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Four Aspects of Autoimmunity and How to Regain Tolerance to Self from an Autoimmune Disease Utilizing the Modified Vaccination Technique

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1. Introduction

The cells of the immune system are exposed to two broad types of antigenic challenges – challenges from the external environment (bacteria, viruses, etc.), and challenges from the internal environment of the host (from both normal and abnormal self). The immune system functions throughout life to preserve the integrity of the organism, allowing its various organs and systems to carry out their intended functions, and maintaining normal health. The cells of the immune system have intimate knowledge of self and non-self. Normal self is allowed to live and function, whereas abnormal self or non-self, e.g. degraded cellular products or abnormal cells, are recognized as non-self and removed by the cells and products of the immune system and processed into reusable small MW peptides (Manson et al., 2005; Quartier et al., 2005; Wermeling et al., 2009). Occasionally, modified self will affect the normally functioning immune system and stimulate a pathogenic immune response causing an autoimmune disease (Barabas et al., 2004c; Heymann et al., 1959). In other instances, because of the minimal antigenicity of cancer specific antigens (ags) on cancer cell surfaces, cancer is not recognized as non-self and is allowed to grow and cause harm (Berinstein, 2007; Engelhard et al., 2002).

The question of how to correct immunological mishaps that not only compromise the normal functioning of an affected organ but can even threaten the life of the host has engaged numerous investigators in the search for curative solutions. So far the options available for treating ailments caused by autoimmune disorders have been mainly limited to drugs (Cattran, 1988; Matsukawa et al., 1992; Penny et al., 1998), which in general have undesirably over-broad effects. Yet there are encouraging signs that targeted, specific cures might be achieved by immunological means (Andreakos et al., 2002; Berinstein, 2007;

Hasegawa et al., 2001; Lollini & Forni, 2002; Yokoyama et al., 1999). Studies have shown that the method of presentation of the ag – whether it be exogenous or endogenous – to the cells of the immune system determines the immune response outcome.

Medical science has learned, over the course of the developmental history of vaccination, how to present antigenic components in an inoculate to stimulate protective immune responses in the vaccinated host against exogenous ags. However, the possibility of using vaccination to achieve protective or curative outcomes in patients with disorders caused by endogenous ags, without causing side effects, has remained elusive (Ben Yehuda et al., 1988; Fox & McCune, 1994; Golbus & McCune, 1994; Hu et al., 2009; Nepom, 2002; Perosa et al., 2005; Thaiss et al., 1989).

Our investigations into the etiology and pathogenesis of an experimental autoimmune kidney disease have resulted in a new immunological approach involving the presentation of native autoimmune disease related ags to evoke a predetermined corrective immune response in the host (Barabas et al., 2004b; Barabas et al., 2006c; Barabas et al., 2006b; Barabas & Lafreniere, 2005). The approach consists of a new vaccination method called modified vaccination technique (MVT) (Barabas et al., 2007b; Barabas et al., 2007a; Barabas et al., 2008a; Barabas et al., 2009a; Barabas et al., 2009b). The MVT involves the injection of a mixture of antibody (ab) inducing components which are predetermined based on the required outcome. So far the MVT has been implemented:

- to prevent an experimental autoimmune kidney disease, and to terminate the already present disease (Barabas et al., 2004b; Barabas et al., 2006c; Barabas et al., 2006b; Barabas & Lafreniere, 2005); and
- to achieve a powerful immune response against an exogenous ag (Barabas et al., 2007d);

Below we give a detailed account of how and why the MVT has the potential of specifically preventing and curing certain chronic disorders such as autoimmune disease and disease caused by chronic infection.

2. Vaccination

Vaccination is the most cost-effective way to protect the public against undesirable medical conditions that can result in acute or chronic ailments. Vaccination by active immunization can prevent serious infectious and contagious diseases from occurring; and vaccination by passive immunization can neutralize existing disease causing/contributing agents (Hjelm et al., 2006; Imbach et al., 1981; Leandro & de, I, 2009; Levesque, 2009; Pirofsky & Kinzey, 1992; Segal et al., 1999). However, neither vaccination technique has been successfully implemented to date to achieve preventative or curative immune response outcomes in endogenous ag initiated and maintained disorders. It has been evident for a number of years that a technique other than those applied to diseases caused by exogenous ags is needed. The danger of using components derived from endogenous ags and causing added complications (e.g. autoimmune disease) has presented obstacles in the search for solutions (Finn & Forni, 2002; Peakman & Dayan, 2001). However, a better understanding of naturally occurring immune events, particularly pathogenic and non-pathogenic immune responses against self (Barabas et al., 2008b) - where the terms “pathogenic” and “non-pathogenic” do not equate with the terms “harmful” and “beneficial” - within the concept of autoimmunity promises to provide a framework for creating new possibilities for designing prophylactic and therapeutic vaccines for mishaps caused by or involving endogenous ags.

