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Editors

Tolerance and Autoimmunity

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The immunologic specificity of the antigen receptors of T cells and B cells is the result of random shuffling of the many genes that form the DNA code for the antigen-binding site of these receptors. Theoretically, this process could generate 10^9 different T-cell receptors, including some that can bind to autoantigens (these cells are often called self-reactive T cells). Tolerance is the process that eliminates or neutralizes such autoreactive cells, and a breakdown in the working of this system can cause autoimmunity.

B-Cell Tolerance

Autoantibodies are characteristic of many autoimmune diseases and may be the direct cause of the lesions in some of these disorders. In Graves’ disease, autoantibodies bind to and stimulate the receptor for thyrotropin, and in pemphigus vulgaris, autoantibodies against the epidermal adhesion molecule desmoglein 3 disrupt the epidermis. In contrast, autoantibodies against intracellular antigens are not usually pathogenic but, instead, have been viewed largely as secondary consequences of the autoimmune process. This view has been challenged recently: in a murine model of autoimmune arthritis, the transfer of IgG from diseased animals induced arthritis in healthy recipients. These pathogenic autoantibodies bind to glucose-6-phosphate isomerase, a ubiquitous intracellular antigen.

Several mechanisms are available to filter autoreactive B cells out of the B-cell repertoire: the clonal deletion of immature B cells in the bone marrow, the deletion of autoreactive B cells in the T-cell zones of the spleen or lymph nodes, functional inactivation (anergy), and “receptor editing,” a mechanism that changes the specificity of the B-cell receptor when an autoantigen is encountered. How important these mechanisms are in preventing autoimmune disease is unclear. There is evidence that B-cell tolerance is predominantly due to a lack of help from T cells. Mice that were genetically manipulated to express a foreign antigen (hen’s-egg lysozyme) on the surface of their thyroid epithelial cells produced numerous B cells with receptors for hen’s-egg lysozyme. Yet these animals showed no signs of thyroiditis, presumably as a result of T-cell tolerance. There is also evidence that under some circumstances, B cells can overcome tolerance in the absence of help from T cells, but it is inconclusive.

More about B-cell tolerance can be found elsewhere; in this review we focus on the dominant role of T cells in immune tolerance and autoimmunity.

Central T-Cell Tolerance

The chief mechanism of T-cell tolerance is the deletion of self-reactive T cells in the thymus. Immature T cells migrate from the bone marrow to the thymus, where they encounter peptides derived from endogenous proteins bound to major-histocompatibility-complex (MHC) molecules. T cells whose receptors have very low affinity for these peptide-MHC complexes do not receive signals that would prevent spontaneous apoptosis, and these cells therefore die in the thymus. T cells with high-affinity receptors for these complexes undergo apoptosis and die in a process called negative selection. The remaining T cells, which have receptors with an intermediate affinity for such complexes, mature in the thymus and migrate to the periphery, a process referred to as positive selection (Fig. 1). The induction of central tolerance requires the presence of autoantigens in the thymus. Not all self-antigens occur in the thymus, which necessitates the existence of peripheral mechanisms that participate in T-cell tolerance.

Peripheral T-Cell Tolerance

Ignorance

Since immunization of normal animals with certain self-antigens in an adjuvant induces autoimmune diseases, it follows that autoreactive T cells must be present in normal animals. Indeed, B cells and T cells that recognize insulin or myelin basic protein can be isolated from persons without diabetes or multiple sclerosis, respectively. Naïve T cells, which cannot enter normal tissues other than lymphoid organs, do not induce tissue damage. Evidently, under normal...
conditions, potentially autoreactive T cells ignore their antigens, thereby maintaining self-tolerance (Fig. 2).

The importance of immunologic ignorance was demonstrated in mice that were genetically engineered to express a T-cell receptor that recognizes a particular viral peptide (transgenic mice). These mice were bred with another transgenic strain that expressed the viral peptide on the surface of their pancreatic islet cells. Surprisingly, diabetes did not develop in the offspring even though in vitro their T cells could kill cells that displayed the viral peptide.25,26

