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Application of the modified vaccination technique for the prevention and cure of chronic ailments

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ABSTRACT

Over the years vaccination has proven to be the most successful health protection program for large populations, to prevent them from acquiring serious infectious and contagious diseases caused by exogenous antigens (ags) such as bacteria and viruses. Protection is generally achieved by an active immunization program, though passive immunization has also been employed, especially in the past, to combat diseases caused by certain bacterial infections (e.g. tetanus, diphtheria, etc.).

Most recently, encouraging research data suggests that therapeutic approaches employing vaccination techniques can also be used to correct or deal with mishaps induced by or involving endogenous ags. However, most attempts at employing conventional vaccination techniques to do so have proven less than successful. In the case of cancer, one of the reasons for this is that the presentation of cancer related ags in presently available immunization frameworks is unable to evoke a powerful, specific cancer killing response. Therefore, drug treatments have been required in order to achieve additional beneficial effects.

Recently, the Barabas group has developed a new vaccination technique (the third vaccination method, after active and passive immunization) called Modified Vaccination Technique (MVT). In experiments the MVT has been able to prevent–and with equal effectiveness, terminate–mishaps induced by or involving endogenous ags, e.g. in an experimental autoimmune kidney disease called slowly progressive Heymann nephritis (SPHN).

The MVT is safe, and is able to initiate a specific immune response in the injected host (provided the injected components are in pure form). The MVT promises to provide the next generation of vaccines for the prevention, treatment, and termination of chronic disorders in humans, such as autoimmune diseases, cancer, and chronic infections.

1. Introduction

From time to time throughout our lives, humans are exposed to pathogenic disease-causing germs. For millennia, human lives have been threatened by these exogenous disease-causing agents, and even if people have survived diseases, they have often been afflicted with untoward complications. Fortunately we have been able to achieve, relatively recently in historical terms, successful vaccination against disease causing germs and germ products having relatively simple chemical structures.

However, while we have succeeded in protecting populations against the effects of simply structured germs (measles, polio, rabies, etc.) and their exo- and endotoxins (e.g. salmonella, diphtheria, tetanus, etc.), we still have major problems in trying to protect people against organisms with more complex chemical structures and/or life cycles (e.g. HIV/AIDS, TB, malaria, etc.) Such agents often cause chronic infections.

We have equally major issues in attempting to use drugs and/or vaccinations to cure patients that have disorders initiated and maintained by endogenous antigens (ags). There are two major autoimmune disorders in whose aetiologies endogenous ags play a principal role: (a) ″typical″ or ″classic″ autoimmune diseases and (b) cancer. Because we have not fully understood the aetiologies and pathogeneses of these disorders, we have not

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known how to prevent their occurrence, or when diagnosed in patients, how to properly treat them. As a result, chronic ailments of humans have been neither preventable nor curable, either by specifically targeted means or with generally acting drugs.

The Barabas group has developed a new vaccination technique called Modified Vaccination Technique (MVT) [1-8]. The MVT is the third vaccination methodology, after active and passive immunization, to display effective control over immune responses. Among its particular benefits is that it enables the induction of corrective immune responses against endogenous ags or the disorders caused by them. For example, it has been shown that an experimental autoimmune kidney disease can be prevented and, when present, terminated by the implementation of the MVT [1, 3, 6, 9].

The MVT holds the promise of preventing, treating, and terminating human chronic ailments that have so far been treatable only with drugs (i.e. autoimmune diseases, cancer, and chronic infections). This review article describes how the MVT can be implemented by appropriate antibody (ab) information transfer methodology [7, 8].

1.1. Autoimmunity revisited

The cells and products (abs) of our immune system are constantly in contact with our intact cells, cell debris derived from damaged cells, blood products, etc. Their aim is to maintain our internal environments " free of change" . Change can cause functional and morphological abnormalities within the system and result in disease (e.g. autoimmune disease and cancer). For example, released intracytoplasmic autoantigens (aags) can become chemically modified (by external agents, such as chemicals, drugs, etc., entering the system) and initiate a pathogenic autoantibody (aab) response [10-14]. If the inciting agent is present for a long time, then damage is maintained by pathogenic immune responses that effectively target as " non-self" the organ from which the aag is derived, causing a progressive disease involving the destruction of the organ [15]. Likewise, though conversely in terms of autoimmune function, if cancer cells emerge in the system and are not recognized as " non-self" , they can cause serious structural and functional disturbances in the organ or tissue in which they originate or take hold.

In the last few years, we have redefined the concept of autoimmunity. According to our new concept, autoimmunity represents a complex network of immune responses against " self" that are mainly beneficial and protective, and only occasionally harmful (Figure 1)[16].