3. Autoimmunity conventional definition

Autoimmunity is conventionally defined in the scientific literature as abnormal immune response against self resulting in autoimmune disease. As such, autoimmunity is viewed as a self-destructive process, involving aberrant immune responses against self by the cells and products of the immune system, along with the wide spectrum of resulting autoimmune diseases which are generally chronic and progressive in nature. An autoimmune process is often irreversible, and currently the only readily available treatment is with drugs. In most cases the prognosis is guarded at best; even with the best medical care the symptoms of autoimmune conditions can generally only be minimized. Autoimmunity can result in morphological changes, including structural alterations in affected organs, that compromise and even destroy the normal functioning of the affected part. For example, in an experimental autoimmune kidney disease called Heymann nephritis (HN), we observe: a collection of symptoms including proteinuria, the presence in the circulation of pathogenic IgG autoantibodies (aabs) directed against the brush border (BB) region of the proximal renal tubules, massive deposition of immune complexes (ICs) in the glomeruli, and overall morphological and functional changes in affected regions of the kidney (Alousi et al., 1969; Andres et al., 1986; Edgington et al., 1967; Farquhar et al., 1995; Heymann et al., 1959; Kerjaschki, 1993; Kerjaschki & Farquhar, 1982; Singh & Kasinath, 1993). As in the case of HN, if the affected part is vitally important to the host and can no longer contribute to health, then premature death due to organ failure can ensue.

It is a common belief that once an autoimmune response is triggered it continues *in perpetuum* (Manz et al., 2002). However, many autoimmune diseases exhibit remission or exacerbation of disease processes, with or without drug treatment. Generally speaking it is not understood why. Autoimmune diseases are treated with immunosuppressive agents (Cattran, 1988; Fox & McCune, 1994; Fox & Ransohoff, 2004; Matsukawa et al., 1992) that have side effects and do not act specifically to terminate disease processes (Perna et al., 2004). In addition, as a result of their non-selective inhibition of the overall function of the immune system, these immunosuppressants expose patients to infection and related complications. The conventional understanding of how immunopathological processes cause autoimmune diseases (Davidson & Diamond, 2001; Feldmann & Steinman, 2005; Hill & Sarvetnick, 2002) does not allow for the possibility of reversing disease processes and re-establishing normalcy (Dorner et al., 2009) by the application of a vaccination technique.

4. Autoimmunity within the concept of beneficial and harmful aspects of immune responses against self in the light of new evidence

Autoimmunity properly understood denotes a complex interconnected network of immune responses against self that are not pathological in the first instance, but rather are designed to maintain the structural and functional integrity of the host's internal environment throughout life. The cells and products of the autoimmune system keep the internal environment of the host in a state of homeostasis. As a result of the proper functioning of the autoimmune system, intracytoplasmic components released from damaged cells (by burns, drugs, infectious agents, ischemia, toxic compounds, etc.) and from normal cells at the end of their life span are assisted in their removal by non-pathogenic IgM aabs (Avrameas, 1991; Casali & Notkins, 1989; Chen et al., 1995; Weir et al., 1966; Weir, 1966) and phagocytic cells (Barabas et al., 2004a; Helmy et al., 2006; Mevorach et al., 1998; UytdeHaag

et al., 1991; Wermeling et al., 2009). Likewise, abnormal cells and cell lines having non-self antigenic surface markers (e.g. cancer cells) are also recognized and removed (Cheent & Khakoo, 2009; Foss, 2002; Topham & Hewitt, 2009). These are the two beneficial aspects of autoimmunity, by which it endeavours to keep the internal environment, composed as it is of endogenous ags, free of change. It is a major undertaking since several factors, both internal and external, have the potential to create an imbalance and cause harmful pathogenic immune responses against self, especially if the right triggers are present.

A well functioning autoimmune system averts most attempts by internal and external agents to create a harmful autoimmune response resulting in autoimmune disorders such as autoimmune disease and cancer (which themselves may be considered the two negative aspects of autoimmunity). It stands to reason that in order to protect against the kinds of insults that could lead to autoimmune disorders, we should engage in healthful consumption and healthful avoidance, eating healthy diets (consisting of fruits, vegetables, etc.) that contain chemicals or trace elements that boost the immune system or contribute to the prevention of cancer, and minimizing exposure to noxious agents (cigarette smoke, legal and illegal drugs, alcohol, and other toxic or infectious agents) that can chemically alter autoantigens (aags) and initiate autoimmune diseases (Greenwald et al., 2001; Howells et al., 2007; Nair et al., 2007). However it would also be advantageous to know more about the workings of the beneficial aspects of the autoimmune system, how it operates, how it maintains tolerance to self, how it might be influenced by naturally occurring or medically induced events to correct harmful immune responses and restore the organism to a normal state of health.

