Physiological Basis of T-cell Vaccination against Autoimmune Disease

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T-cell vaccination denotes a procedure whereby autoimmune T cells are administered to individuals in a way that induces active resistance to a specific autoimmune disease, the disease with which the T cells are associated (Ben-Nun et al. 1981a; Cohen 1986). T-cell vaccination is analogous to the use of attenuated or avirulent microbes to specifically immunize individuals against the disease caused by the particular virulent microbe, except that here the vaccine is a population of T cells and the pathogens to be controlled are not foreign microbes but endogenous clones of autoimmune lymphocytes.

In T-cell vaccination, the antigens are specific T cells and, as I discuss here, the responders are T cells. The vaccination phenomenon thus is a special case of T cells recognizing T cells or, more specifically, autoimmune T cells recognizing autoimmune T cells.

The aim of this paper is to review the results of experiments, particularly those not yet published or about to be published, that document the effectiveness of T-cell vaccination in treating autoimmune diseases (that it works) and shed light on the mechanisms of resistance mobilized by T-cell vaccination (how it works). Finally, I discuss new observations relating to the physiological basis of T-cell vaccination (why it works).

EXPERIMENTAL PROCEDURES

T-cell lines and clones. Autoimmune lines and clones of the $CD4^+$ $CD8^-$ phenotype were raised and maintained as described previously (Ben-Nun et al. 1981b; Ben-Nun and Cohen 1982a; Holoshitz et al. 1984; Vandenbark et al. 1986).

T-cell vaccination. Cells activated by incubation with specific antigen or with the T-cell mitogen, concanavalin A (Con A) (Naparstek et al. 1983), were inoculated (10×10^6 to 20×10^6) subcutaneously or intraperitoneally into recipient Lewis rats after treatment with gamma radiation (2500 rads) (Ben-Nun et al. 1981a) or the chemical cross-linker glutaraldehyde (0.3%) (Lider et al. 1987). Vaccination was also done using subpathogenic doses (10^2–10^4) of virulent T cells (Lider et al. 1988, 1989; Beraud et al. 1989).

Autoimmune diseases. Acute monophasic experimental autoimmune encephalomyelitis (EAE) was induced actively in Lewis rats by immunization to myelin basic protein (BP) emulsified in complete Freund's adjuvant (Ben-Nun and Cohen 1982b) or by intravenous inoculation of 1×10^6 to 10×10^6 activated, virulent anti-BP T cells (Ben-Nun et al. 1981b). Adjuvant arthritis was induced in Lewis rats by active immunization to 1 mg of pulverized, killed *Mycobacterium tuberculosis* organisms (H37Ra) (MT) in oil (Holoshitz et al. 1983b). Insulin-dependent diabetes mellitus (IDDM) occurs spontaneously in mice of the NOD strain, beginning at about 4 months of age and reaching a peak incidence at about 8 months of 90% in females and 50% in males (Rossini et al. 1985).

RESULTS

Therapeutic Effectiveness of T-cell Vaccination

Investigation of T-cell vaccination has taken two divergent but complementary routes. One path of research is utilitarian; it is directed to exploiting its potential as a specific therapy for clinical autoimmune disease. The other path of research can be called basic; it aims at elucidating the cellular and molecular basis for the phenomenon and to see what the process can tell us about the physiology of immune regulation. Neither path is a detour.

The utilitarian path has led to a number of empirical observations. It was discovered that no T cell would induce resistance to an autoimmune disease unless it was activated before inoculation into the recipient. Activation is accomplished by incubating the particular T cells with their specific antigen or with a T-cell mitogen, such as Con A (Naparstek et al. 1983). The changes resulting from activation critical for vaccination are yet unknown but require about 6–8 hours of culture in vitro.

Even after activation, not all CD4 T cells appear to be capable of vaccinating. However, it was discovered, again empirically, that the effectiveness of vaccination can be enhanced considerably by treating the activated T cells with agents that cause aggregation of components of the cell membrane (Cohen 1986). At present, the simplest way to produce this aggregation is to treat the activated T cells with chemical cross-linkers such as glutaraldehyde or formaldehyde (Lider et al. 1987). Cross-linking is useful clinically because as it improves their ability to vaccinate; the treatment kills the autoimmune cells and inactivates any virus or oncogene that might inadvertently be expressed in them.

