

Emmanuel Donnadieu

The immune synapse and T cell activation: regulation by chemokines

Summary

To mount an appropriate immune response, T cells rely on a physical interaction with antigen-presenting cells (APCs). The contact site between both cells is a highly specialized structure referred as the immunological synapse (IS). Initially described as a central accumulation of small signalling molecules surrounded by a ring of larger adhesion molecules, the structure of the IS is in fact much more variable and depends on the nature of the T cells and APCs. Recent findings obtained in physiological systems such as intact lymph nodes (LNs) have provided important insights into the dynamics of T cell-APC interactions as well as the elements that control the formation of the IS. Here, I review progress in this field of research with a particular focus on the modulation of immune synapse formation and functioning by chemokines.

Key words: T cell, dendritic cell, antigen-presenting cell, immune synapse, signal transduction, migration, lymph node, chemokine, CCR7, cytokines, regulatory T cell

Luis Graca

The induction of regulatory T cells by targeting the immune synapse

Summary

In recent years, a T lymphocyte subset known as regulatory T cells (Treg) was shown capable of controlling inappropriate immune responses. Recent studies have been demonstrating that therapeutic induction of dominant tolerance relies on either the expansion of Treg cells from pre-existent precursors, or the peripheral conversion of non-regulatory T cells into Treg cells. The mechanisms responsible for peripheral Treg conversion remain one of the major unresolved issues in the field. However, evidence from several groups suggests that the common feature of such tolerogenic protocols is their interference with molecules participating in the immune synapse. Therefore, creating the conditions appropriate for suboptimal T cell activation appears to lead to conversion towards a Treg cell fate. The corollary of this hypothesis is that T cell fate does not simply rely on qualitative stimuli (such as the presence or absence of a particular molecular signal) but rather depends on quantitative differences in the T cell activation status.

Key words: regulatory T cells, dendritic cells, immune tolerance, immune synapse, monoclonal antibodies, transplantation, autoimmunity, immunotherapy, Foxp3

Paul J. Fairchild

Infiltrating the immunological synapse: prospects for the use of altered peptide ligands for the treatment of immune pathology

Summary

Precision has long been considered the most fundamental aspect of the immune response, with which T cells have been entrusted. Various lines of evidence over the past decade have, however, revealed a degree of flexibility involved in the way in which T cells recognise their cognate peptide: while subtle changes in amino acid sequence may be tolerated, the effect on antigen recognition may be inherently unpredictable resulting in outcomes as diverse as anergy, immune

deviation and the polarisation of responding cells towards a regulatory phenotype. The rational design of so-called altered peptide ligands (APL) may, therefore, provide an important means of leverage at the very heart of the immunological synapse, capable of influencing cell fate decisions downstream of the immediate signaling events and profoundly altering the nature of the subsequent immune response. Here we review these recent advances in our understanding and discuss prospects for harnessing APL for intervention in pathogenic immune responses.

Key words: altered peptide ligand, autoimmunity, alloreactivity, immunological synapse, anergy, immune deviation, regulatory T cell

Damien Bresson and Matthias von Herrath

Anti-CD3: from T cell depletion to tolerance induction

Summary

Immunosuppressants are the most potent agents to prevent graft rejection in transplantation and induce remission in autoimmune diseases. These drugs share a common mechanism of action which consists of depleting the body from all immune responses. Unfortunately, such compounds have to be permanently administered to maintain protection, but exposing chronically the patients to immune suppressors often leads to the risk of recurrent infections and increases frequency of tumors. After several decades of research in developing new therapeutic avenues to prevent or treat immune disorders, few non-immunosuppressive drugs were able to effectively translate from bench to bedside. Short-term treatment with anti-CD3 antibodies is one of those inducing potent immune regulation with a risk versus benefit ratio sufficiently low to apply this treatment to patients suffering from various immune pathologies. CD3 monoclonal antibodies exert unique properties by inducing immunological tolerance that is an antigen-specific unresponsiveness in the absence of long-term immunosuppression.