Observation tells us that the autoimmune system has the inbuilt ability to self-correct – with or without medical intervention – and restore the host to health, provided the correction occurs prior to overwhelming injury to the host's immune system and/or organs, tissues, or cells. We have conducted several recent experiments in this area, and have observed through these experiments that corrective immune responses can in fact be initiated by providing the right "information" to the cells of the autoimmune system. We have shown that with a vaccination technique that induces a predetermined immune response, autoimmune diseases can not only be prevented, but also, when present, terminated (Barabas et al., 2004b; Barabas et al., 2006c; Barabas et al., 2006b).

4.1 Beneficial aspects of autoimmunity resulting in tolerance to self

There are two beneficial aspects of autoimmunity, both characterized by maintenance of the integrity of the host's internal environment (homeostasis/healthy state) and involving the clearing and elimination of cellular waste and abnormal cell lines that are not conducive to the morphological and functional unity of the organism. Immunological cell lines are dedicated to surveyance and recognition of self and difference, or self and non-self (Kreuwel & Sherman, 2001; Sakaguchi, 2000). When difference is recognized there is usually enough time for the host to mount an immune response to avoid the establishment of an autoimmune disorder. Such protective immune responses are carried out by the normally functioning autoimmune system and as such the host is not aware of them. On the other hand, if the autoimmune system's natural ability to correct mishaps is compromised by age, dysfunction, suppression, misinformation, etc. then there exists a stronger likelihood of the host not being able to regain tolerance to self, and the host has a greater chance of experiencing ill health in the form of an autoimmune disorder.

4.1.1 Removal of cellular waste

Cells damaged by various agents or events (e.g. chemicals, drugs, ischemia, trauma, toxic compounds, UV irradiation, etc.) release their intracytoplasmic components into intra- and extravascular spaces. These cellular wastes are assisted in their removal by specific non-pathogenic IgM aabs (Avrameas, 1991; Weir, 1964; Weir et al., 1966; Weir, 1969; Zwart et al., 2004) and subsequently phagocytosed and broken down into reusable small MW peptides (Ciurana et al., 2004; Manson et al., 2005; Ogden et al., 2005; Quartier et al., 2005). It was shown by Weir and associates that in a physiological sense we are not *per se* tolerant to our own intracytoplasmic components, and specific IgM aabs are present in the circulation throughout life to clear the system of cellular breakdown products (Weir et al., 1966; Weir & Elson, 1969; Weir & Pinckard, 1967). Specific IgM aab production increases following excessive release of aags (secondary ab response) from an organ damaged by toxic agents, pathogenic IgG aabs, or ischemia at the site of rapid tumour growth etc. (Barabas et al., 2003; Pinckard & Weir, 1966; Weir, 1966). Circulating specific IgM aabs also contribute to rapid and efficient removal of cellular wastes to prevent not only their toxic accumulation in the system but also their possible chemical modification, which could trigger a tissue to be targeted and damaged by a pathogenic IgG aab response, an event which has the potential to initiate an autoimmune disease (Weir, 1969; Weir & Elson, 1969). IgM aabs are able to assist in the removal from the intracytoplasmic space not only of normal native aags released into the intra- and extravascular spaces but also of native-like ags (molecular mimicry) and native aags that are chemically or otherwise modified (Barabas et al., 2004b). Specific IgM aabs in the circulation are present with high titres measurable during the chronic phase of an autoimmune disease, as they assist in the removal of both disease causing and maintaining aags (modified aags that stimulate pathogenic IgG aab production) and disease contributing aags (target aags from the targeted organ) (Barabas et al., 2003; Barabas et al., 2004b). These cross-reactive specific IgM aabs are greatly responsible for the maintenance of tolerance to self during life by efficiently clearing the system of native and modified aags. If they can effectively clear the system of both native and modified aags during an autoimmune disease, then remission will occur, as manifested in signs of improvement and diminished symptoms (Barabas et al., 2004b; Barabas et al., 2006c; Barabas et al., 2006b; Barabas & Lafreniere, 2005). If the stimulus agent – that produces the modified self – ceases to be present in the system then spontaneous remission and termination of the autoimmune disease process will follow. However, as long as the modifying agent remains present in the system and is able to alter the chemical nature of self into non-self, the immune responses that cause the disease will continue, and the condition will be exacerbated and will manifest in a chronic progressive disease.

The autoimmune system's specific IgM aab production cell line will lose its ability to carry out its intended beneficial function in such circumstances where the modifying agent is continuously present in the system and maintains a pathogenic immune response. Its work may also be compromised in cases where the immune system is dysfunctional or has low IgM aab production because of old age, ill health, genetic predisposition, malnutrition, immune suppression, ineffective phagocytosis, etc. (Schulze et al., 2008; Wermeling et al., 2009).