The T cells in these double-transgenic mice were therefore not tolerant in vivo, they simply ignored their target cells. Several mechanisms can cause immunologic ignorance: the level of the antigen may be below the threshold required to induce the activation or deletion of T cells,20,27 antigens may be physically separated from T cells (e.g., by the blood–brain barrier) (Fig. 2),28 and antigens presented by MHC molecules in the absence of costimulation cannot induce T-cell responses.29 Furthermore, in the absence of help from CD4+ T cells, CD8+ T cells cannot damage tissue.30 Thus, self-reactive T cells do not lead to disease as long as they ignore or are kept away from self-antigens. Nevertheless, immunologic ignorance is not always beneficial. Pathogens with exclusively peripheral-tissue tropism (such as papillomavirus) and low levels of harmful antigens may also be ignored.31

Deletion

The presentation of antigens in the absence of costimulation not only fails to prime T cells but can also delete them.20,27,32 Another mechanism of peripheral deletion results from the lack of growth factors for which all activated T cells compete.33 The death of T cells is also mediated by the pathway involving Fas (also called CD95) and its ligand. Engagement of the Fas receptor induces apoptosis in Fas-positive cells.34 Since T cells express both Fas and its ligand on activation, the interaction between the two molecules can induce apoptosis.35-37 The importance of this mechanism is illustrated by the fact that patients with defective Fas have a severe lymphoproliferative disease.38,39 Some tissues, such as the anterior chamber of the eye, normally express Fas ligand.40 Consequently, when CD95+ T cells enter these tissues, they undergo apoptosis without damaging the tissue (Fig. 2). The human immunodeficiency virus subverts this mechanism by increasing the expression of Fas ligand by the macrophages it infects, thereby inducing apoptosis in T cells that come into contact with such...
macrophages. The same mechanism may allow tumor cells to escape immune surveillance.

**Regulation**

**Anergy**

T cells that do not produce interleukin-2 on encountering their antigen (and that therefore cannot be completely activated) are called anergic. Anergy may have widespread consequences, because certain anergic T cells produce interleukin-10, which suppresses the activation of T cells. No specific phenotypic markers of anergy have yet been discovered, but the availability of DNA-microarray analysis may lead to the identification of such markers.

**Inhibition**

CD152 (also referred to as cytotoxic-T-lymphocyte–associated protein 4, or CTLA-4) on T cells binds CD80 (B7-1) and CD86 (B7-2) on B cells with a higher affinity than the costimulatory receptor CD28. In this way, CD152 inhibits the activation of T cells (Fig. 2). For example, blockade of CD152 accelerates the progression of autoimmune diabetes in mice. Furthermore, the type 1 diabetes susceptibility locus IDDM5 in humans and mice cannot be dissociated in mice from the 

**Suppression and Deviation**

Transgenic mice with T cells that bear a T-cell receptor for myelin basic protein are usually healthy, because the autoreactive T cells do not cross the blood–brain barrier (immunologic ignorance). However, encephalitis develops after they receive an injection of myelin basic protein in an adjuvant. Several weeks later the disease often spontaneously remits. When these transgenic mice were genetically modified to prevent the development of normal T cells, the encephalitis that occurred after immunization with myelin basic protein did not remit. The protective T cells that caused remission of the encephalitis are CD4+ but their mechanism of action is unknown. It is likely that more than one type of cell and a variety of mol-
BREAKDOWN OF TOLERANCE
How can T-cell tolerance, induced in the thymus and then reinforced by multiple extrathymic mechanisms, be overcome and thus give rise to autoimmune diseases? One reason is that the extent of intrathymic deletion of autoimmune T cells varies. For example, the genes that confer susceptibility to autoimmune diabetes include one that determines the intrathymic level of insulin. Another mechanism is the activation of potentially self-reactive T cells in the normal repertoire by infectious agents.

Considerable evidence implicates infection as a cause of autoimmune diseases, such as multiple sclerosis and type 1 diabetes. Mechanisms that could lead from infection to autoimmunity include the release of sequestered autoantigens through tissue damage, the activation of a large fraction of the T-cell population by superantigens, and the induction of inflammatory cytokines and costimulatory molecules by microbial products. In mice, so-called bystander activation of this type can precipitate autoimmune diabetes.

Alternatively, a structural similarity between microbial and self-antigens (“molecular mimicry”) could have a key role in activating autoreactive T cells.

Indeed, some T cells can recognize both a microbial peptide and a self-peptide with a similar amino acid sequence. However, in vivo evidence that molecular mimicry precipitates autoimmune disease is lacking. Actually, a single T-cell receptor can recognize many peptides, not all of which show strong sequence homology. The idea that cross-reactivity between a microbial peptide and a self-peptide causes autoimmunity may therefore be simplistic. Infections may be capable not only of triggering autoimmunity but also of activating a protective cell population. Multiple infections during the first year of life are associated with a significant reduction in the risk of autoimmune diabetes.