Key words: anti-CD3 antibodies, OKT3, autoimmunity, autoimmune diseases, transplantation, type 1 diabetes, multiple sclerosis, tolerance, regulatory T cells, immunosuppressive drugs

Yuan Zhai and Jerzy W. Kupiec-Weglinski

Immune modulation by CD40L blockade

Summary

CD40L-CD40 costimulatory pathway is one of the most extensively studied in the immunology research in recent years. Despite the therapeutic success of its blockade in many disease models, in vivo mechanisms remain to be fully elucidated. In this review, CD40L immunobiology was briefly summarized, followed by the discussion of its role in both adaptive and innate immune responses. Focus was on CD40L blockade in transplantation models with emphasis on issues related to its potential clinical application, such as interactions with conventional immunosuppressive agents, impact of T cell activation status and concurrent innate immune activation on its efficacies. The in vivo mechanisms of immune suppression/tolerance in CD40L blockade induced long-term transplant recipients are analyzed. This review is not a comprehensive summary of what's known, but rather extractions from recent literature to better understand and appreciate putative mechanisms of CD40L blockade in disease models.

Francesca Fallarino, Carmine Vacca, Claudia Volpi, Maria T. Pallotta, Stefania Gizzi, Ursula Grohmann and Paolo Puccetti

CTLA-4-Ig and indoleamine 2,3-dioxygenase (IDO) in dominant tolerance

Summary

An improved understanding of basic immunoregulatory mechanisms together with advances in protein engineering have culminated in the development of therapeutic proteins targeting specific costimulatory targets, which include receptors on T cells with either activating or inhibitory properties. One of the most important costimulatory pathways for T cell activation involves CD28/CTLA-4 (cytotoxic T lymphocyte-associated antigen-4) molecules on the one hand, and their ligands B7.1 (CD80) and B7.2 (CD86) on the other. When engaged by B7, CTLA-4 acts as an immunosuppressant, leading to down-regulation of T cell responses. Both T cell intrinsic and extrinsic mechanisms do, however, contribute to the inhibitory function of CTLA-4. Recent findings suggest that “reverse signaling” through B7 molecules by CTLA-4 results in activation of the immunosuppressive pathway of indoleamine 2,3-dioxygenase (IDO) in dendritic cells (DCs), and that this effect may represent one important mechanism of action of regulatory T (Treg) cells expressing surface CTLA-4. Similar to membrane-bound CTLA-4, the soluble fusion protein CTLA-4-Ig is thought to prevent activation of CD28 by interacting with B7-1 and B7-2 and to trigger tryptophan catabolism. Here we review recent data on how IDO induction by CTLA-4—as well as conventional and innovative forms of soluble CTLA-4—may initiate immunoregulation at the interface of inflammation and tolerance. We also discuss the potential for therapeutic application of IDO modulation as a regulatory maneuver targeting specific DC subsets.

Key words: CTLA-4, IDO, tryptophan, kynurenine, tolerance

Mark R. Nicolls and Rasa Tamosiuniene

Adhesion molecules as therapeutic targets

Summary

Cellular adhesion molecules (CAMs) play a key role in leukocyte migration and, to a more variable extent, costimulation and the immune synapse. Because of these properties, anti-adhesion therapies have been utilized in a variety of inflammatory conditions including asthma, burns, inflammatory bowel disease, multiple sclerosis, myocardial infarction, psoriasis, psoriatic and rheumatoid arthritis, stroke, transplantation and trauma. The principle adhesion molecules involved in leukocyte migration include three major classes of molecules: 1) members of the immunoglobulin supergene family, 2) integrins and 3) selectins. This chapter will focus on pre-clinical and clinical studies which have utilized anti-adhesion immunomodulatory therapies and on the potential future for this broad class of compounds. Therapies have targeted a wide array of adhesion molecules in pre-clinical models and clinical trials and have been variably effective. To date, LFA-1 and $\alpha 4$ integrins have represented the two most explored and exciting adhesion targets.

Key words: adhesion, immunoglobulin superfamily, integrin, selectin, LFA-1, monoclonal antibodies, immunotherapy, immunosuppression, inflammation, autoimmunity, transplantation

Irene Puga and Fernando Macian

E3 ubiquitin ligases and immune tolerance: targeting the immune synapse from within?