4.1.2 Removal of abnormal cell lines

Just as intracytoplasmic waste is recognized as unwanted self and assisted in its removal by physiological non-pathogenic IgM aabs, cells with non-self markers, i.e., cancer cells, are also recognized by lymphocytes and their products – NK cells, cytolytic IgG aabs, etc. – and

are eliminated from the system (Cheent & Khakoo, 2009; Kim et al., 2007; Topham & Hewitt, 2009). Such naturally occurring autoimmune responses are necessary to maintain the morphological and functional integrity of the host's organs, tissues, cells, etc. Without this beneficial aspect of autoimmunity, normal cells exposed to carcinogens, genetic influences, or even to normal aging could become cancerous, non-functional tissue, infiltrating the body and compromising its health. It is well documented that the incidence of cancer in the young is considerably lower than in the elderly, presumably because in the young a more efficient autoimmune system recognizes and responds to changes more readily, and/or cell cycles are more precisely regulated. (However, the autoimmune system's beneficial function of recognizing and eliminating cancer can be compromised at any age by a hazardous lifestyle [diets known to cause cancer, smoking, drinking, excessive exposure to the sun], genetic predisposition, exposure to certain infectious agents, malnutrition, immune suppression, etc. (Arver et al., 2000; Baniyash, 2006; Beral et al., 1991; Birkeland et al., 1995; Greenwald et al., 2001; Khuder et al., 1998).

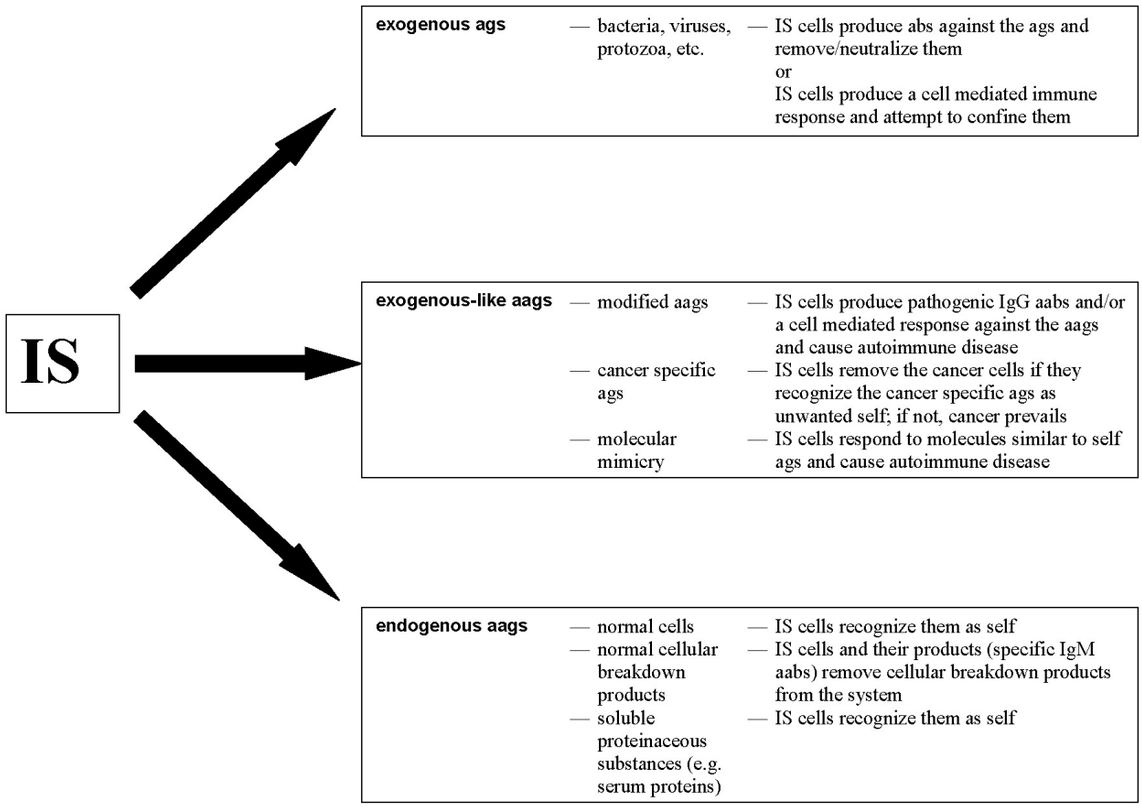

Fig. 1. A normally functioning immune system's immune responses against exogenous ags, exogenous-like and endogenous aags.

The IS is designed to remove exogenous ags, exogenous-like aags, and cellular breakdown products of normal cells from the system to maintain homeostasis and tolerance to self. However, prolonged exposure to exogenous ags can result in chronic infections, exogenous-like aags can induce autoimmune diseases, and deficient processing of cancer specific aags on the surface of cancer cells can permit the growth of cancer.