Occasionally, the activation of self-reactive T cells induces only transient autoimmunity, an indication that there are additional “checkpoints” that can lead to measures to prevent autoimmune disease. Optic neuritis is a common initial manifestation of multiple sclerosis and one from which patients often recover. Yet both patients with a single episode of optic neuritis and those in whom multiple sclerosis is eventually diagnosed have T cells that recognize central nervous system antigens. In murine models of autoimmune diabetes, insulin can be detected several weeks before the onset of diabetes as frequently in male mice as in female mice, yet diabetes rarely develops in male mice. Insulin without progression to diabetes also occurs in mice with certain polymorphisms and candidate genes that influence the progression from insulitis to diabetes have been identified in mice and humans. In mice with autoimmune diabetes, T cells that enter the pancreatic islets are initially kept in check by their inhibitory receptor CD152.

Table 1 summarizes the various mechanisms that can help prevent progression to autoimmune disease.

### GENETIC SUSCEPTIBILITY TO AUTOIMMUNITY
Linkage analysis of the human genome has revealed candidate loci for susceptibility to multiple sclerosis, type 1 diabetes, systemic lupus erythematosus, and Crohn’s disease. The chromosomal regions identified in this way include some that span genes for cytokines, cytokine receptors, and other immunoregulatory molecules. Suggestive as these data are, there were major differences in the results of two studies that attempted to identify susceptibility genes for autoimmune diabetes. Moreover, in these studies and in similar studies of multiple sclerosis the only unambiguous links identified were to the HLA complex, a finding that merely confirmed previous knowledge.

The genetic analysis of a rat model of rheumatoid arthritis showed that different loci were associated with the onset of arthritis, the severity of joint erosion, and the chronicity of the disease. And genes were identified in a murine model of systemic lupus...
erythematous that conferred resistance to the disease.94 A more focused approach led to the identification of point mutations in the gene coding for a hitherto unknown transcription factor (AIRE) that causes the autoimmune polyendocrinopathy–candidiasis–ectodermal dystrophy (APECED) syndrome.92,93 Other well-defined genetic lesions occur in primary immunodeficiency94 and complement deficiency95 that increase the likelihood of autoimmunity.96

“Background” genes, which are unrelated to genes of the immune system, are important in the development of type I diabetes88 and autoimmune encephalitis. For example, two inbred strains of mice have the same MHC haplotype and have T cells that recognize the same epitope on myelin basic protein, yet one of the strains is susceptible to autoimmune encephalitis and the other is not.97,98

**THERAPEUTIC IMPLICATIONS**

In animal models, literally hundreds of therapies prevent type I diabetes, experimentally induced arthritis, chronic inflammatory bowel disease, and experimental autoimmune encephalitis.99 Yet very few, if any, of these interventions cure established disease. Therapies are needed that not only prevent T-cell reactivity but also reestablish tolerance once the autoreactive T cells have been activated and an autoimmune disease is diagnosed (Table 2). One example of immunomodulation is the treatment of patients with hemophilia. In about 30 percent of patients with hemophilia A who receive infusions of factor VIII concentrates, antibodies against factor VIII develop. To overcome the effects of these antibodies, tolerance can be induced by long-term daily infusions of large amounts of factor VIII.100 This treatment induces tolerance that lasts for years in approximately 80 percent of patients.100

Systemic injection of deaggregated antigen induces tolerance in helper T cells101 and can prevent experimentally induced autoimmune encephalitis.102 Clinical investigations of parenteral administration of peptides derived from the autoantigens thought to be involved in diabetes, various allergies, and multiple sclerosis have been performed. Whereas the prophylactic treatment of persons at risk for autoimmune diabetes yielded encouraging results,102 the beneficial effects of such treatments in patients with established disease were limited.103-105