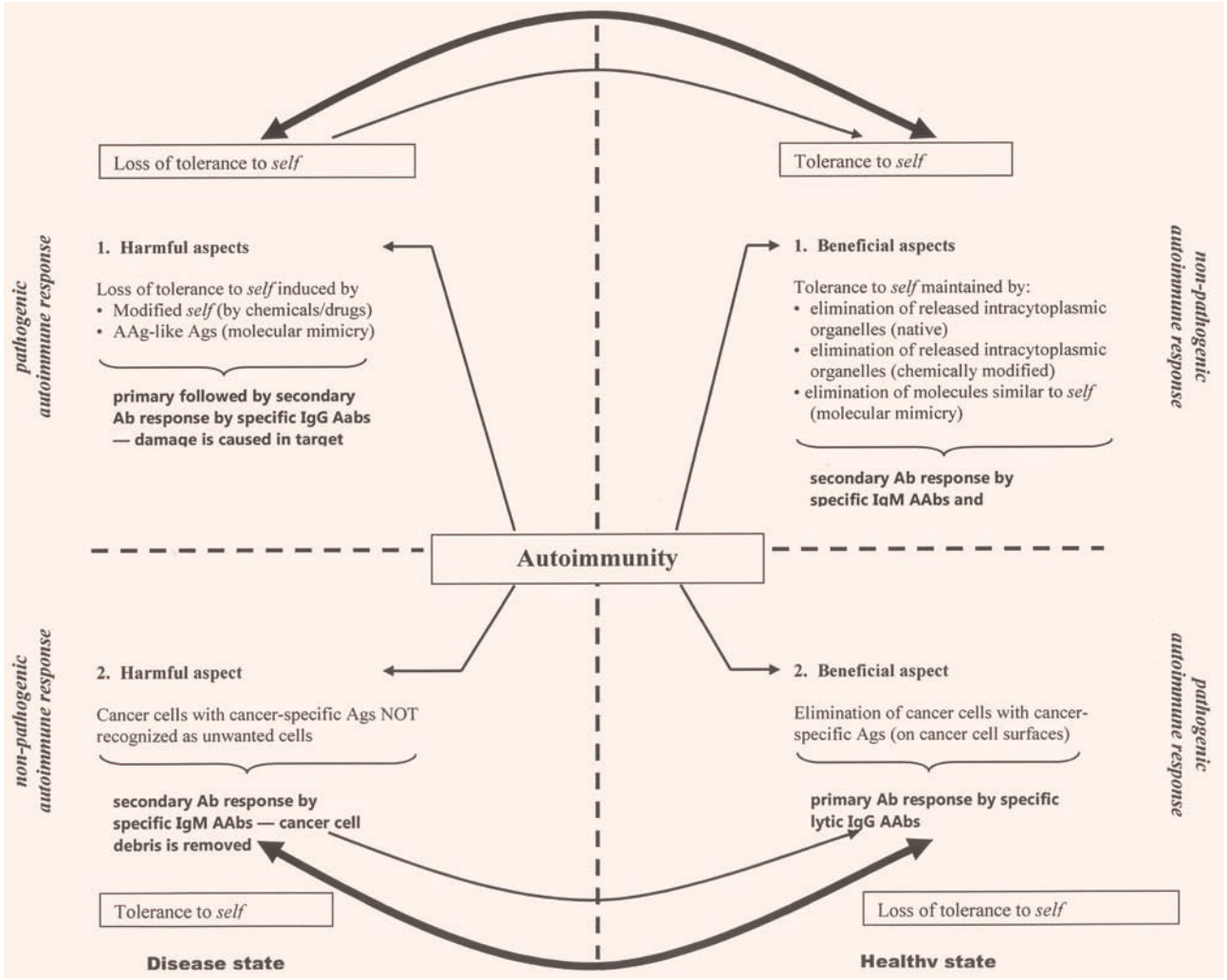

Figure 1. The diagram depicts the complex network of autoimmune responses. The right-hand side of the figure shows the beneficial aspects of autoimmunity, i.e. how homeostasis is maintained. The left hand side of the figure shows the harmful aspects of autoimmunity, which lead to autoimmune diseases and cancer. The MVT has the potential to initiate and maintain corrective autoimmune response outcomes specifically and without side effects restoring normal health. [Figure reproduced by permission from *BioProcessing Journal*, 2007 Winter;6(4):12-18.]