Abbreviations: aabs, autoantibodies; aags, autoantigens; abs, antibodies; ags, antigens; IgG, immunoglobulin G; IgM, immunoglobulin M; IS, immune system

In order for the autoimmune system to respond for the benefit of the host, the cancer specific ags on cancer cell surfaces must be readily available for immune processing. In this regard, the cancer specific ag must be somehow detached, chemically degraded, and made available separately from normal cell membrane components or other normal self molecules shared with normal cells to stimulate immune cell lines to produce pathogenic lytic IgG aabs (primary ab response) against the cancer cell line bearing that specific ag. If this process occurs and pathogenic lytic IgG aabs are produced, then regardless of where those cancer cells are located in the body they will be lysed and the cellular breakdown products eliminated by non-pathogenic IgM aabs (secondary ab response).
It is noteworthy that in cancer defence one of the most important aspects of autoimmunity is manifested in a pathogenic IgG aab response against a self-like group of cells (Jager et al., 1999; Tureci et al., 2006) (Figure 1).
Pathogenic autoimmune response against altered self (i.e., cancer specific ag on cancer cells) is clearly a highly beneficial aspect of autoimmunity. In such circumstances tolerance to self (to a self-like group of cells) is lost, but the host's internal environment is protected from possible changes that could result in tumour growth. However, pathogenic lytic IgG ab response may fail to occur for the following reasons:

- the cancer specific ag is minimally antigenic (Foss, 2002; Lollini & Forni, 2002) (and a small MW protein), is closely associated with normal cell surface components, and does not detach easily to allow its recognition as non-self for pathogenic immune response inducement; or
- the host's immune system is prevented from functioning against an apparent self ag by inbuilt protective regulatory cells and molecules (Cheent & Khakoo, 2009; Musiani et al., 1997).

4.2 Harmful aspects of autoimmunity resulting in autoimmune disorders

There are two harmful aspects of autoimmunity, both of which have the potential to manifest in disease states, one being an adverse immune response against normal self, causing an autoimmune disease; and the other being tolerance of an abnormal cell line, so that cancer growth is permitted. These disease states, or autoimmune disorders, come about when the immune system's surveying ability is mislead into situations of improper response or non-response to changes in self. It is observed in many autoimmune diseases that modified self initiates and/or maintains pathogenic aab responses against a target ag, causing a disease state (Barabas et al., 2004c; Heymann et al., 1959), whereas in cancer, ags identifiable as cancer specific are minimally antigenic and not recognized as unwanted self, and therefore fail to induce an immune response that eliminates the cancer cells (Foss, 2002; Kim et al., 2007).
In many respects the autoimmune system responds correctly during the development and maintenance of autoimmune disorders. In fact, the immune system does what it is instructed to do or not to do by the "information" it receives. In the case of self reaction, for instance, the cells and the products of the cells of the autoimmune system are virtually predestined to react against altered self, in that altered self is non-self and non-self should provoke a pathogenic immune response. Unfortunately, such an immune response against altered self can cause an autoimmune disease, as the developing pathogenic aabs are cross-reactive, i.e., in addition to reacting against the modified self ag that initiates and maintains their production, they also react with normal self, causing harm to the tissue and providing

more substrate for the reaction to continue. In the case of cancer, on the other hand, the cells and the products of the autoimmune system do not react with the minimally altered self on cancer cell surfaces and the cancer cells are not be eliminated, therefore allowing the cancer to prevail (Foss, 2002).

4.2.1 Initiation and maintenance of an autoimmune disease

The induction and maintenance of autoimmune diseases, as well as the associated immunopathological and functional changes, have been extremely well studied in experimental animals (Andres et al., 1986; Barabas et al., 1969; Barabas & Lannigan, 1969; Grupe & Kaplan, 1969; Heymann et al., 1959; Kerjaschki, 1993; Kerjaschki, 2000b; Kerjaschki & Farquhar, 1982); and by comparative study the etiology and pathogenesis of human autoimmune diseases are equally well understood (Davidson & Diamond, 2001; Kretz-Rommel et al., 1997; Kretz-Rommel & Rubin, 1999; Sinha et al., 1990; Theofilopoulos, 1995; Tung, 1994; Von Herrath & Oldstone, 1995). In most instances for an autoimmune disease to begin, a modified self (Barabas et al., 2004c) or self-like (molecular mimicry) (Ebringer et al., 1997; Ebringer, 2003; Mokhtarian et al., 1999; Orbach & Shoenfeld, 2007) ag has to present itself as a foreign-like, exogenous-like ag to the cells of the immune system. There are numerous agents that are able to modify self ags (toxins, chemicals, infectious agents, drugs, adjuvants, vaccines, smoking, chemical dyes, UV irradiation, etc.) and initiate a pathogenic IgG aab response (Barabas et al., 2004c; Conti et al., 2008; Davidson & Diamond, 2001; Hess, 1999; Heymann et al., 1959; Rao & Richardson, 1999; ten Veen & Feltkamp, 1972) (initially a primary immune response, as the immune system has not previously been exposed to the modified ag). If the modifying agent is continuously present in the system, then the modified self ag will continue to stimulate the appropriate T and B cells to maintain the production of pathogenic IgG aabs by the plasma cells (secondary ab response) (Barabas et al., 2003). The developing pathogenic IgG aabs are cross-reactive (Barabas & Lafreniere, 2005). They react with the modified self ag and the normal target ag in an organ. ICs made up of modified self and anti-modified self IgG aab form as a result. The fate of these ICs is twofold. In part they are neutralized and eliminated. However, insofar as they are not fully or quickly enough removed from the body they operate to maintain the pathogenic IgG aab production.