The utilitarian aim has two components: safety and effectiveness, both of which can be related to immunological specificity. T-cell vaccination is relatively specific; the vaccine is most effective when it contains the T cells to be controlled. It was seen, for example, that two T-cell lines responding to two different BP molecules, bovine or guinea pig, each vaccinated rats against EAE induced by immunization with the specific type of BP (Holoshitz et al. 1983a). This early observation was compatible with a mechanism of anti-idiotype immunity. The T-cell vaccine, however, was effective even if the specific autoimmune T cells were only a small part of the administered cells; antigen-primed lymph node cells, not only defined lines or clones, were found to vaccinate effectively against disease (Lider et al. 1987; Cohen 1988).

Since only activated T cells serve as effective vaccines, a relatively specific T-cell vaccine can be formulated from a mixed population of T cells by using the specific antigen to activate primarily the desired autoimmune T cells. The nonresponding T cells specific for other antigens, T cells whose functions might be best left intact, would not effectively arouse an anti-idiotypic response because they would not be activated by the autoantigen. Nevertheless, the specific autoantigen in many human autoimmune diseases is not known. How, then, can one construct a specific vaccine without the specific autoantigen?

This question was studied by F. Mor in our laboratory (F. Mor et al., in prep.). Mor was able to exploit the fact that T cells already having been activated in vivo transiently enjoy a growth advantage over naive T cells upon culture in vitro with a T-cell mitogen. Using a limiting dilution analysis, Mor found that the frequency of MT-specific T cells obtained from arthritic rats increased about 40-fold after one cycle of activation in vitro with Con A (from ~1:1000 to 1:25). Similarly, activation with Con A increased the frequency of BP-specific T cells obtained from rats with EAE.

Drawing on this information, D. Elias and A. Lohse (D. Elias et al., in prep.) were able to vaccinate therapeutically NOD mice against autoimmune diabetes, a disease whose target antigen is unknown. We reasoned that the spleen cells of 4-month-old NOD mice, a period of marked insulitis preceding clinical diabetes, would contain specific autoimmune T cells since such cells can transfer disease (Bendelac et al. 1987). We therefore cultured the spleen cells with Con A in the manner of Mor, hoping to augment the concentration of the unidentified autoimmune T cells while activating them. The cell population was then treated with a chemical cross-linker to attenuate the cells and aggregate their membrane components. Groups of 12–14 NOD mice, males or females, were sham-vaccinated or vaccinated with the treated spleen cells (5×10^6) at 6 weeks of age, the onset of insulitis, and three more times at monthly intervals. At the age of 8 months, the sham-vaccinated mice showed the expected incidence of diabetes, approximately 50% for males and 90% for females. In contrast, the T-cell-vaccinated males had no diabetes, and only 25% of the treated females were ill.

These results indicate that T-cell vaccination can be therapeutic in spontaneous autoimmune disease, using a vaccine made from the T cells of autoimmune animals without specific antigen. Results such as these, combined with a lack of toxicity, suggest that the T-cell vaccination might indeed have utilitarian value in clinical disease.

Mechanisms of Resistance: Anti-idiotypic T Cells

T-cell vaccination raises many difficult questions about underlying mechanisms responsible for the observations. What are the molecular signals borne by the vaccine? What does cell activation contribute? Why do some T clones require treatment with chemical cross-linkers, whereas others vaccinate without membrane aggregation? How are the vaccinating signals processed, presented, and received?

