



Protective Role of Infections and Vaccinations on Autoimmune Diseases

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Infectious agents may induce autoimmune disease through several mechanisms, notably antigen mimicry and inflammation of the target organ; conversely, infections may protect from autoimmune diseases. This paradoxical effect has been demonstrated for a number of bacteria, viruses and parasites on a variety of spontaneous or experimentally induced animal models of autoimmune diseases (e.g. experimental allergic encephalomyelitis, lupus mice, non-obese diabetic mice). The mechanisms of the protection are still ill-defined, and probably vary according to models. Stimulation of immunoregulatory CD4 T cells has been shown to play a central role in several major models. The role of superantigens is also important, like that of Toll-like receptors. Antigen competition is another major mechanism, itself open to several interpretations. Epidemiological data support a protective role of infections on human allergic and autoimmune diseases. These diseases are much more common in countries with high socio-economic development (typically Northern countries in Europe). The reason for this cannot be fully explained by genetic differences because migrating populations develop these diseases with the same incidence of the adoptive country rather than that of the country of origin. It is interesting that the frequency of these diseases has been increasing in developed countries over the last 20 years but not in undeveloped ones.

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Introduction

There is little doubt that a number of infections may trigger the onset of autoimmune diseases, as is documented in this issue of the *Journal of Autoimmunity*. This is well exemplified by the case of rheumatic fever where cross-reactivity (mimicry) between streptococcal and heart antigens induces the appearance of pathogenic anti-heart autoimmune response. Guillain-Barré syndrome is another well-documented example, even if the modalities of the mimicry are less well established. Local inflammation induced in a selected organ by viruses is another potentially important mechanism illustrated by the encephalomyelitis animal model of Theiler's disease. Note also that infections of diabetes-resistant bio breeding (BB) rats by Kilham's virus induces the onset of diabetes [1]. One might also mention the possible role of superantigens (e.g. endogenous retroviruses), as recently evoked for insulin-dependent diabetes mellitus (IDDM) [2].

Conversely data have been collected over the last decade to suggest that infections might, more

surprisingly, protect the host from the development of autoimmune diseases. This hypothesis has derived from three lines of evidence that will be the matter of this article: (1) infections may suppress immune responses directed to antigens unrelated to those borne by the pathogen; (2) infections may prevent the onset of a variety of autoimmune diseases; and (3) decreased incidence of infections represents the most likely explanation for the selective, increased frequency of autoimmune (and allergic) diseases in developed countries, leading to a North/South gradient.

Infections May Induce Immunosuppression

The most severe case of infection-induced immunosuppression is undoubtedly that of acquired immunodeficiency syndrome (AIDS), where the infection of CD4 T cells (and macrophages) by human immunodeficiency virus (HIV) leads to major depletion or functional inhibition of these cell types.

A more unexpected finding is the observation that some viral infections, which do not target the immune system, may also induce a state of deep immunosuppression. This situation has been studied in detail

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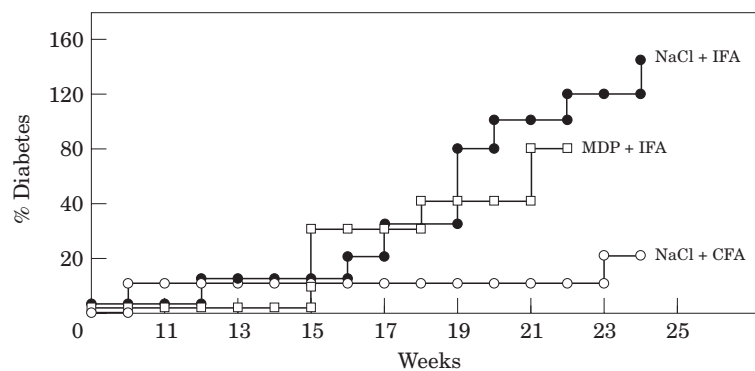


Figure 1. Prevention of diabetes in non-obese diabetic (NOD) mice by administration of complete Freund's adjuvant (CFA). No prevention is observed after administration of incomplete Freund's adjuvant (IFA) or muramyl didpeptide (MDP), an active adjuvant component of CFA (L. Chatenoud and J. F. Bach, unpublished results).

by Coutelier [3–5] in the lactate dehydrogenase virus (LDV) model.

