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Preventing and treating chronic disorders using the modified vaccination technique

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1. ABSTRACT

It is anticipated that the ultimate solution for the prevention and termination of autoimmune disorders will be based on somehow manipulating the cells of the immune system to attain antigen (ag) specific downregulation and termination. In the last few years we have developed a new vaccination technique that we call "modified vaccination technique" (MVT). It has with equal effectiveness both prevented and terminated autoimmune disease causing events in an experimental autoimmune kidney disease model. We expect that our technique will be similarly applicable to the specific treatment and cure of numerous other chronic disorders presently treated only by drugs. The vaccine is composed of two components, an ag and a specific antibody against it. When these are combined at slight ag excess they constitute a vaccine which is capable of treating chronic ailments by redirecting immune response outcomes in the vaccinated host. Both components, like drugs, will have to be produced *ex vivo* in order to maintain uniformity, safety, efficacy, and specificity.

2. INTRODUCTION

The medications (*i.e.* drugs) presently used to treat patients for chronic ailments are nonspecific in their actions and can cause undesirable side effects. Even the monoclonal antibodies (abs) that have recently been produced for the treatment of certain disorders are nonspecific. Many, like Rituximab (1-4), control the progression of a disease by nonspecifically depressing the immunological cell lines that maintain the disease. The process affects not only those cells that contribute to the disease per se or to its progression, but also numerous other cell lines that are vitally important for normal immune system response against exogenous and endogenous antigens (ags).

Medication, monoclonal abs, and active and passive immunization programs have their roles to play in preventing, treating, and controlling numerous disorders. In the past few years, however, it has become evident that the prevention and cure of both endogenous source ag initiated and maintained disorders and chronic infections

require a different approach (5-11). It is apparent from the medical literature that the solution for curing autoimmune disorders might very well lie in somehow influencing the immune system's cell lines by the appropriate presentation of the ag against which we want to upregulate (cancer, agents causing chronic infection) or downregulate (autoimmune diseases) an immune response.

We have developed a vaccination program, namely modified vaccination technique (MVT) (12,13). In a milder form of Heymann nephritis (HN) called slowly progressive Heymann nephritis (SPHN) (14), our MVT prevented the development of severe HN kidney lesions (12,15,16). When employed after the induction of SPHN, it terminated the pathogenic Immunoglobulin G (IgG) autoantibody (aab) mediated disease processes (15).

We have successfully employed the MVT in different situations (12,16,17) and found that it provided the desired immune response outcome in each case; namely downregulation or upregulation of immune events. This third method of vaccination (active and passive immunization being the other two) for the first time offers hope for the equally effective prevention and termination of endogenous source ag induced disorders and diseases caused by chronic infections.

3. BACKGROUND TO AUTOIMMUNITY

The key to preventing and curing chronic ailments (autoimmune diseases, cancer) is to determine the underlying immunological mechanisms responsible for the disease. The immune system is comprised partly of a complex autoimmune network that deals with endogenous source ags (18-23). Because of the complexity of the network, consensus as to the etiology, pathogenesis, prevention, and treatment of various autoimmune disorders has not yet been reached (24-28). However, the many publications on the topic provide insight into the beneficial aspects of autoimmunity. Certain observations provide encouraging prospects for working with these beneficial aspects (6,7,11,29). For example, there is evidence that by manipulating the immune system, autoimmune disorders could be terminated without employing immunosuppressive and cytotoxic agents (14).

The question is how to present the appropriate ags to the cells of the immune system to evoke favorable responses, (a) specifically downregulating and terminating the disease process in autoimmune disorders, and (b) specifically upregulating lytic aab production to eliminate corrupt cells no matter where in the body they are located as in cancer.

The many attempts at treating autoimmune diseases and cancer by immunological and other means attest to the present reality that the task is not easy. Various methods of ag specific prevention and termination of autoimmune disease causing processes have already been tried (7,8,11). While many of the techniques have achieved prevention, none, whether in experimental animals or in patients with autoimmune diseases, has attained satisfactory outcomes evidenced by discernable experimental or clinical results such as functional or morphological improvements (10,30-34).

Our expertise is in an experimental autoimmune kidney disease called HN (35), which has two variants. The first variant is called active HN. This experimental kidney disease model was described by Heymann and colleagues in 1959 (35). The disease is produced by IP injections of renal tubular ags in Freund's complete adjuvant, causing immune complex (IC) glomerulonephritis associated with proteinuria in a susceptible strain of rats (36). The second variant of active HN is called SPHN, as described recently by us (37). SPHN is induced by injections of renal ags in alum or of aqueous chemically modified renal tubule ags (14,37).