The immunologically specific resistance resulting from T-cell vaccination seems to involve anti-idiotypic T cells. O. Lider et al. (1988, 1989) demonstrated that T-cell vaccination with lines or clones led to recipient T-cell proliferative responses that were much greater to the vaccinating T cells than they were to syngeneic CD4 T clones of unrelated specificity. To analyze this anti-T-cell response, we vaccinated rats in the hind footpads with anti-BP T cells and studied the response of the draining lymph nodes. Anti-idiotypic proliferative responses appeared in the popliteal lymph nodes about 5 days after vaccination and then spread systemically several days later (Lider et al. 1989). Removal of the anti-idiotypic lymph nodes before systemic spread robbed vaccinated rats of their protection to EAE, whereas transfer of the lymph node cells to naive recipients transferred protection. Thus, resistance to EAE appeared to be a function of the anti-idiotypic lymph node population. Cloning of the anti-idiotypic cells yielded CD4 anti-idiotypic T cells that stimulated the anti-BP T cells in vitro and CD8 anti-idiotypic T cells that suppressed the anti-BP T cells in vitro (Lider et al. 1988). Sun et al. (1988) have shown that CD8 anti-anti-BP T cells can actually suppress EAE in vivo. Thus, anti-idiotypic T cells, stimulated by T-cell vaccination, might indeed contribute to resistance to disease.

How anti-idiotypic T cells regulate autoimmune effector T cells is not clear. The CD8 anti-idiotypic T cells studied by Sun et al. (1988) were specifically cytotoxic to the anti-BP T cells in vitro, suggesting that resistance to EAE might involve cytotoxicity in vivo (Sun et al. 1988). Killing of the autoimmune T cells, however, cannot explain the observation that virulent anti-BP T cells persist in rats that have acquired resistance to EAE (Ben-Nun and Cohen 1982b; Naparstek et al. 1982). It seems that anti-BP T cells can survive in rats in a quiescent or suppressed state (Cohen 1986).

W. van Eden (unpubl.) has found in cell-culture experiments that the lymph node cells of vaccinated rats suppress the proliferation to antigen of idiotype-positive T cells but do not suppress syngeneic T-cell clones responding to other irrelevant antigens. However, adding the idiotype-specific T cells to the cultures induces the anti-idiotypic lymph node cells to suppress the responses of unrelated syngeneic T cells to their antigens. Thus, a specific idiotype can activate anti-idiotypic T cells to produce a suppressive effect on adjacent T cells that is not immunologically specific.

Specific triggering of a nonspecific effect could also account for the surprising fact that vaccination with a single T clone can induce resistance to adjuvant arthritis caused by immunization to MT (Lider et al. 1987). Clone A2b, recognizing a 9-amino-acid peptide in the sequence of the MT 65-kD heat-shock protein (hsp65) (van Eden et al. 1988), can be used to either prevent arthritis or induce remission of established arthritis (Lider et al. 1987). Recently, D. Markovits (unpubl.) has isolated a new T-cell line specific for the hsp65 molecule, designated M1. M1 recognizes a peptide sequence other than that recognized by A2b. In addition, M1 and A2b do not share idiotypes; anti-idiotypic T cells responding to either A2b or M1 do not recognize the other clone. Nevertheless, M1 can vaccinate rats against arthritis at least as efficiently as clone A2b does, implying that the same autoimmune disease can be regulated by different anti-idiotypic T cells.

It is conceivable that both A2b and M1 represent common idiotypes that appear together in lesions of arthritic rats. Therefore, an anti-idiotype specific for either one could affect all of the T cells in the lesion by releasing the putative nonspecific suppressor lymphokine.