The human counterpart of this phenomenon is the well-documented negatigation of delayed-type hypersensitivity (e.g. to tuberculin), temporarily observed during measles infection [6].

Prevention of Experimental Autoimmune Diseases by Infections

Administration of complete Freund's adjuvant (CFA) to mice 15 days before myelin basic protein (MBP) (incorporated in conventional CFA) prevents the onset of experimental allergic encephalomyelitis (EAE) [7]. Similarly, treatment of mice with staphylococcal enterotoxin B prevents the onset of EAE, probably through a superantigen effect [8].

Infection of young (NZB×NZW) F_1 mice with LDV prevents the onset of antinuclear antibodies and lupus in these mice [9].

Administration of CFA to prediabetic non-obese diabetic (NOD) mice or BB rats prevents the onset of IDDM [10, 11]. Protection is not seen with incomplete Freund's adjuvant (IFA) (without mycobacteria), and is not afforded when giving muramyl dipeptide alone, one of the adjuvant components of CFA (Figure 1). CFA shows an effect until 10 weeks of age in NOD mice [12]. A similar effect is obtained with *Mycobacterium bovis* [13] and *Mycobacterium avium* [14].

Prevention of diabetes is also obtained when NOD mice are infected by a variety of viruses including lymphochoriomeningitis virus (LCMV) [15], murine hepatitis virus (MHV) [16] and LDV [17], as well as by parasites such as *Schistosoma mansoni* [18].

These findings are in keeping with the widespread observation that specific pathogen-free NOD mice [19] or BB rats [20] show a much higher rate of diabetes than conventionally reared animals. In fact, in our own experience it was sufficient to decontaminate NOD mice bred in conventional facilities by delivering newborns by caesarean surgery and placing them in isolation to increase the 50% diabetes incidence two- to three-fold in a single generation.

Such protective role of infections on autoimmunity is not, however, an absolute rule. Contradictory findings have been reported in transgenic mice expressing an MBP specific T cell receptor (TCR) [21], and in the development of spontaneous thyroiditis and diabetes in sublethally irradiated rats [22]. One may wonder, however, whether such differences could not be explained by the somewhat artificial conditions of autoimmunity induction in these models which bypass some steps of the spontaneous autoimmune response.

Mechanisms of Infection-induced Immunosuppression

A large number of mechanisms may be proposed to explain the protective role of infections on autoimmune diseases. Mechanisms involving the immune response induced against the infectious agent will be described under the general heading of antigenic competition. Other mechanisms that may relate to a non-antigen specific effect of pathogens on the immune system will also be discussed.

Antigenic competition

The phenomenon of antigenic competition has been known for several decades [23, 24]. Basically, it is defined by the decreased immune response to an antigen B when administration of this antigen is preceded by that of an unrelated antigen A. Many studies have been devoted to the precise determination of the optimal interval between administration of the two antigens and to the types of immune responses that could elicit antigenic competition or be sensitive to its effects [23, 24].

Production of antithyroglobulin autoantibodies and subsequently thyroiditis following administration of thyroglobulin (incorporated in CFA) is significantly reduced if it is preceded by immunization against bovine serum albumin [25]. Similar results have been reported for EAE.

In the same vein, administration of bacterial extracts [26, 27] (e.g. streptococcal or *Klebsiella* extracts) prevents the onset of diabetes in NOD mice when they are given in young prediabetic mice. The same effect is obtained with mycobacteria, as mentioned above.

Phagocytic cells play a major role in the triggering and orientation of immune responses. Their solicitation by one or several infectious agents provide a sound basis for antigenic competition. The capacity of phagocytes to process antigens may be subjected to some level of saturation or pre-emption. Fc receptors may be saturated by preformed antibodies. The saturation of major histocompatibility complex (MHC) molecules is another important hypothesis that has found some experimental support [28, 29].

The presence of antigen-activated T cells, found after many infections, could also intervene, notably by consumption of some cytokines such as interleukin (IL-) 2. This mechanism has been evoked in a similar setting for uremic patients where deficient IL-2 levels are best explained by IL-2 consumption by pre-existing activated T cells [30].