The pathogenic IgG aabs also react with the target ag not just as it appears in the circulation, but also *in situ* within the organ where it originates; e.g. in HN circulating anti-nephritogenic IgG aabs attack renal tubular BB localized nephritogenic ags and release them into the circulation (Barabas et al., 2003; Barabas et al., 2006c). Released aags will join IC deposits on the epithelial side of the glomerular basement membrane enlarging the deposits and thus causing morphological and functional injury to the kidney (Barabas et al., 2003). Continuously produced pathogenic IgG aabs and aags continually released from the damaged normal renal tubules will continue to enlarge the deposits in the glomeruli together with complement components, causing a chronic progressive autoimmune kidney disease (Barabas et al., 2003). The progression of disease processes or diminution of disease intensity depends mainly on the presence of the modifying agent in the system, because as stated above the immune response outcome depends on the presentation of the ag to the cells of the immune system. The continuous alteration of self by the modifying agent in the system drives the pathogenic autoimmune response to produce high levels of circulating pathogenic IgG aabs. As long as a pathogenic IgG aab is present in the circulation, the

disease process will continue. The level of pathogenic IgG aab must be at zero for no autoimmune disease process to be detectable in the host (Barabas et al., 2004b).

In contrast to the common belief, we and a few other scientists believe that the normal target ag on its own will not under normal circumstances initiate a pathogenic IgG aab response (Barabas et al., 2004c; Barabas et al., 2006a; Rich, 1996; Totoritis & Rubin, 1985; Weir & Elson, 1969; Weir & Pinckard, 1967). Administration of native ags during autoimmune disease states, e.g. during slowly progressive Heymann nephritis (SPHN), other experimental situations, do not make the disease process progress more intense (Barabas et al., 2006a; Bielekova et al., 2000; Peakman & Dayan, 2001; Prakken et al., 2004). Rather the opposite, in most instances they reduce the pathogenic immune response (Barabas et al., 2004c; Barabas et al., 2006a). It seems that even during a disease state the native target ag preferentially stimulates IgM aab production. The IgM aabs being cross-reactive, their increased levels remove from the circulation both the disease contributing native target ag and the disease causing modified target ag (Barabas et al., 2007a), contributing to remission.

It is worth noting, in reference to a broader context, that the initiation and intensification of an autoimmune disease are undoubtedly complex, and may involve numerous factors or processes besides those described above, such as:

- genetic predisposition;
- dysfunctional autoimmune system response (e.g. reduced phagocytosis and reduced specific IgM aab production due to age, malnutrition, vitamin deficiency, overwhelming infection, etc.);
- presentation of modified self aags or exogenous self-like ags to dendritic cells prior to antigenic information being processed by T and B cells for plasma cells to produce pathogenic IgG aabs;
- regulatory molecules (cytokines, chemokines, etc.) attempting to accelerate or decelerate autoimmune processes;
- complement systems or components playing dominant roles in aag and aab reactions during an autoimmune disease (in both pathogenic and non-pathogenic immune responses) (Blom, 2010):
    a. assisting in the complement-dependent clearance of modified/unmodified self that causes the autoimmune disease (Gaipl et al., 2001; Taylor et al., 2000; Zwart et al., 2004);
    b. in contributing to the continuously layered aag/aab depositions, e.g. in the glomeruli (Barabas et al., 2003; Barabas et al., 2004b; Barabas et al., 2004c) (pathogenic immune response) causing complement mediated C3, $C_5 9_b$ injury (Barabas et al., 2003; Barabas et al., 2004c) resulting in compromised glomerular filtration;
- overwhelming infection by an infectious agent presenting a whole range of potentially antigenic peptides that may initiate autoimmune disease by molecular mimicry;
- environmental factors;
- potentially self reactive clones of T cells can react with self because of immune regulation failure;
- in a few instances self ags can act to initiate and maintain pathogenic autoimmune responses against self, e.g. when regulatory T cells are out of control.

Notwithstanding the influence of such other factors, the set of processes described above appear to be fundamental to autoimmune disease involving misdirected auto-reaction, and understanding them has assisted in the development of a powerful technique to deal with autoimmune disease, as we will describe further below.

4.2.2 Inability to recognize and remove abnormal cell lines

Throughout life abnormal cell lines (some being cancerous) can emerge. They are most often recognized as non-self and removed by the cells of the autoimmune system. NK cells play a dominant role in this regard (Cheent & Khakoo, 2009; Foss, 2002; Topham & Hewitt, 2009).