1.2. The two beneficial aspects of autoimmunity

1.2.1. Elimination of intracytoplasmic waste

Intracytoplasmic ags are constantly released from the body's cells, both from intact cells damaged by cytotoxic influences such as chemicals, trauma, burns, ischemia, heat and cold, and from normal cells at the end of their life span. This cell debris is removed by specific IgM aabs [17, 18]. IgM aabs are physiologic, and their function is to assist in the removal of spent cell products [19-21]. The final degradation of released large-MW substances into small-MW reusable peptides takes place in phagocytic cells [22]. If such a clearance mechanism does not efficiently remove degraded tissue components from the system, then toxic accumulation and possibly chemical alteration of released intracytoplasmic components can occur [12, 13, 23-25]. This beneficial function of the autoimmune system operates throughout life (secondary aab response), and for this reason we are not tolerant, in a physiological sense, of our own " self" large-MW intracytoplasmic components [18, 26, 27].

Another beneficial aspect of this autoimmunity is to assist in the removal of subcellular components that do become chemically modified by external agents such as drugs, chemicals, etc [13, 28]. If a chemically modified aag stays in the system, it can initiate an autoimmune disease, because the immune system can and will recognize the " modified self" ag as " non-self" , and produce a pathogenic response that ends up attacking the native tissue. If the modified aag remains present or is continuously produced in the system, it will maintain this pathogenic aab response and cause a progressive autoimmune disease (exacerbation) [28].

Occasionally, low levels of pathogenic aabs can be detected in the circulation-presumably because relatively small amounts of " modified self" aags stimulate their production-before a clinically discernable autoimmune disease is diagnosed [29]. On the other hand, even during the disease state, increased production of specific IgM aabs is increased to remove both " native" and " modified self" aags from the circulation [28], with the aim of reducing and terminating the pathogenic autoimmune response (remission) [2, 9].

1.2.2. Elimination of cancer cells

The second beneficial aspect of autoimmunity is the elimination of cancer cells from the system by pathogenic IgG aab response directed against the cancer-specific ags residing on those cells. Lytic aab response ensues when the tumour-associated cancer-specific ag is strongly antigenic and able to dissociate from the cancer cell membrane surface. If an active and powerful anti-cancer immune response is generated, then the host is cured without being aware of the cancer cell elimination taking place. Cancer elimination requires a primary pathogenic aab-mediated immune response against the target " non-self" aag on the cancer cells [30-33]. Unfortunately, since these aags are generally only weakly antigenic, immune response required for cancer cell lysis does not occur in every instance, hence the manifestation of the disease.

1.3. Two harmful aspects of autoimmunity

There are two harmful aspects of autoimmunity that are described in the medical literature with respect to causing autoimmune disorders. One results in autoimmune disease, and the other in cancer.

1.3.1. Autoimmune diseases

Autoimmune diseases can occur in normal and genetically predisposed humans (with a preponderance in females) as the result of multiple factors [34-36]. Amongst the agents that trigger or are predispositional toward autoimmune diseases, there are a long list of identifiable inciters (smoking, toxins, genetic susceptibility, chemicals, trauma, burns, ultraviolet irradiation, drugs, vaccines, alcohol, etc.) [11, 37-45]. There are also inciters in our environment [46, 47] whose particulars we may not be precisely aware of (chemicals, pollutants, etc.).

Useful information about the etiology and pathogenesis of autoimmune diseases has been obtained from animal studies [15, 48-54]. Though such experimental information may not be directly applicable to the etiology and pathogenesis of non-experimental human autoimmune diseases, information gained from animal studies have shed light on why and how autoimmune diseases are initiated and maintained, and how immunosuppressive agents presently in use function to control autoimmune disease-causing processes.

There are several accepted explanations as to how and why autoimmune diseases can inflict a host. One commonly accepted view ascribes autoimmune disease to the emergence of B or T cells that are autoreactive against particular target ags [39, 55-60]. Another view maintains that once a pathogenic immune response is triggered against " self" , it is propagated by an immortalized plasma cell line continuously producing pathogenic autoimmune disease-maintaining aabs [61]. It is thought as well that an autoimmune disease can also be caused by certain chemical compounds (e.g. bacterial products) whose structural make-ups are similar to those of " self ags" (molecular mimicry) [35, 36, 62, 63].

The most plausible explanation for the development of human autoimmune disease is obtained from animal experiments. In one example it was observed in a series of experiments that " native self" ags injected repeatedly into the same species of animals from which the ags were derived did not initiate autoimmune diseases [11]. However, when the same ags were injected in a modified form, as with an adjuvant (such as Freund's complete adjuvant) [15], or modified chemically by presenting the native ags in the form of hapten-protein conjugates[11], then the animals developed autoimmune diseases.