In 1911, Wells reported that anaphylaxis could be prevented in guinea pigs by first feeding them the offending antigen.103 Oral administration of soluble collagen has prevented collagen-induced arthritis in mice,104 and oral administration of myelin basic protein and insulin has induced tolerance and prevented disease in murine models of encephalitis and diabetes, respectively.105,106 However, in another murine model oral administration of autoantigen induced autoimmune diabetes.107 Moreover, mucosal application of an autologous heat-shock protein induced uveitis in rats,108 and feeding of the central nervous system autoantigen myelin oligodendrocyte glycoprotein induced a delayed, yet exacerbated, form of encephalitis in monkeys.109 Clinical trials of oral antigen for the treatment of multiple sclerosis,110 uveitis,111 rheumatoid arthritis,112,113 and autoimmune diabetes128 have not yielded beneficial effects. The oral delivery of DNA coding for allergens has shown promising results in mice,114 as has the nasal delivery of peptides.115

A peptide that inhibits the activation of a T-cell clone is called an antagonist.116 Some viruses escape the host’s immune response by producing such antagonistic variants of important antigens,117 and the administration of antagonist peptides has prevented autoimmune encephalitis in mice.118 A drawback to this therapeutic approach is that the immune response to autoantigens in humans is polyclonal. A peptide that inhibits one clone may stimulate another. A recent phase 2 clinical trial of an altered peptide for the treatment of multiple sclerosis was halted because of exacerbations of the disease in three patients.119

**IMMUNOMODULATION**

Because treatment with antibodies against molecules important for T-cell function induced T cells to become unresponsive in rodents, several of these antibodies have been evaluated in clinical studies.100 A soluble form of CD152 inhibits the interaction of the costimulatory molecules CD80 and CD86 on antigen-presenting cells with their shared receptor, CD28, on T cells. Treatment with this form of CD152 prevented or ameliorated lupus,110 autoimmune encephalitis,115 and arthritis116 in mice. In a phase I study, this form of CD152 decreased disease activity in patients with psoriasis.117

Such an approach can, however, have unexpected effects. Blocking CD28-mediated costimulation in mice with autoimmune diabetes exacerbates rather than ameliorates the disease, seemingly because CD28-mediated signals are essential for the survival of CD4+CD25+ T cells that have been implicated in the down-regulation of T-cell–mediated immune responses.60

T cells can be categorized according to the cytokines they produce. Type 1 helper T (Th1) cells produce mainly interferon-γ, tumor necrosis factor β, and interleukin-2, whereas type 2 helper T (Th2) cells produce mainly interleukin-4, interleukin-5, and interleukin-13.118 Since multiple sclerosis and type 1 diabetes are mainly mediated by Th1 cells and allergic diseases by Th2 cells, alteration of the cytokine balance is an appealing therapeutic possibility. There is already evidence that the shift in the balance between Th1-type cytokines and Th2-type cytokines that occurs during pregnancy alleviates the symptoms of rheumatoid arthritis.119 Such changes in the cytotoxic T lymphocytes or antigen-presenting cells are achieved indirectly by altering the cytokine balance of the overall immune response. Some therapies prevent Th1 responses by blocking interferon-γ or tumor necrosis factor β, whereas others stimulate Th2 responses by blocking interleukin-12 or interleukin-23.120
The past decade has witnessed an enormous expansion in the knowledge of lymphocyte physiology. The cytokine profile may be responsible for the beneficial effects of allergen desensitization and of glatiramer acetate, a polypeptide used to treat multiple sclerosis. The subcutaneous or intrathecal application of peptide antigens, however, has had very limited success in allergic or autoimmune diseases.

Antigen-specific tolerance Parenteral application of antigen Allergen desensitization works well in many cases of allergy. The subcutaneous or intrathecal application of peptide antigens, however, has had very limited success in allergic or autoimmune diseases.

Mucosal application of antigen Although the results were promising in many animal models, clinical studies have had only limited success. A small minority of animal models, oral application of antigen caused an exacerbation of the disease in one clinical trial.

Administration of altered peptide ligands Results were promising in some animal models, but there was an exacerbation of the disease in one clinical trial.

Vaccines Vaccines may be effective in a minority of patients at high risk for autoimmunity against a known self antigen (e.g., the siblings of patients with autoimmune diabetes).

