MINERVA MEDICA

VOL. 98 · SUPPL. I · N. 3 · GIUGNO 2007

5TH NATIONAL CONFERENCE

SIICA

ITALIAN SOCIETY IMMUNOLOGY, CLINICAL IMMUNOLOGY AND ALLERGOLOGY

Trieste - June 6-9, 2007

EDIZIONI · MINERVA · MEDICA

PUBBLICAZIONE PERIODICA BIMESTRALE - POSTE ITALIANE SPED. IN A. P. 45% ART. 2 COMMA 20/B LEGGE 662/96 AUT. 584/DC/DCI/CN - ISSN 0026-4806 TAXE PERÇUE

Potential Role of Dendritic Cells differentiated in the presence of IL-10 in Controlling the Immune Response to Allergens

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IL-10 is a potent immunomodulatory cytokines that plays a central role in controlling inflammatory processes, suppressing T cell responses, and maintaining immunological tolerance. Several line of evidence demonstrate that IL-10 modulates antigen-presenting cells including dendritic cells (DC). The aim of this study is to determine whether DC differentiated in the presence of IL-10 (DC10) are able to modulate allergen-specific T cell responses in children affected by allergic asthma. Twelve children (4-14 years) allergic to House Dust Mite (HDM), and 3 healthy age-matched children were recruited. DC were differentiated from peripheral blood $CD14^+$ precursors culturing with GM-CSF and IL-4 for 5 days in the presence of IL-10 (DC10) and pulsed with Der p2 (a major HDM allergen) for additional 48 hours to obtain Dp2-DC10. As control Dp2-DC were generated. The ability of the resulting DC to stimulate allergen-specific autologous T cells and to promote allergen-specific T cell anergy was analyzed.

Dp2-DC promoted allergen-specific T cell proliferation and Th2 cytokine profile in 10 out of 12 patients but not in healthy controls. Dp2-DC10 induced a significantly lower allergen-specific T cell proliferation in all responders associated with a marked reduction of both IL-5 production and IL-13 with a parallel decrease of IL-5/IFN-γ ratio.

T cell lines generated with Dp2-DC10, compared to those generated with Dp2-DC, were hypo-responsive to reactivation with Der p2 in 4 out of 5 patients tested, both in terms of proliferation and cytokine production: IL-5, IL-13 and IL-5/IFN-γ ratio.

Therefore, differentiation of DC in the presence of IL-10 resulted in a population of DC with low stimulatory capacity that inhibit allergen-specific Th2 response. Moreover, Dp2-DC10 induce allergen-specific T cell anergy. These results represent an important step forward to the prospective clinical application of Dp2-DC10 to modulate allergen-specific T cell responses *in vivo*.

Role of mitochondria and reactive oxygen species in dendritic cell differentiation and functions

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Among the antigen-presenting cells (APCs) of the immune system, dendritic cells (DC) result the most potent APCs with a unique ability in inducing T and B cell response as well as immune tolerance. In their immature state, DCs are located in peripheral non lymphoid tissues to detect and capture foreign antigens (Ags) by specialized endocytic activity and pattern recognition receptors. After exposure to Ags, DCs acquire the mature phenotype with a high antigen-presenting activity and migrate from peripheral tissues to draining lymph nodes to present processed Ags to naïve T cells and to initiate an immune response. Recent studies suggest a role for Reactive Oxygen Species (ROS) as essential second messengers for DC response to several physiological stimuli. The mitochondrial electron transport chain, mostly at the level of Complex I and III, represents the main source for ROS generation in the cell. Our preliminary results show that i) the differentiation process of monocytes into dendritic cells is characterized by a significant increase of endogenous respiration, ii) the citrate sinthase activity (a marker enzyme of mitochondrial matrix) resulted up-regulated in DCs as compared to monocytes, and ii) the presence in the culture medium of sub-saturating concentrations of rotenone, an inhibitor of the respiratory chain complex I, reduces hydrogen peroxide generation and inhibits DC differentiation process. Accordingly, it was found that rotenone-treated cells showed phenotype expression and metabolic functions more similar to monocytes than to dendritic cells. These results suggest a role of ROS in the differentiation process of monocytes into dendritic cells. Given the strategic localization of DC at the interface of innate and adaptive immunity, this study may provide the rational for the identification of new targets in the regulation of DC functions.

MILTENYI LECTURE

Regulation of NK cell responses by cytomegaloviruses

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Cytomegaloviruses (CMV) have evolved different strategies aimed at regulating the innate immune responses mediated by natural killer (NK) cells. Among other mechanisms, murine CMV (MCMV) encodes ligands for activating and inhibitory NK cell receptors and blocks the expression of cellular ligands for the NKG2D receptor. Since the NKG2D receptor is important in controlling both NK- and T cell-mediated immunity, it is of paramount importance to understand the mechanisms and consequences of viral regulation of NKG2D ligands. So far, we have characterized four MCMV genes encoding proteins that participate in down-modulation of NKG2D ligands. With the exception of m138, all of these genes belong to the m145 gene family. The first one to be discovered, the m152, was originally identified as one of MCMV genes involved in MHC class I down-modulation. The m152/gp40 protein targets RAE-1 ligands for down-regulation, and therefore helps the virus in evading NK cell mediated control. Our current study indicates that not all RAE-1 isoforms are equally sensitive for regulation by the MCMV. By using MCMV deletion mutants lacking genes of the m145 gene family, we have shown that m155 and m145 are responsible for the down-modulation of cell-surface H60 and MULT-1 proteins, respectively. Moreover, deletion mutants for either m145 or m155 were attenuated *in vivo* in an NK cell-dependent manner. Recently we have shown that m138, previously characterized as a viral Fc binding protein, also down-modulates the surface expression of MULT-1 and H-60 thus contributing to MCMV resistance to NK cell-mediated control. The molecular mechanism of the regulation of NKG2D ligands by MCMV and the biological significance of these and several other MCMV immunoevasins in the control of acute and chronic MCMV infection will be discussed.