ISSN 0025-7680

MEDICINA (Buenos Aires) 2004; 64 (Supl. II): 36-37

SIMPOSIO 5.
CÉLULAS DENDRÍTICAS EN PROCESOS PATOLÓGICOS Y EN LA REGULACIÓN DE LA RESPUESTA INMUNE

DENDRITIC CELL-T CELL INTERACTIONS FOR THE INDUCTION OF PRIMING AND TOLERANCE

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The induction of both immunity and tolerance require direct contacts, between dendritic cells (DCs) bearing a specific antigen and naïve T lymphocytes. These contacts occur within the lymph nodes, during the first 48h after immunization. After this initial activation, T lymphocytes either proliferate extensively and differentiate into effector and memory cells, or divide a restricted number of times and die, thus contributing to the maintenance of peripheral tolerance.

We have shown that the initial encounters between mature DCs and naive T cells include two distinct steps, controlled by Rac1 and Rac2: (i) Initial interactions are mediated by dendrites, which are projected in all directions by mature DCs, and (ii) a first contact between the dendrites and a naýve T cell modifies the membrane activity of the mature DC, causing the directional projection of abundant membrane extensions toward the naýve T cell and the short range displacement of the cell body in the same direction. Immature DCs, which do not extend dendrites, and which do not polarize toward naive T cells or entangle them in the course of the interaction, do not prime naive T cells efficiently. Therefore, mature DCs have adapted their cytoskeletal activity to optimize the encounters and to stabilize interactions with naive T cells.

Using 2-photon microscopy, we have also analyzed the interactions of lymph node resident DCs with naïve T lymphocytes during the induction of either antigen-specific immunity or tolerance. We found that during the induction of immunity, a strong «stop signal» was delivered to T lymphocytes 15 h after the initiation of the response. This stop signal resulted in the establishment of stable interactions between the two cell types that lasted for at least 5 h. Most T cells then resumed mobility, after 30-48h of stimulation. This peculiar kinetics of T cell migration is dictated by DC maturation rather than by T cell stimulation.

During the induction of tolerance, despite the effective T cell activation and proliferation observed during the first two days, no stable interactions with DCs, nor «stop signal» cells were observed. Instead, naïve T lymphocytes established sequential transient contacts with several DCs. Therefore, the dynamics of the initial interactions between DCs and naïve T cells may profoundly affect the outcome of immune responses, inducing either T cell immunity or tolerance.

LONG-TERM ISLET GRAFT SURVIVAL IN NOD MICE BY ABROGATION OF RECURRENT AUTOIMMUNITY

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Islet transplantation has great potential for curing Type I diabetes; however, long-term islet survival using conventional immunosuppression remains elusive. Whether this loss of islet function is due to cellular attrition, autoimmunity and/or chronic rejection is not known; however, the future success of islet transplantation in curing Type I diabetes critically depends on the design of alternative, clinically relevant strategies for achieving long-term islet graft survival. Numerous strategies that prevent primary disease in NOD mice are wholly ineffective against recurrent disease suggesting that the presence of preprimed autoreactive T cells in diabetic individuals may evade and/or hamper the success of known immunosuppression and tolerance induction strategies. Therefore, functional tolerization and/or modulation of the primed autoreactive T cell pool has great potential to ameliorate islet graft survival *in vivo*. We have developed a clinically relevant model of islet transplantation in NOD mice

through portal vein injection that results in rapid rejection of syngeneic islets in untreated diabetic NOD mice. We present here a novel strategy for inducing long-lasting islet graft survival in diabetic NOD mice in the absence of post-transplant immunosuppression, by initial treatment with anti-lymphocyte serum (ALS) followed by co-administration of donor pancreatic lymph node cells (PLNC). When treated with ALS/PLNC, diabetic NOD mice become normoglycemic and tolerate minor antigen-disparate islet grafts for >100 days and syngeneic islet grafts indefinitely. Donor T cells are required for graft prolongation, and tolerant hosts maintain 10-20% donor T cell chimerism. Most strikingly, this treatment results in a switch in cytokine profile of the host autoreactive GAD65- and insulin-specific T cells, from predominantly IFN-g-producing to a preponderance of IL-4 producers. Our results present a clinically relevant model for enabling islet graft acceptance without post-transplant immunosuppression, by ablation of recurrent autoimmunity via alteration of the resident host autoreactive T cells.

VIRAL INFECTIONS AND AUTOIMMUNITY - GOOD OR BAD?

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Intuitively one tends to associate viral infections that frequently induce profound inflammation in multiple organs with enhancement of autoimmune processes and diseases such as type 1 diabetes and multiple sclerosis. There is substantial evidence that viral infections can increase the incidence of autoimmune diseases (i.e., NOD mouse and Coxsackie B3 infection) or precipitate inflammatory disorders with autoimmune components (Theiler's virus). This can occur either by antigen-nonspecific bystander events or through cross-reactivity between viral and self-components. We will show data for the second scenario (mimicry) and illustrate that molecular mimicry is more likely to enhance an already ongoing autoimmune process rather than precipitating disease de novo. However, recently it has become increasingly clear that the opposite situation, prevention of autoimmunity by viral infections, might be more common. There is accumulating evidence that viruses such as Coxsackie B or LCMV can prevent diabetes. How can viral infections be good for us? We will show recent findings that demonstrate how chemokine gradients established by viral infections can lure autoaggressors away from the site of organ or tissue inflammation. The reversal of disease appears in most cases to be permanent. This finding fits with the recent increasing trend in autoimmune ('hygiene hypothesis').