Antigen competition may also be explained by the effect of various types of regulatory cells. CFA-induced diabetes protection in NOD mice is transferable to naive (non-CFA-treated) NOD mice by CD4+ T cells [12]. It was initially believed that the regulatory T cells in question were T helper (Th) 2 cells as CFA-induced protection is abolished by combined administration of anti-IL-4 and anti-IL-10 antibodies [31], this is in keeping with the polarization towards expression of Th2 cytokines in the islets [32]. The recent report that the CFA effect is not observed in interferon (IFN) $\gamma^{-/-}$ mice but is in IL-4 $^{-/-}$ (A. Rabinovitch, submitted) is against this hypothesis. If Th2 cells do play a role in antigenic competition, one would still have to explain where and how they interfere with Th1 cells which have a different specificity and homing location. Anti-infectious responses induce other types of immunoregulatory T cells such as CD8 anti-idiotypic T cells whose role is less well documented.

Non-antigen-specific mechanisms

It has been recently shown that bacterial lipopolysaccharides (LPS) could stimulate the production of various cytokines through binding and activation of Toll-like receptors on macrophages and other cell types [33–35]. Several distinct Toll-like receptors have now been recognized, and pathogen products could stimulate them, for example, CPG motifs present on bacterial DNA. The spectrum of cytokines produced in these conditions is wide and do include regulatory cytokines.

Superantigens may delete T cells harbouring the V β chain to which they selectively bind. The preventive effect of superantigens in autoimmune diseases is well illustrated by the effect on EAE of staphylococcal enterotoxin B, as mentioned above [8]. One must probably assume that such superantigen effect targets

a selective V β T cell subset involved in disease pathogenesis, the existence of which has been indicated in some models of experimentally-induced autoimmune diseases such as EAE and collagen-induced arthritis (CIA).

Viral infections usually induce the production of large amounts of IFN α and β , that may in turn regulate autoimmune responses. The regulation may be of the positive type, notably for IFN α , which has been shown to promote Th1 cell-mediated autoimmunity. It can also be negative in the case of IFN β [whose immunoregulatory properties are currently used in the treatment of multiple sclerosis (MS)]. In fact, even IFN γ may have a protector role, as illustrated in some animal models (EAE) and to a lesser extent in human autoimmune diseases [rheumatoid arthritis (RA)].

Several viruses show a clear tropism for the cells of the immune system, notably lymphocytes and macrophages. This is best documented for HIV but also applies to many other viruses such as lymphocytic choriomeningitis virus (LCMV) [36]. The depletion of the infected cells induces a decrease in immunocompetence either directly through a cytopathic or indirectly through an autoimmune response to the viral antigens expressed by the infected cells.

The Protective Role of Infections in Human Allergic and Autoimmune Diseases

There is only limited direct data showing prevention or improvement of autoimmune diseases by infections. One should mention, however, the transient improvement of nephrotic syndrome during measles infection [37], as well as the improvement of myasthenia gravis (MG) or more controversially of RA in HIV infected patients [38–40]. Arguments supporting the above hypothesis are derived from epidemiological studies developed from three sets of observations: (1) allergic and autoimmune diseases are more common in developed than in underdeveloped countries; (2) the incidence of these diseases selectively increases in these countries; (3) there is a negative correlation between occurrence of these diseases and socio-economical factors or frequency of some infections.

Epidemiological data

The incidence of most immunologically mediated diseases has increased in a very significant fashion over the last two or three decades. This applies to both autoimmune diseases (such as MS [41] and type I diabetes [42, 43]), and allergic diseases [44].

In developed areas the incidence of the major autoimmune diseases varies significantly from country to country. A large number of epidemiological studies have been devoted to the quantitative analysis of the incidence or the prevalence of the major autoimmune diseases. However, interpretable data only

exist on a wide scale for a limited number of these diseases: MS, IDDM and Crohn's disease. It has been a general finding that in both Europe and North America there is a North/South gradient with a much higher incidence in Northern countries [42, 45–47]. It is realized that the quality of epidemiological data varies with countries but the convergence of the trends noted for the major diseases mentioned above is compelling. An important and interesting exception is noted with Eastern European countries which do not fit with the North/South gradient, but this apparent exception could be explained in the discussion below for allergic diseases. Another exception is Sardinia where the frequency of both MS and IDDM is higher than that found in surrounding regions [48–50].

The data concerning allergic diseases also show a contracted pattern of incidence but with a different gradient, at least as far as Europe is concerned [44]. There has been interesting data indicating that asthma is more common in Western Germany than in Eastern Germany [51]. This is particularly noteworthy since ethnies are *a priori* very similar or identical in the two parts of Germany and pollution is at least as great if not greater in Eastern than in Western Germany.

