

Immunology / Immunologie

Induction of immunological tolerance using monoclonal antibodies: Applications to organ transplantation and autoimmune disease

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Received 7 December 2005; accepted after revision 20 December 2005

Available online 4 April 2006

Presented by Roger Monier

Abstract

Immunologic tolerance is a state of immune paralysis specific to a given antigen (the tolerogen) coexisting with the maintenance of normal immunocompetence towards other antigens. Anti-T cell monoclonal antibodies allow its induction in organ transplantation and autoimmune disease essentially through the stimulation of regulatory T cells. Very promising results obtained in animals have been recently confirmed in the human in recent-onset insulin-dependent diabetes mellitus with an anti-CD3 antibody (with long-term remission of the disease following a treatment of only six days). **To cite this article: J.-F. Bach, C. R. Biologies 329 (2006).**

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Résumé

Induction d'immunos tolérance par les anticorps monoclonaux : application à la transplantation d'organe et aux maladies autoimmunes. La tolérance immunitaire est un état de paralysie immunitaire spécifique d'un antigène donné (le tolérogène) coexistant avec le maintien d'une immunocompétence normale vis à vis des autres antigènes. Les anticorps monoclonaux anti-cellules T permettent de l'induire dans les greffes et les maladies auto-immunes. Les résultats très prometteurs obtenus chez l'animal viennent d'être confirmés chez l'homme dans le diabète insulino-dépendant, de découverte récente, avec un anticorps anti-CD3 (rémission durable de la maladie suivant un traitement de seulement six jours). **Pour citer cet article : J.-F. Bach, C. R. Biologies 329 (2006).**

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Keywords: Monoclonal antibodies; Tolerance; Insulin-dependent diabetes mellitus; Organ transplantation; Anti-CD3

Mots-clés : Anticorps monoclonaux ; Tolérance ; Diabète ; Greffes d'organe ; Anti-CD3

1. Introduction

Immune tolerance is defined as a state of immune paralysis specific to an antigen, keeping the capacity to develop an immune response against any antigen that does not share its antigenic determinants with the tolero-

gen (the antigen used to induce tolerance). It often happens in immunopathology that the antigen targeted by the pathogenic immune reaction is not precisely known or there is no reliable test to quantifiably measure the cellular response to the antigen. It is difficult to define tolerance in this setting. One must be content with the less rigorous, but nonetheless very medically meaningful, notion of operational tolerance. One means by this

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term the protection of the target organ by the specific and long-term inhibition of effector mechanisms in the absence of systemic immunosuppression.

The induction of tolerance to the HLA antigens of the donor is the prime goal of all organ transplant teams. Also, the restoration of self-tolerance, the physiological phenomenon whose rupture is at the origin of autoimmune diseases, is the ideal solution for their treatment, very preferable to non-specific, tumour and infection-generating immunosuppression.

In the follow-up to Medawar's pioneering experiments in newborn mice, the first approach consisted in administering the tolerogen in favourable conditions to tolerance induction (notably host immunocompetence). In spite of the very encouraging results in certain experimental models, no conclusive results were obtained in humans in a small number of patients in whom the strategy was used.

The isolated administration of a tolerogen is not sufficient to induce tolerance outside the very specific context of very young animals whose immune system is still immature. It remains ineffective in adults, especially when the targeted immune response has already been triggered.

It was the introduction of anti-T cell monoclonal antibodies that was the breakthrough, first in animals, then more recently in humans.

2. Experimental models

The first results were obtained in transplantation (skin or organ). Administering monoclonal antibodies specific to the CD4 molecule (an essential molecule for the recognition of antigens by helper T cells), against the CD40L molecule (a molecule that acts as a cofactor in T cell stimulation), the CD3 molecule (a molecule that is closely linked to the T cell receptor whose transduction it initiates), or the CD45RB molecule (a membrane receptor of a major population of CD4⁺ T cells) permits the induction of tolerance to transplantation. Simultaneously administering the organ donor's bone marrow cells facilitates tolerance induction, but is not absolutely necessary [1]. These results should be related to the induction of tolerance observed with polyclonal antilymphocyte sera in the seventies.