While typical morphological and functional changes can be studied very well in HN, this autoimmune kidney disease cannot be successfully treated by any of various means because of its rapid progression (38-45). SPHN, on the other hand, progresses more slowly, as its name indicates, and therefore it allows more time to investigate various treatment options, including the manipulation of the cells of the immune system by various means (12,15).

In SPHN we have investigated the new vaccination technique that we call MVT. The investigation entailed injecting ICs composed of the nephritogenic ag and specific Immunoglobulin M (IgM) ab directed against it at slight ag excess, at weekly intervals either pre and post induction of SPHN or post induction only. In the former case we managed to prevent the disease from occurring; and in the latter, where the progressive autoimmune kidney disease was already underway, we were able to terminate the immunopathological processes that were responsible for maintaining it (12,15).

The rationale behind successfully preventing and/or terminating autoimmune disease causing and maintaining events is based on previous observations and findings especially of Weir and associates (46,47), and also by Grabar (48) and others. Weir and colleagues have described the presence and role of naturally occurring IgM aabs in the circulation, and have shown conclusively that experimental animals have specific IgM aabs in their circulations against intracytoplasmic organelles. The role of these specific IgM aabs is to assist in the removal of liberated intracytoplasmic components from the circulation following injury to cells by trauma, chemicals, toxic compounds, drugs, and ischemia, or from cells at the end of their lifespan etc. These scientists have subscribed to the view that in a physiological sense we are not tolerant to our intracytoplasmic components, and naturally occurring specific IgM aabs carry out a physiological role by assisting in the removal of cellular waste (47).

By removing intracellular breakdown products quickly and efficiently, IgM aabs serve at least four very important functions:

1. they preclude toxic accumulation of cellular waste;

2. they prevent possible chemical modifications of released intracytoplasmic ags;
3. together with macrophages they assist in the reutilization of large MW subcellular components by breaking them down into reusable small MW components; and
4. they maintain tolerance against "self" components.

Following injections into normal rats of ICs composed of high titred specific IgM abs (directed against the nephritogenic ag) and nephritogenic ags at slight ag excess:

- specific IgM aab cell lines were stimulated to produce elevated levels of IgM aabs against the nephritogenic ag;
- specific IgM aabs were produced rapidly, since rats are not tolerant to the nephritogenic ag (secondary ab response); and
- high levels of circulating IgM aabs were maintained by weekly injections.

By being able to react with the released native autoantigen (aag) from the renal tubules and also with the modified renal ag that causes the disease, these specific IgM aabs (rat anti-renal tubular ag IgM aabs) neutralize and assist in the elimination of both modified and native disease causing and maintaining ags.

4. THE BENEFICIAL ASPECTS OF IMMUNE COMPLEXES IN INITIATING AND MAINTAINING PREDETERMINED IMMUNE RESPONSE OUTCOMES

In experimental animals we have investigated the effect of the injected ICs in redirecting immune response outcomes using tissue derived ags and abs produced in donor animals. While such components are very effective in specifically downregulating and upregulating immune responses against target ags (15), they cannot be employed to treat humans with chronic ailments. To prevent and/or treat human disorders it is necessary to produce the essential ags and abs *ex vivo*, by available techniques, so as to provide consistently uniform, safe, pure, and potent products.

4.1. The biologics needed to make up the relevant immune complexes to combat human chronic disorders

4.1.1. To prevent or treat/terminate autoimmune diseases

- the aags that contribute to the autoimmune disease will have to be made by various chemical procedures to provide pure chemical compositions equivalent in MW and structural make up etc. of the target aag (49,50);
- the IgM aabs required to prevent or treat autoimmune diseases will have to be made by monoclonal ab techniques (51);

4.1.2. To prevent or treat/terminate cancer

- cancer specific ags will have to be constructed by presently available and by improved future technologies that will be able to provide absolutely pure cancer specific ags (52,53);
- specific lytic abs against cancer specific ags residing on cancer cell surfaces will have to be produced by monoclonal ab techniques (54).

4.1.3. To prevent or treat/terminate presently incurable chronic diseases

- antigenic component(s) responsible for the invading organism establishing and maintaining a chronic disease must be identified and chemically produced;
- specific abs against the target ag(s) could be produced either by monoclonal ab techniques or in genetically programmed animals able to produce humanized specific abs.

To prevent interference with vitally important immunological cell lines (*i.e.* suppressing, upregulating, or eliminating them) precise preparatory techniques must be employed to produce specific tissue ag equivalent composition(s) and specific ab(s) against the target ag(s) before implementing the MVT to prevent and treat autoimmune diseases and cancer in humans. Furthermore, such production will have to meet the detailed procedural descriptions and protocol approvals of regulatory bodies. This means that in the future:

- all the target ags (exogenous and endogenous) will have to be produced to meet the highest standards as far as their composition, purity, safety, efficacy etc. are concerned; and
- corresponding abs against the target ags will have to be made by monoclonal or by other production technologies.