Immunomodulatory mechanisms and agents for the treatment of autoimmune disease.*

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A variety of other treatments have been tested in animals and patients with autoimmune diseases. FDA denotes Food and Drug Administration, and TNF-α tumor necrosis factor α.
and the mechanisms that induce and maintain self-tolerance. In large part this new understanding is due to technical advances such as the development of transgenic and “knockout” mice, the ability to detect and isolate rare lymphocyte populations, and “high-throughput” analysis of genetic information. Oligonucleotide arrays, which can detect several thousand genes that are expressed in healthy or diseased tissue, have been used to elucidate molecular mechanisms of the activation, tolerance, and autoimmunity of T cells. Several genes that were hitherto not suspected to participate in chronic inflammatory processes have already been identified through the use of this technique. Gene-mapping studies have demonstrated that allergy and autoimmunity must involve not only the recognition of antigen by T cells, but also the crucially important immunoregulatory effects of cytokines, inhibitory receptors, and survival factors. The challenge is to make therapeutic use of this new knowledge.

It is easy to point out disappointments encountered when treatments based on animal models were transferred to the clinic. But by no means does this end our hope for clinical applications of novel strategies that are emerging from the laboratory. Notably, interferon beta for multiple sclerosis and tumor necrosis factor alpha antagonists for rheumatoid arthritis and Crohn’s disease are the first new treatments for autoimmunity approved by the Food and Drug Administration in 20 years. Moreover, a wealth of recent data points to the importance of the innate immune system in determining whether T cells become activated and functional. This information has already been used to improve immunization strategies and should also lead to new approaches to the reinduction of immune tolerance. Finally, the characterization of self antigens that threaten high-risk groups (e.g., siblings of patients with autoimmune diabetes) could result in the development of an effective vaccine.