Autoimmune diseases can culminate in structural damage to vitally important organs, causing functional disturbances to the point where life can no longer be sustained[15]. To slow down pathogenic immune response and disease progression, immunosuppressive agents are used [64-70]. These agents are non-specific in their actions and can result in numerous side effects, of which complications caused by opportunistic infections are the worst.

1.3.2. Cancer

Whereas the autoimmune disorders of the " classic" type referred to above result from the perpetuation of a pathogenic autoimmune reaction, the other type of disorder in which these autoimmune functions are implicated, cancer, manifests in circumstances of pathogenic autoimmune non-reaction.

Patients with cancer have a group of cells in their body which are " non-self" because of the presence of " non-self markers" on their outer cell membranes [71-73]. These

″ non-self markers″ are quite often minimally antigenic, bound as they often are to cell membrane surface-related structural proteins, and hidden from immune surveillance. When the cancer specific ags on cancer cell surfaces are recognized and consequently attacked and eliminated by immune mediated responses, the patient uneventfully recovers from the cancer. However, when the cancer specific ags on the cancer cells are not recognized, a serious autoimmune disorder manifests in the host. The cancer has the potential of causing major structural damage both at its primary site of development and by metastatic spread at numerous other locations. In addition to structural damage, infiltrating cancer cells can cause significant functional disturbances in the system by the displacement of normally functioning cells within an organ.

If the cancer fails to take hold, e.g. if the cancer growth is too fast and a sufficient blood supply is unable to establish itself in the newly formed tissue, causing the cancer to be destroyed by ischemia, the released cellular components will be assisted in their removal by specific IgM aabs to prevent toxic accumulation of tissue breakdown products.

1.4. State of the art treatment of autoimmune disorders

Present treatment of autoimmune diseases includes the use of immunosuppressive agents, and, in cancer, cytotoxic drugs.

1.4.1. Future preventative and treatment options for autoimmune disorders

Avoiding harmful agents (such as cigarette smoke, alcohol, certain drugs, chemicals, infectious agents, excessive exposure to the sun, etc.) [38, 40, 63, 74] that could, especially in genetically susceptible patients, cause autoimmune diseases or cancer should be paramount in any strategy for the prevention of such diseases [13]. However, to achieve prevention, or when present, cessation, of ailments caused by autoimmune disorders, the immune system's natural abilities are also available to be utilized in a program of medical treatment. In this regard, an "instruction"-based vaccination technology that is able to evoke predetermined down-regulative immune responses to achieve termination of events that are induced or maintained by pathogenic immune responses and sustain autoimmune diseases should be achievable [1, 6, 9]. In cancer, we should be able to evoke specific lytic aab responses against cancer-specific ags residing on cancer cells to eliminate these cells from the system without causing collateral damage. Already hundreds of attempts have been made with active and passive immunization techniques-to correct immune events associated with autoimmune disorders, both in animal experiments and in human patients [30-33, 66, 67]. So far none of the techniques on their own have been able to prevent or terminate these disorders [31, 69, 70, 75-77]. The implementation of a new and effective immunization technique that is able to evoke specific immune regulatory responses against endogenous ag induced mishaps to correct autoimmune anomalies is a most urgent enterprise.

1.4.2. Modified vaccination technique to combat autoimmune disorders presently only treatable with drugs

The Barabas group, working with an experimental autoimmune kidney disease in rats called Heymann nephritis (HN) and its variants, has been able to decipher the immunopathological events that initiate and maintain the disease[28, 50]. They have also been able to observe how immunopathological events can be prevented, and, when the disease is in its progressive phase, terminated[1-3, 6, 9]. They have based their observations and conclusions not only on their research results but also on the extensive research work of others [15, 52, 53, 78-94]. The possibility of preventing and/or terminating a pathogenic IgG aab induced experimental autoimmune disease has become a reality. The vaccination method that the Barabas group has developed is called MVT [1-3, 8, 95]. It has been given this name because in order to utilize it in correcting mishaps either initiated by a harmful autoimmune response (i.e. in an autoimmune disease) or exhibiting a lack of beneficial autoimmune response (i.e. in cancer), one has to know the etiology and pathogenesis of the particular disease in order to properly constitute the vaccine [4-8]. For example, in slowly progressive Heymann nephritis (SPHN, a variant of HN), it was necessary to determine: (1) how a pathogenic IgG aab response was initiated and maintained against a tubular brush border (BB) like aag residing on the epithelial side of the glomerular basement membrane (GBM), causing immune complex (IC) glomerulonephritis [28]; and (2) how to terminate this pathogenic IgG aab response, and thereby terminate autoimmune-mediated injury to the BB region of the renal proximal convoluted tubules and the GBM [1].

