils were infected in the left hind footpad with 6×10^6 S. schenckii yeast cells. Ten of these gerbils received intraperitoneal injections of 500 ng of rmIL-12 diluted in phosphate buffer solution (PBS) everyday for five days starting at the same time as the infection. The other 10 infected gerbils received only intraperitoneal PBS. Another 10 healthy control gerbils also received PBS alone. Two weeks post-infection neutrophils were obtained by cardiac puncture, subsequently phagocytic and fungicidal index were measured by Cunningham method and by colony-forming units (CFU) counts, respectively. Myeloperoxidase activity was determined using the Kaplow method. *Results:* Phagocytic and fungicidal index as well as myeloperoxidase activity of neutrophils from rmIL-12-untreated infected gerbils were significantly lower compared with neutrophils from healthy controls ($p < 0.001$ and $p < 0.002$, respectively). Moreover, these gerbils developed ulcerous lesions in the infected footpad. Conversely, phagocytic and fungicidal index as well as myeloperoxidase activity of neutrophils from rmIL-12-treated-gerbils were significantly higher compared with neutrophils from healthy controls ($p < 0.001$ and $p < 0.002$, respectively). Interestingly, no cutaneous lesions were developed in rmIL-12-treated infected gerbils. *Conclusions:* These results suggest that IL-12 plays an important role in host defense against S. schenckii infection by increasing the phagocytic, fungicidal, and mieloperoxydase activity of neutrophils.

doi:10.1016/j.cyto.2008.07.355

274

Identification of small RNAs produced by cleavage of hepatitis C viral RNA with RNase L that bind RIG-I

Krishnamurthy Malathi [1], Michael Gale [2], Robert H. Silverman [1], [1] *Department of Cancer Biology, Lerner Research Institute, Cleveland Clinic, Cleveland, OH 44195, USA,* [2] *University of Washington School of Medicine, Department of Immunology, Seattle, WA 98195, USA*

The innate immune recognition of viral infection triggers antiviral responses that include production of type I interferons and a variety of other cytokines. Type I interferon in turn activates the classical innate immune OAS/RNase L pathway which recognizes the pathogen associated molecular pattern (PAMP), dsRNA, and degrades viral and cellular RNA thereby limiting viral spread. Recently, we reported that cleavage of cellular (self) RNA by RNase L results in the production of short RNA segments that activate RNA helicases, RIG-I and MDA5 and the adapter IPS-1. These events signal to transcription factors IRF3 and NF-κB that activate the IFN-β gene. Therefore, RNase L provides an amplification of IFN production in vivo during the antiviral innate immune response. To investigate the precise structures of the RNAs generated by RNase L that are recognized by RIG-I/MDA5, we used HCV as a model system. The RNase L cleavage products of HCV RNA that bound RIG-I were cloned, sequenced and identified. No HCV RNA cleavage products with affinity for MDA5 were obtained thus far. We are exploring the structural requirements of the short RNAs for binding and activating RIG-I and correlating their ability to induce IFN-β.

doi:10.1016/j.cyto.2008.07.356