Cancer specific non-self antigenic markers on the cell surfaces of emerging cancer cells are sometimes weakly antigenic; for this reason, they do not lend themselves to immune recognition and provoke immune response (Foss, 2002; Kim et al., 2007). In addition, tumour ags associated with cancer cell surfaces are camouflaged or protected on the cell membranes of these self-like cancer cells. The combination of minimal antigenicity and firm integration into and protection by the cell surface membrane means that even after cell death, these cancer specific ags do not detach to form individual small MW antigenic fragments that might be recognized as non-self for immune response processing. Further, if these cells are growing in a well vascularised space and allowed to spread into secondary sites without undermining influences such as ischemia, lack of nutrients, vitamins, or trace minerals, immune attack, etc. then the emerging cancer cells are more readily accepted as self. Several factors, such as old age, compromised immune system function (e.g. from treatment with immunosuppressive agents), overwhelming infections, exposure to harmful substances (smoking, alcohol, chemicals, drugs, etc.), and tumour derived soluble factors, can interfere with the normal functioning of the cells of the immune system in carrying out the surveillance of the somatic cells of our internal environments (Kim et al., 2007).

The lack of adjuvant in a mixture of the disintegrated components of dead cancer cells which include cell membrane associated ags has been shown to prevent pathogenic immune response against cancer specific ags, though it also prevented immune response against normal cell membrane associated ags (Ichim, 2005). And as we have noted elsewhere, normal self ags administered in adjuvants can induce pathogenic autoimmune responses, causing autoimmune disease – especially in the case of experimental autoimmune diseases (Barabas et al., 2004c; Heymann et al., 1959). Therefore, although a pathogenic autoimmune response is required against the cancer specific ag in order to kill (lyse) the cancer cells in the system, the use of an adjuvant to induce such an autoimmune response would likely have a deleterious effect against normal self as well. The question is how to overcome the immune system's inability to respond only against the non-self parts of cancer cells without causing harm to their normal functioning counterparts either in the organ where the primary tumour originated or elsewhere.

5. MVT for the prevention and cure of diseases caused by chronic immune disorders

Our MVT, which involves the administration of IC formed with condition-specific components that initiate and maintain a predetermined immune response, has the potential to prevent chronic ailments, and to cure already present diseases (Barabas et al., 2004b; Barabas et al., 2006c; Barabas et al., 2006b; Barabas et al., 2009a). This is the first time that the promise has existed to prevent, treat, and cure endogenous ag induced mishaps in humans specifically and without side effects.

The study of the affects of injection of ag:ab ICs at different ratios is not new, nor is the use of ICs in increasing ab production (Klaus, 1978; Kunkl & Klaus, 1981; Nie et al., 1997; Stoner et al., 1975; Stoner & Terres, 1963; Terres et al., 1972; Terres & Stoner, 1962; Terres & Wolins, 1959; Terres & Wolins, 1961) and even in vaccination (Haddad et al., 1997; Jeurissen et al.,

1998; Whitfill et al., 1995; Xu et al., 2005; Yao et al., 2007). So far most of the pertinent investigations have described the role that ag:ab ICs play in immune response upon injection of such complexes at various ratios, and how enhanced ab production occurs during primary and secondary ab responses (Barabas et al., 2007d; Heyman, 2000; Stoner & Terres, 1963; Xu et al., 2005; Yao et al., 2007).

To date, we are the only group to have described how specifically composed ag:ab complexes can redirect the immune response for the health benefit of the vaccinated host (Barabas et al., 2004b; Barabas et al., 2006c; Barabas et al., 2006b; Barabas et al., 2007c; Barabas et al., 2009a; Barabas & Lafreniere, 2005). The possibility of such an approach has just recently become a reality, following the categorization of autoimmunity into four clearly definable functioning immunological responses (Figure 2) against self (Barabas et al., 2008a;