Anti-ergotypic T Cells

In addition to the evidence for anti-idiotypic T cells outlined above, A. Lohse and other investigators in the laboratory have detected a second type of T-cell response that could contribute to the effect of T-cell vaccination. We have termed this type of response anti-ergotypic (ergon = activity or work) because it seems to recognize the state of activation of the target T cell not the idiotype (Lohse et al. 1989). These studies were initiated by the observation that along with the specific proliferative response to the T clone used for vaccination, the T cells of vaccinated rats often showed a lesser degree of proliferation when stimulated by syngeneic T cells of diverse unrelated specificities (Lider et al. 1989). Lohse isolated the nonspecific T blasts and found that they responded to any activated syngeneic CD4 T cell, regardless of its specificity, but not to resting syngeneic T cells. In contrast with anti-ergotypic T cells, anti-idiotypic T cells respond to both resting and activated T cells. Anti-ergotypic T cells, which include CD4 and CD8 T cells, seem to be important because they are capable of suppressing autoimmune diseases upon inoculation into recipients. For example, an intraperitoneal injection of 10^7 isolated anti-ergotypic T blasts can protect syngeneic Lewis rats against either adoptive EAE produced by intravenously transferred anti-BP T clones or active EAE induced by immunization to BP (Lohse et al. 1989). The response of T cells to syngeneic-activated T cells has been noted by other investigators in the past (Damle and Gupta 1982). The present findings indicate that such cells can regulate an autoimmune response in vivo. It is conceivable that anti-ergotypic T cells might function physiologically as negative feedback on immune responses generally. Nevertheless, the efficiency of idiotype-specific T-cell vaccination is clearly much greater than nonspecific anti-ergotypic vaccination. Anti-BP T cells vaccinate strongly against EAE but negligibly against arthritis, and anti-hsp65 T cells vaccinate strongly against arthritis but negligibly against EAE (Lider et al. 1986). The relative weakness of vaccination with immunologically nonspecific, activated T cells may be because the anti-ergotypic response, unlike the anti-idiotypic response, does not persist beyond several days and does not appear to have a memory (A. Lohse et al., unpubl.). Indeed, to observe suppression of EAE, the anti-ergotypic T cells had to be amplified in vitro and transferred to recipients as a concentrated cell population. However, as idiotype-specific T-cell vaccines mobilize both anti-idiotypic and anti-ergotypic mechanisms, some nonspecific effects of T-cell vaccination might be detectable, at least transiently. The significance of this in clinical T-cell vaccination remains to be seen.

Physiological Basis of T-cell Vaccination

In T-cell vaccination, does the autoimmune T cell merely serve as a conventional immunogen or is it a signal for implementation of a naturally prearranged program? Is T-cell vaccination pharmacology or physiology?

A number of observations suggest that the immune system is preprogrammed to receive the autoimmune T-cell vaccine. The mass of vaccinating T-cell antigen can be remarkably small: As few as 10^4, 10^3, or even 10^2 anti-BP T-clone cells can induce resistance to an otherwise lethal dose of millions of virulent anti-BP T cells (Beraud et al. 1989). The lag time for the anti-idiotypic response may be as short as 4 or 5 days (Lider et al. 1989). A de novo immune response to a conventional antigen might be expected to require more antigen and more time to produce such marked effects.

Another indication that the autoimmune idiotype may be a signal and not merely an antigenic structure is the requirement for cell activation; 5×10^7 nonactivated T cells do not induce a detectable anti-idiotypic response, whereas 10^4 activated T cells do. Apparently, it is not the amount of the idiotypic structure alone that triggers the system but its combination with additional signals. Perhaps the system is built to deal with activated autoimmune T cells that require attention, not with quiescent ones that cause no harm.

Direct evidence for the preexistence of selected anti-idiotypic networks has been obtained in our laboratory by N. Karin et al. (in prep.). Karin induced adjuvant arthritis by immunizing rats to whole MT and investigated the evolution of T-cell proliferative responses in the draining lymph nodes to the hsp65 molecule and to other MT antigens and to various clones of syngeneic T cells. Remarkably, Karin found that 4 days after immunization to MT, the lymph node cells responded strongly to the M1 anti-hsp65 T-cell line. This anti-anti-hsp65 response was all the more striking because the response to hsp65 and to other MT antigens was barely detectable. By day 10, the responses to MT antigens became greater than the response to the M1 line although the anti-M1 response continued to rise.

More experiments must be done to document the details of the evolution of the T-cell response to hsp65 and to the M1 T-cell line. Nevertheless, it seems that an anti-idiotypic response to M1 might actually precede, at least in its magnitude, the response to the hsp65 antigen itself.

Karin found that the anti-anti-hsp65 response was selective; it was directed to M1 T cells but not to A2b T cells, which recognize a different epitope on the hsp65 molecule (N. Karin et al., in prep.). Thus, the arthritogenic hsp65 antigen may actually impinge on a preformed anti-idiotypic network.

In addition to the networks associated with the BP and hsp65 molecules described here, we have detected a natural, preexisting network related to the autoimmune response to insulin (Shechter et al. 1982, 1988; Cohen et al. 1984). Autoimmune networks related to acetylcholine (Cleveland et al. 1983) and to thyroid-stimulating hormone (Farid 1988) also have been described.