Summary

New functions of ubiquitin have emerged in the last decade, highlighting the important role of ubiquitination not only in targeting of proteins for proteasomal degradation but also in the regulation of many other cellular processes. Several E3 ubiquitin ligases, including Itch, GRAIL and Cbl-b, have recently been identified as essential players in the regulation of immune tolerance. In this chapter we will review our current knowledge on how these enzymes interfere with T cell activation by targeting and modulating the activity of key signaling proteins in anergic T cells.

Key words: E3 ligase, ubiquitin, anergy, T cell, calcium, NFAT, Itch, GRAIL, Cbl-b

Bin Li, Xiaomin Song, Arabinda Samanta, Kathryn Bambas, Amy Brown, Geng Zhang, Makoto Katsumata, Yuan Shen, Sandra J. Saouaf and Mark I. Greene

FOXP3 biochemistry will lead to novel drug approaches for vaccines and diseases which lack suppressor T cells

Summary

Regulatory T cells (Treg) play a dominant role in regulation of the immune response ensuring that activated immune cells are efficiently downregulated following activation by pathogens, protecting against unchecked immune responses that could cause tissue damage. The level and duration of FOXP3 protein expression in Treg cells determines their suppressive function. Understanding the biochemistry of FOXP3 activities, including the signals regulating FOXP3 level and duration, the posttranslational modification of FOXP3, the FOXP3 complex ensemble with other transcription factors as well as histone modification and chromatin remodeling enzymes in Treg cells will lead to novel pathways for drug development in immune related diseases including allergy, inflammation, autoimmune syndromes, vaccine development and cancer.

Key words: FOXP3, regulatory T cells, histone acetyltransferase, histone deacetylase, histone deacetylase inhibitor, chromatin remodeling

Ramireddy Bommireddy and Thomas Doetschman

Transforming growth factor- β : From its effect in T cell activation to a role in dominant tolerance

Summary

TGF β 1 is an important immunoregulatory cytokine produced by several cell types. TGF β 1 signals through both SMAD-dependent and SMAD-independent pathways depending on the cell type and cytokine environment. TGF β 1 inhibits T-bet and GATA3 expression during T cell differentiation and inhibits production of T_h1 and T_h2 cells. In contrast, it induces FOXP3 and ROR γ t in T cells which favors the generation of T_{reg} cells and T_h17 cells, respectively. TGF β 1 also induces CTLA-4 expression which in turn induces FOXP3 in T_{reg} cells. The E3 ubiquitin ligase CBLB mediates TGF β 1 effects in T_{reg} cell generation. These diverse actions of TGF β 1 on T cells are determined by the signal strength of their cell-cell interactions. Stimulation of naïve T cells by immature dendritic cells (DC) leads to T cell tolerance, whereas mature DC activates naïve T cells. TGF β 1 signaling in DC causes conditioning

which down regulates co-stimulatory molecules resulting in T cell anergy upon DC encounter. Therefore, blocking TGFβ1 signaling in T cells causes T cell activation and autoimmunity, and TGFβ1 deficiency in T cells causes breakdown of tolerance. Consequently, it is the effects of TGFβ1 signaling on several arms of immune surveillance that make it essential for immunological tolerance.

Key words: autoimmunity, CBLB, CTLA-4, FOXP3, knockout mice, T_h17 cells, T_{reg} cells, TGFβ1, tolerance

Wan-Fai Ng and John D. Isaacs

From mice to men: the challenges of developing tolerance-inducing biological drugs for the clinic

Summary

Over the past decade the development of biological therapies has revolutionised the treatment of autoimmune diseases and transplant rejection. The results of these new therapies are promising, but are we approaching clinical therapeutic tolerance? Data from animal models are certainly encouraging but it remains to be seen whether these therapeutic strategies can be successfully translated into clinical practice. This final chapter considers the challenges to be faced in this endeavour and strategies that should help to make clinical therapeutic tolerance a reality.

Key words: Tolerance-inducing therapy, clinical tolerance, biologics, monoclonal antibodies, autoimmunity, transplantation, clinical trials, animal models, immunogenicity

The Immune Synapse as a Novel Target for Therapy

Graca, L. (Ed.)

2008, XII, 192 p., Hardcover

ISBN: 978-3-7643-8295-7

A product of Birkhäuser Basel