The biologics produced by the various techniques should have the same stringent regulatory requirements as for manufactured drugs.

5. PERSPECTIVES

Autoimmune diseases and cancer are presently treated with immunosuppressive and cytotoxic agents (55,56). These medications are nonspecific in their actions and can cause numerous side effects of which infection-caused complications are the worst. Yet these agents have to be employed in the treatment of patients as there is currently no alternative for interfering with the pathogenic autoimmune disease causing immune events that maintain their diseases.

We have noted and described how specific ICs can be produced to correct autoimmune system breakdown related irregularities (12,15). There are two possible major irregularities of the autoimmune system that can lead to

major structural and functional disturbances of tissues and organs in the affected host. One of these, which is produced by a pathogenic immune response against self components, causes an autoimmune disease. The other, because pathogenic immune responses against cancer specific ags on cancer cell surfaces do not generally occur, allows unhindered multiplication of cancer cells. In the first instance, pathogenic immune responses against self components cause harm; and in the second instance, pathogenic immune responses against cancer-specific ags terminate cancer cell growth/spread.

Weir and colleagues showed that released intracytoplasmic ags are assisted in their removal by specific IgM aabs (46). These aabs are able to remove native, modified, and native-like (molecular mimicry) ags from the circulation and thereby prevent disease causing pathogenic IgG aab production (12). The beneficial autoimmune events that keep our inner environments free of accidental mishaps are operating at all times under normal conditions. When unusual presentation of self ags, e.g. in SPHN, overwhelms the clearing processes that normally would remove native and modified cell breakdown products, then a genuine manifestation of an autoimmune disease condition can occur by the modified aags inducing and maintaining a pathogenic aab response.

We understand both the immune events that cause an autoimmune disease and those that are responsible for the prevention or termination of autoimmune disease processes in the experimental autoimmune kidney disease model SPHN (12). We have shown how immunopathological events can be prevented prior to the initiation of an experimental autoimmune disease (15), and, following induction of the same disease, how the disease can be specifically terminated by the MVT (15). Prevention and termination of the autoimmune disease was achieved specifically by injections of ICs composed of the target nephritogenic ag and nonpathogenic IgM aabs directed against the target nephritogenic ag at ag excess.

We have clearly outlined the possible application of the MVT for prophylactic and therapeutic use in humans to deal with autoimmune diseases, cancer, and diseases caused by chronic infections. We have stated that in order to have reproducible, safe, and efficacious vaccine components it would be necessary to produce *ex vivo* purified ags that are in every aspect identical (in MW, chemical composition, structure etc.) to the target ags in question (*i.e.* the native target ag, cancer specific ag, etc.) Similarly, specific abs against the target ags must also be produced (against specific epitopes on the target ags). Specific IgM abs against native target ags and specific lytic IgG abs against cancer specific ags are necessary to make ICs for the control and termination of autoimmune diseases and cancer, respectively.

The presentation of the ag to the cells of the immune system determines the immune response outcome. With our MVT, having pure *ex vivo* prepared components assembled into ICs at the right proportions would make it possible to redirect the immune response outcomes specifically without interfering with vitally important immunological cell lines. The vaccination technique initiates and with repeated injections maintains high levels of circulating abs which are made up of the same class of immunoglobulin with the same specificity against the target ag as resides in the inoculum. The MVT reestablishes tolerance to self in certain autoimmune diseases (though memory of the modified ag is retained), and when implemented in various cancers we believe it has the potential of lysing only cancer cells, no matter where in the body they are located.

Several well defined "normal self components" have been described in human and experimental animal studies that are involved in autoimmune disease development (49,57-61), as have cancer specific ags that are involved in cancer development and progression (53,62,63,64). In the future it will be essential, using presently available techniques and soon by more refined procedures, to identify and produce the self-antigenic components that contribute to autoimmune diseases and cancer.

When the technologies for the manufacture of desired normal self-like ags, both autoimmune disease and cancer related, are able to produce uniformly safe, pure, and effective ags, then the future of the MVT can become actualized to prevent, terminate, and cure human autoimmune diseases, cancer, and chronic infection caused ailments.

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Abbreviations: aab: autoantibody, aag: autoantigen, ab: antibody, ag: antigen, HN: Heymann nephritis, IC: immune complex, Ig: Immunoglobulin, IgG: immunoglobulin G, IgM: immunoglobulin M, IP: intraperitoneal, MVT: modified vaccination technique, MW: Molecular weight, SPHN: slowly progressive Heymann nephritis,

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