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REFERENCES

19. Suda T, Takahashi T, Golstein P, Nagata S. Molecular cloning and ex-
pression of the Fas ligand, a novel member of the tumor necrosis factor family. Cell 1993;75:1169-78.
35. Dhein J, Walczak H, Bäuml C, Debatin K-M, Kramer PH. Auto-
crine T-cell suicide mediated by APO-1/Fas/CD95. Nature 1995;373:
430-1.
36. Brunner T, Mogil RJ, LaFace D, et al. Cell-autonomous Fas (CD95)/
Fas-ligand interaction mediates activation-induced apoptosis in T-cell hy-
37. Jo ST, Pankiewicz D, Cui H, et al. Fas (CD95)/FasL interactions re-
quired for programmed cell death after T-cell activation. Nature 1995;373:
444-8.
38. Rieux-Laucat F, Le Deist F, Hivroz C, et al. Mutations in Fas asso-
ociated with human lymphoproliferative syndrome and autoimmune. Sci-
gen mutations impair apoptosis in a human autoimmune lymphoprolif-
40. Griffith TN, Brunner T, Fletcher SM, Green DR, Ferguson TA. Fas lig-
and-induced apoptosis as a mechanism of immune privilege. Science
41. Badley AD, Dockrell D, Simpson M, et al. Macrophage-dependent ap-
optosis of CD4+ T lymphocytes from HIV-infected individuals is mediat-
42. Hahne M, Rimoldi D, Schroter M, et al. Melanoma cell expression of
Fas(Apo-1/CD95) ligand: implications for immune tumor escape. Science
1997;278:1643-6.
43. Lamb JR, Skidmore BJ, Green N, Chiller JM, Feldmann M. Induction of
tolerance in influenza virus-immune T lymphocyte clones with synthetic
44. Jenne DE, Mennel RH. Antigen presentation by chemically modi-
fied splenocytes induces antigen-specific T cell unresponsiveness in vitro
receptor-transgenic mice: evidence for T cell energy. Eur J Immunol
cpecific for tumor-associated antigens in melanoma patients. Nat Med
A. Interleukin 10 secretion and impaired effector function of major histo-
compatibility complex class II-restricted T cells anergized in vivo. J Exp
Med 1997;185:177-83.
48. Teague TK, Hildeman D, Kedl RM, et al. Activation changes the spec-
trum but not the diversity of genes expressed by T cells. Proc Natl Acad
49. Chambera CA, Allison JP. Costimulatory regulation of T cell function.
50. Shevach EM. Regulatory T cells in autoimmunity. Annu Rev Immunol
51. Kurtzke JE. Epidemiologic evidence for multiple sclerosis as an infec-
1994;7:441.
52. Miller SD, Vanderlugt CL, Smith-Begolka WS, et al. Persistent infec-
tion with Theiler's virus leads to CNS autoimmunity via epitope sprea-
53. Perron H, Garson JA, Bedin F, et al. Molecular identification of a nov-
el retrovirus repeatedly isolated from patients with multiple sclerosis. Proc
54. Tough DF, Sun S, Sprent J. T cell stimulation in vivo by lipopolysac-
55. Infante-Duarte C, Horton HF, Byrne MC, Kamrad T. Microbial lip-
opolysaccharide induce production of IL-17 in Th cells. J Immunol 2000;165:
6107-15.
56. Kamrad T, Solorow PD, Perkins DL, Gepter ML. Pertussis toxin pre-
vents the induction of peripheral T cell anergy and enhances the T cell re-
sponse to an encephalitogenic peptide of myelin basic protein. J Immunol
57. Kliman DM, Yi AK, Beaucage SL, Conover J, Krieg AM. CpG mo-
tern present in bacteria DNA rapidly induce lymphocytes to secrete inter-
leukin 6, interleukin 12, and interferon gamma. Proc Natl Acad Sci U S A
1996;93:2879-83.
A. Maturation, activation, and in vivo protection of dendritic cells induced by
k N. Diabetes induced by Coxsackie virus: initiation by bystander damage
60. Fujimani RS, Oldstone MBA, Wroblewski Z, Frankel ME, Koprowski
H. Molecular mimicry in virus infection: crossreaction of measles virus
phosphoprotein or of herpes simplex virus protein with human intermedi-
61. Albert LJ, Inman RD. Molecular mimicry and autoimmunity. N Engl
62. Jahnke U, Fischer EH, Abvod EC. Sequence homology between cer-
tain viral proteins and proteins related to encephalomyelitis and neuritis.
63. Fujimani RS, Oldstone MB. Amino acid homology between the en-
cephalitogenic site of myelin basic protein and virus: mechanism for auto-
Arthritis induced by a T-lymphocyte clone that responds to Mycobacterium
tuberculosis and to cartilage proteoglycans. Proc Natl Acad Sci U S A 1985;
82:5117-20.
65. Hemmer B, Vergelli M, Gran B, et al. Predictable TCR antigen rec-
ognition based on peptide scans leads to the identification of antigen lig-
66. Grogan JL, Kramer A, Denko NA. Cross-reactivity of myelin basic
protein-specific T cells with multiple microbial peptides: experimental au-
toimmune encephalomyelitis induction in TCR transgenic mice. J Immunol
1999;163:3764-70.
epitopes and molecular mimics in chronic Lyme disease. Nat Med 1999;5:
1375-82.
68. Maier B, Molinger M, Cope AP, et al. Multiple cross-reactive self-lig-
ands for Borrelia burgdorferi-specific HLA-DR4-restricted T cells. Eur J
69. Gibbon C, Smith T, Egger P, Betts R, Phillips D. Early infection and
subsequent insulin dependent diabetes. Arch Dis Child 1997;77:384-
17.
peptides of myelin basic protein are found in blood and enriched in cere-
brospinal fluid in optic neuritis and multiple sclerosis. Scand J Immunol
1999;37:355-68.
polymorphism in susceptibility to spontaneous autoimmunity. Immunol
73. Pakala SV, Chivetta M, Kelly CB, Katz JD. In autoimmune diabetes
the transition from benign to pernicious insulitis requires an islet cell re-
74. Lyons PA, Hanscock WW, Denny P, et al. The NOD Idd9 genetic in-
feral influences the pathogenicity of insulitis and contains molecular vari-
75. Becker KG, Simon RM, Bailey-Wilson JE, et al. Clustering of non-