Weir and colleagues had noted earlier that intracytoplasmic ags released following damage to cells by ischemia, toxins, trauma, etc. are assisted in their removal from the circulation by naturally occurring tissue-specific IgM aabs [18, 20, 21, 26, 96, 97] prior to being degraded into reusable small-MW peptides by phagocytic cells [22]. These events take place continuously throughout the life of the animal, preventing toxic accumulation or chemical modification of tissue breakdown products.

Weir's observations led us toward finding solutions to increase the level of specific non-pathogenic aabs in the circulation against the native nephritogenic aag that contributes to disease progression by IC depositions on the epithelial side of the GBM. To increase specific IgM aab response in the rats we injected ICs (the modified vaccine), made up of the nephritogenic ag, rat kidney fraction 3 (rKF3), and IgM ab against rKF3 [1] (produced in normal rats injected with intraperitoneally administered rKF3) [4-8]. Elevated levels of IgM aab against the nephritogenic aag neutralized both disease-maintaining modified nephritogenic aags and disease-contributing native nephritogenic aags. The lack of modified nephritogenic ag in the system halted pathogenic IgG aab production and disease progression, resulting in specific termination of the autoimmune disease events without side effects [1-3, 9].

The MVT uses the immune system's natural ability to correct harmful responses against "self" [98, 99]. Even during the course of an autoimmune disease the cells of the immune system produce elevated levels of IgM aabs against the native nephritogenic ag [28]. These aabs are responsible for slowing down immune events that would otherwise be accelerated and cause more harm [98]. However, as long as pathogenic IgG aabs against the target aag(s) are present in the circulation there is no termination of harmful reactivity against ″ self″ [9, 100].

In cancer, pathogenic IgG aab response against the target ag residing on cancer cells, i.e. against the cancer cell specific ag, is required. Lytic IgG abs against cancer cell

specific ags, in the presence of complement, are able to lyse (i.e. kill) cancer cells, and non-pathogenic IgM aabs assist in the removal of cell debris [32]. Thus a pathogenic aab response against "non-self" cancer-specific ags on cancer cell surfaces can terminate what is essentially a life threatening autoimmune disorder. This is the only case when a pathogenic autoimmune response induced against ags deemed "non-self", and functioning to destroy the target group of cells that are "partially self", is beneficial to the host (i.e. cancer cell kill and elimination). Such specific pathogenic autoimmune response against cancer is not easily evoked in the host. However, it can be achieved with the MVT.

The following agents must be present in the modified vaccine: absolutely pure cancer cell specific ag (prepared ex vivo by presently available techniques) [72, 101], and monoclonal or polyclonal homologous lytic IgG ab directed against the cancer-specific ag residing on the cancer cell. To constitute a working vaccine, the cancer-specific ag has to be mixed with the lytic cancer ag specific IgG ab at slight ag excess. Injected with the IC, the host will produce the same ab with the same specificity against the target ag as is present in the inoculum, namely, lytic anti-cancer ag-specific IgG aab [7].

With the appropriate components to produce the IC, patients could be vaccinated to prevent cancer, and when diagnosed with cancer, to terminate tumour growth and spread. In our opinion, cancer can only be beaten by utilizing the immune system's natural abilities to mount a pathogenic aab response against cancer cells. To evoke the correct immune response, the right "information" must be supplied. The MVT promises to deliver the required information to the cells of the immune system to achieve cancer cell kill and elimination [4, 7].

2. Summary

Presently applied vaccination techniques (i.e. active and passive immunization) are not effective on their own at either preventing or curing ailments caused by chronic disorders. At the present time these techniques are accompanied by drug treatments, which are not specific enough in their actions to prevent side effects.

We have described a new vaccination method called MVT[2-9], which surmounts these obstacles. As a prerequisite for the application of the MVT, it is necessary to have a comprehensive understanding of the etiology and pathogenesis of the particular chronic ailment to be treated. To achieve a desired immune response using the MVT, specific ICs have to be produced to evoke preventative or therapeutic outcomes in the vaccinated host.

The MVT is well suited to initiate and maintain corrective immune responses in endogenous ag caused autoimmune disorders (i.e. cancer, autoimmune diseases) and in chronic infections (Figure 1). The MVT uses the immune system's natural ability to correct immunological mishaps. The MVT is specific and safe to apply, provided the injected components are pure in form. The MVT promises to be the next generation of vaccine to have far-reaching effects in human medicine, with the ability to deal specifically and effectively with chronic ailments presently treatable only with drugs.

Conflict of interest statement

We declare that we have no conflict of interest.

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