By the same token, administering these antibodies to animals that develop spontaneous or provoked autoimmune disease induces the prevention or long-term remission of the disease. The most spectacular results were obtained with an anti-CD3 monoclonal antibody in insulin-dependent diabetes in the NOD mouse [2], experimental allergic encephalomyelitis, an animal model

of multiple sclerosis [3], and inflammatory bowel disease [4]. It was shown to be possible to induce long-term diabetes remission in fully diabetic NOD mice by administering the antibody for only five days.

The anti-CD3 antibody's mode of action in tolerance induction is partially known [5,6]. As a general rule, there is no lymphocyte depletion. Experimental arguments converge to indicate that tolerance is the direct consequence of the induction of regulatory T cells that are able to suppress the pathogenic T lymphocyte reaction [6]. The regulatory T cells in question are still being characterized. They notably include a sub-population of CD4⁺ T cells bearing the CD25 marker (the alpha chain of the interleukin-2 receptor) and the CD62L molecule (L-selectin) [7]. The reality of this protective immunoregulation is shown by the transfer of tolerance to a 'naive' animal by CD4⁺ T cells from a tolerant animal. At the molecular level, a debate persists on the possible intervention of cytokines. The role of interleukin-10 and above all transforming growth factor β (TGF β) is suggested by abundant experimental data. However, one cannot exclude the possibility that in certain models, direct contact between the regulatory cell and the effector cell may be necessary [8].

3. First results in humans

Anti-CD4 antibodies were the first to be used in humans, both in transplantation and autoimmune disease. The initial results were disappointing and the use of antibodies was complicated by the usual consequence of very long-term depletion of CD4⁺ T cells. It was difficult to produce human anti-CD4 antibodies that represented the equivalent of mouse anti-CD4 antibodies which could have been efficacious in inducing tolerance without causing such depletion [1].

The use of anti-CD40L antibodies had raised high hopes [9], the more so because results obtained in the mouse had been confirmed in organ transplantation in the monkey [10]. Unfortunately, it was shown in humans that anti-CD40L antibodies cause thrombosis that could be explained by the presence of the CD40L molecule on human platelets.

No human anti-CD45RB antibody exists. However, there is an antibody of close specificity (anti-CD45RO) that was developed in humans on the basis of promising *in vitro* results showing the capacity of the antibody to induce interleukin-10-producing regulatory T cells [11].

The most demonstrative results are, again, those obtained with anti-CD3 antibodies. We were recently able to confirm the remarkable efficiency of an anti-CD3 antibody whose mitogenic effect (induction of a prolifer-

eration of T cells with release of cytokines) had been attenuated by mutations corresponding to the Fc fragment in recent-onset diabetic patients. The availability of such an antibody allows the implementation of this therapeutic approach [12]. In spite of the short duration of the treatment (six days), long-term remission of diabetes was observed with a quasi-insulin independency in the majority of patients 18 months after treatment. As we had expected, the best response was observed in patients who still had a significant quantity of residual β cells at diabetes onset (shown by C peptide production after stimulation by glucose or glucagon). The side effects were moderate. The only concern was a reactivation, fortunately very transient, of the EBV virus in the B lymphocytes. The efficient response of CD8⁺ T cells against EBV peptides, which was observed in all patients, explains the rapid virus-clearance. This strong immune response confirms tolerance induction, since it has been shown in this way that, simultaneously to the inhibition of the anti-islet autoimmune reaction, patients keep a normal capacity to develop a strong anti-viral immune reaction.

4. Conclusion

Immune tolerance in transplantation and autoimmune disease appears to be close at hand. It is no longer a hope, but an authentic reality. This great step forward, long anticipated, was made possible by monoclonal antibodies. Let us hope that the hesitation on the part of large pharmaceutical companies, which hindered the development of therapeutic monoclonal antibodies in the 1980s, will not delay patient access to this new strategy.

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