88. Men CA, Esposto L, Dunn MG, et al. A search for type I diabetes sus-
89. Elbers GC, Dymten DA. Genetics of multiple sclerosis. Semin Neur-
90. Vingos-Lundberg C, Nordquist N, Olofson P, et al. Genetic control of arthritis onset, severity and chronicity in a model for rheumatoid arthri-
91. Morel L, Tian XH, Croker BP, Wakeland EK. Epistatic modifiers of autoimmunity in a murine model of lupus nephritis. Immunology 1999;11: 
131-9.
93. The Finnish-German APECED Consortium. An autoimmune disease, 
94. Rosen FS. Autoimmunity and immunodeficiency disease. Ciba Found 
96. Mitchell DA, Taylor PR, Cook HT, et al. Cutting edge: C1q protects 
against the development of glomerulonephritis independently of C3 acti-
97. Chamaillard M, Shirwack EM, Segal EM. Regulation of interleukin (IL)-12 
receptor beta2 subunit expression by endogenous IL-12: a critical step in 
98. Anderson AC, Nicholson LB, Legge KL, Turchin V, Zaghouani H, 
Kuchroo VK. High frequency of autoreactive myelin proteolipid protein-
99. Atkinson MA, Letter EH. The NOD mouse model of type 1 diabetes: 
100. Kalden JR, Breedveld FC, Burkhart H, Burmester GR. Immunolo-
102. Keller RJ, Eisenbarth GS, Jackson RA. Insulin prophylaxis in individ-
103. Norman PS, Nicodemus CF, Creticos PS, et al. Clinical and immu-
nologic effects of component peptides in Allercat Int Arch Allergy Immunol 1997;113:224-6.
104. Barrett JH, Brennan P, Fiddler M, Silman AJ. Does rheumatoid ar-
105. Mani CA, Esposto L, Dunn MG, et al. A search for type I diabetes sus-
106. Moreland LW, Baumgartner SW, Schiff MH, et al. Treatment of rheumatoid arthritis with a vitamin-combining human tumor necrosis factor re-
chimeric monoclonal antibody cA2 to tumor necrosis factor a for 
108. The Lenenerct Multiple Sclerosis Study Group, University of British 
Columbia MS/MSI Analysis Group. TNF neutralization in MS: results of a 
randomized, placebo-controlled multicenter study. Neurology 1999;53: 
457-65.
109. Brackmann HK, Gormsen J. Massive factor-VIII infusion in a hae-
110. Mariani G, Ghirardini A, Bellocco R. Immune tolerance in hemo-
philus-principal results from the International Registry: report of the Factor 
111. Chiller JM, Habicht GS, Weigl WO. Cellular sites of immunologic 
112. Levine S, Sowinski R, Kees MW. Treatment of experimental allergic 
encephalomyelitis with encephalitic basic proteins. Proc Soc Exp Biol 
113. Wells HG. Studies on the chemistry of anaphylaxis III. Experiments 
with isolated proteins, especially those of the hen's egg. J Infect Dis 1911, 
9:147-71.
114. Nagler-Anderson C, Bober LA, Robinson ME, Siskind GW, Thor-
becke GJ. Suppression of type II collagen-induced arthritis by intragastric 
administration of soluble type II collagen. Proc Natl Acad Sci U S A 1986; 
83:7443-6.
115. Bittel DM, Whartac CC. Suppression of experimental autoimmune 
encephalomyelitis by the oral administration of myelin basic protein. Cell 
116. Zhang ZI, Davidon L, Eisenbarth G, Weiner HL. Suppression of di-
betes in nonobese diabetic mice by oral administration of porcine insulin. 
117. Genain CP, Abel K, Belmar N, et al. Late complications of immune 
and residual beta-cell function in recent-onset type 1 diabetes: a multicen-
119. Roy K, Mao HQ, Huang SK, Leong KW. Oral gene delivery with 
chitosan-DNA nanoparticles generates immunologic protection in a mu-
120. Howe GE, Pfeifer RE, Wraith DC, Thomas WR, Lamb JR. Inhi-
bition of T cell and antibody responses to house dust mite allergen by in-
halation of the dominant T cell epitope in naive and sensitized mice. J Exp 
121. Sloan-Lancaster J, Allen PM. Altered peptide ligand-induced partial 
t cell activation: molecular mechanisms and role in T cell biology. Annu 
122. Bertoletti A, Sette A, Chisari FV, et al. Natural variants of cytotoxic 
epitopes are T-cell receptor antagonists for antiviral cytotoxic T cells. Na-
123. Franco A, Southwood S, Arhenius T, et al. T cell receptor antagonist 
peptides are highly effective inhibitors of experimental allergic encephal-
tial of the myelin basic protein peptide (amino acids 83-99) in multiple 
sclerosis: results of a phase II clinical trial with an altered peptide ligand. 
murine experimental autoimmune encephalomyelitis using CTLA-4-Fc 
pathway: requirement for both B7-1 and B7-2. Eur J Immunol 1996;26: 
3239-50.
108-17.
128. Barrett JH, Brennan P, Fidler M, Silman AJ. Does rheumatoid ar-
thritis remit during pregnancy and relapse postpartum? Results from a 
national study in the United Kingdom associated with selection for late 
ison of copolymer-I-reactive T cell lines from treated and untreated sub-
jects.


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