These variations in immune disease incidence could be due to genetic factors. Indeed, Scandinavians tend to show a higher incidence of DR3 and DR4 alleles than other Europeans. However, there is no convincing data providing direct evidence for a genetic factor to explain the range of incidence differences observed. Conversely there are more data suggesting the predominant role of environmental factors. Studies of migrating populations indicate that the disease incidence is that of the country where the people have emigrated rather than that of the one from which they originate if migration occurred before adolescence. This has been shown in particular for MS and IDDM [52–54].

Interpretation

The most important question is to determine which factors in the environment could be responsible for these differences in disease incidence. A number of hypotheses have been proposed, some on the basis of specific data.

The role of socioeconomical factors has appeared as a major possibility. In fact, the correlation between such factors and disease incidence was directly demonstrated in several studies dealing with IDDM [55] and allergy (Germany) [51]: disease incidence is lower in populations with a low income. However the nature of the link between such socioeconomical factors and disease incidence is unknown. It could be possible that lower hygiene, education and medical care conditions and the increased risk of intrafamilial contamination is higher in people living in low economic standards but other interpretations are possible.

The role of temperature has been emphasized [56, 57]; the average temperature is obviously lower in

the North than in the South, and this could favour prevention of microbial proliferation.

Many other differences exist, known and unknown, and direct prospective studies are needed to test further the hypothesis within a given population. It is interesting though that the theory discussed above is compatible with all these data. In fact there are some results that bring further support to the plausibility of the hypothesis. In particular, there is a South/North gradient of some common infections such as hepatitis A. The frequency of anti-hepatitis A virus (HAV) antibody carriers is the mirror image of that of IDDM or MS in Europe [47]. This is of course not to say that HAV protects from these diseases but rather that HAV is possibly a marker of some common waterborne infections with contrasted distribution over countries.

The Role of Vaccinations

The potential role of vaccinations in stimulating the onset of autoimmune diseases has been advanced on the basis of very limited and questionable evidence. Even if there is immunological basis for such an effect, secondary to antigen mimicry or tissue contamination of the vaccine as in the case of post-rabies vaccine, the predisposing effect of vaccination on autoimmune diseases remains elusive. It is interesting in the context of the hypothetical protective role of infections presented above to discuss the potential influence of vaccination on autoimmune diseases which could be of two very different natures.

One might assume that vaccinations have a negative role by preventing the onset of the protective infections. This is probably unlikely in view of the limited number of infections protected by vaccination among all other current infections. This argument is probably much more valid for widespread antibiotic treatment, as currently applied in most developed countries.

Alternatively, one may assume that vaccination may contribute to the stimulation of the immune system secondarily to the repeated injections of the vaccine with their adjuvant. In fact, two vaccines have been evaluated for the prevention of diabetes in children at risk of developing the disease, BCG [58–61] and Q fever vaccine [62]. The problem however may be that these vaccinations are not given in a repeated fashion, and that isolated immune stimulations may not be sufficient to generate protective mechanisms as obtained in experimental models.

Therapeutic Perspectives

A logical application of the above concepts is to attempt testing the efficacy of *de novo*-induced infections (or immune stimulation) in order to prevent the onset or the progression of autoimmune or allergic disease. This approach would have the double interest of testing the hypothesis discussed in this paper in a direct prospective fashion, and even more importantly

to open new perspectives in the prevention of these diseases.

Unfortunately, prospective clinical trials are difficult to organize in man for several reasons. First, the number of subjects to be included would need to be very large (several thousand) because of the relatively low incidence of the diseases in question and the trials would be very lengthy because of the long follow-up needed to see the appearance of the disease in the control group. Second, one would need a totally harmless treatment since the subjects to be treated would be healthy and would remain so for most of them even if one focuses the study to high-risk subjects (for example relatives of patients with the disease). Additionally, one has to be aware of the risk of undesirable exacerbation of the autoimmune or allergic potential, as has been suggested for some vaccinations (although on a very loose basis).

To circumvent these difficulties two complementary approaches should be considered: first, develop further experimental studies using the exact conditions of a human clinical setting; second, use products that have been proven to be totally innocuous in extensive clinical trials.

In spite of these problems, the question is sufficiently important to warrant further thinking.

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