These immune networks and, in fact, any network may be viewed as a ready-made system for channeling information into prearranged categories. Antigens for which anti-idiotypic networks exist will be dealt with in ways different than other antigens. The system seems to anticipate such antigens, i.e., the existence of a preformed anti-idiotypic network constitutes a representation of the antigen already encoded in the system. Elsewhere, I have referred to the set of network-encoded antigens as the immunological homunculus (Cohen 1989). The term is derived from the neurological homunculus, the representative of the body mapped onto the motor and sensory cortices of the brain, which allows the nervous system to organize and structure neurological experience and activity related to self. So, too, might the immunological homunculus of preformed networks serve as a reference library directing the attention of the immune system to selected self-antigens.

The long-standing belief that self-tolerance is based on deletion of the T-cell receptor repertoire has now been demonstrated experimentally, at least for some self-antigens (von Boehmer et al. 1989). However, major histocompatibility complex (MHC) restriction in or out of the thymus cannot account for the immunological dominance of some self-antigens, a dominance that cuts across individuals and species. For example, BP is the dominant antigen in the central nervous system for mice and rats, dogs and cats, and monkeys and humans. The MHC appears to determine which peptides will be chosen for the T-cell response, but the dominance of the BP molecule seems to be independent of the MHC. Likewise is the immunological dominance of the hsp65 molecule (Young et al. 1988) or the array of lupus antibodies shared by mice and humans (Mendlovic et al. 1989). Perhaps these particular self-antigens are dominant across MHC alleles and species because preformed networks have already encoded them in the various immune systems. The systems are therefore compelled to give these antigens undivided attention. MHC gene products will only restrict the response to particular segments of the antigen; the dominance of the molecule as a whole, irrespective of peptide restrictions, is apparently not the business of the MHC.

Obviously, to say that preformed networks are responsible for the uniformity of autoimmune responses merely prompts the question of why some autoantigens have dominating networks and others do not. Recently, it has become apparent that the major autoantigens monotonously chosen for autoimmune attack are functional molecules: receptors (myasthenia gravis, Grave's disease), hormones (type 1 diabetes), or enzymes (autoimmune thyroiditis, autoimmune liver disease). Regrettably, a function for BP has yet to be defined. However, heat-shock proteins, now beginning to be associated with autoimmunity (Minota et al. 1988; Res et al. 1988; van Eden et al. 1988), must have very important functions because they are highly conserved throughout biological evolution from prokaryotes to humans (McMullin and Hallberg 1988). These observations suggest that the dominant autoantigens may achieve their status by virtue of their functions. How the physiological functions of various self-antigen molecules might influence the network organization of the immune system is an open question.

Irrespective of how self-antigen networks may arise, their malfunction may produce disease. For example, Mendlovic et al. (1988, 1989) found that administering the 16/6 human idiotypic anti-DNA antibody to some strains of mice can unleash full-blown systemic lupus erythematosus with all of its attendant autoantibodies. These mice with idiotype-induced lupus are not of strains that develop lupus spontaneously and do not respond to immunization to DNA itself. Thus, an idiotype interacting with its network can generate a more powerful response than the putative antigen itself does.

Antibodies to the insulin receptor may arise through anti-idiotypic networks in both mice (Cohen et al. 1984) and humans (Shoelson et al. 1986). Moreover, the human and mouse antibodies share idiotypes (Elias et al. 1987). Thus, dysfunction of a network might produce a particular autoimmune disease and also account for the characteristic dominance of its target antigen. A healthy network ideally should prevent disease.

The fact that T-cell vaccination can be effective in preventing or inducing remission of established autoimmune disease is valid, irrespective of whether natural networks are involved in autoimmunity in the real world. Nevertheless, it would be fortunate if T-cell vaccination derived its effectiveness from its ability to exert control through manipulation of preexisting T-cell networks. The network whose malfunction was responsible for initiating the disease might be the most efficient network to control the disease, once its regulatory anti-idiotypic T cells have been augmented by T-cell vaccination. Physiology should promote utility.

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