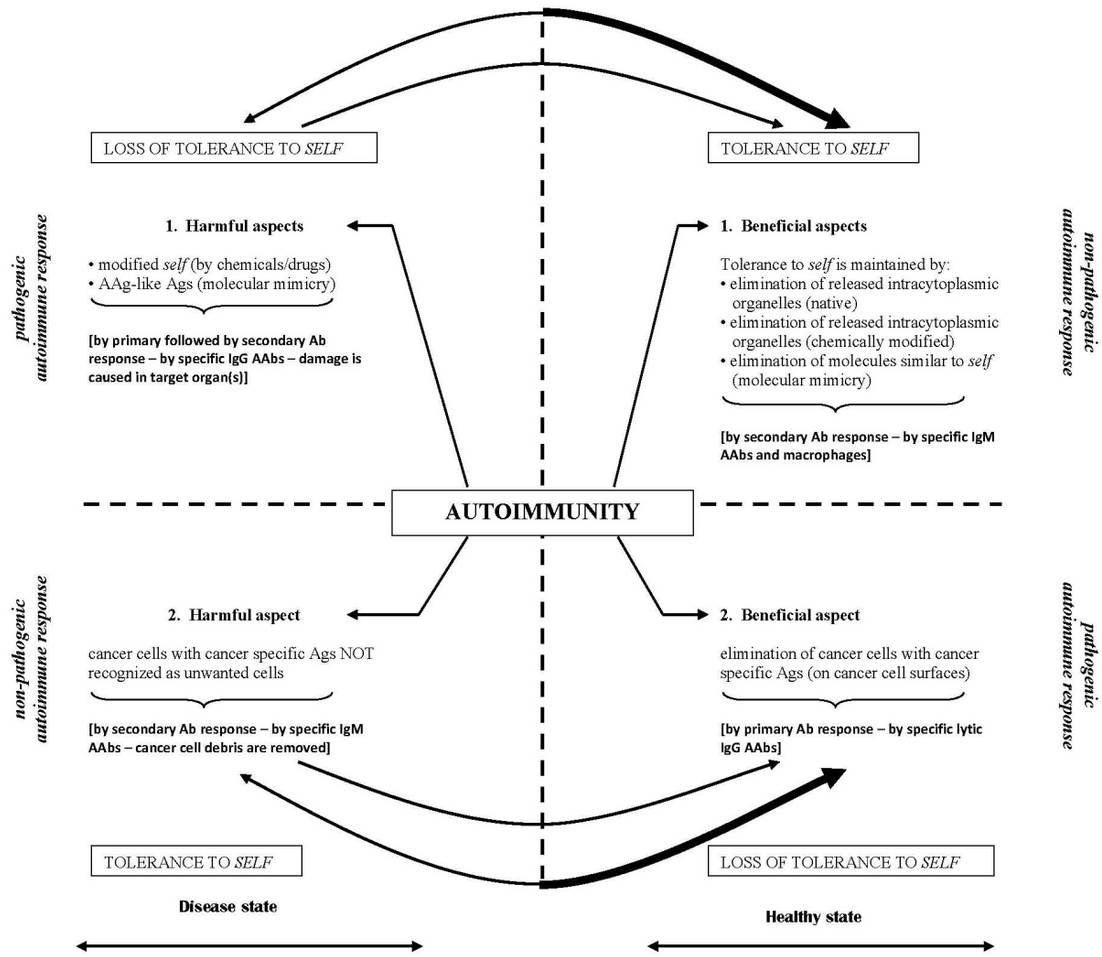

Fig. 2. Beneficial or harmful aspects of pathogenic and non-pathogenic immune responses.
The diagram illustrates the beneficial and harmful aspects of pathogenic and non-pathogenic aspects of autoimmunity. The MVT can restore non-pathogenic tolerance, ending an autoimmune disease. [Figure reproduced by permission from BioProcessing Journal, 2007 Winter;6(4):12-18.]
Abbreviations: AAb, autoantibody; AAg, autoantigen; Ab, antibody; Ag, antigen; MVT, modified vaccination technique

Barabas et al., 2009a), and the development of our understanding of autoimmune disease etiology and pathogenesis, in particular the role of non-pathogenic and pathogenic aabs (Figure 1) in both disease development and in its prevention and cure (Barabas et al., 2004b; Barabas et al., 2006c; Barabas et al., 2006b) (e.g. in autoimmune disease).
NOTE:

- The concept of autoimmunity is presently understood as pathogenic immune response against self, causing autoimmune disease.
- Autoimmune anomalies cannot be specifically prevented or treated by any of the presently available vaccination techniques.
- The concept of autoimmunity, according to our definition, encompasses four possible immune responses against self: two beneficial and two harmful ones.
- The harmful aspects of autoimmunity manifest in autoimmune diseases and cancer.

The immune system's natural ability can be utilized to bring about corrective immune responses which can cure/terminate chronic ailments by proper presentation of the target ag. In other words, the ag that causes or contributes to the disease can also terminate it, provided the antigenic information is presented to the cells of the immune system in the proper format.
The vaccination method we have developed – which is essentially the third vaccination rubric to have arisen, coming as it has after the conventional active and passive immunization techniques – promises to be able to deal with chronic ailments that are presently only treatable with drugs. Called MVT, it is so named because every time a vaccine is produced it must be formulated of components that are tailor-made to induce a specific corrective immune response. In order to achieve specificity – and to avoid collateral damage to normal body constituents – the production of absolutely pure and specific target ags and their abs is required. This can be done by present techniques, and soon more sophisticated methodologies will be available.

6. Components of the modified vaccine and how it works

6.1 Target ag against which the desired ab response is required

- For application in an autoimmune disease: ag prepared *ex vivo* that is identical in molecular composition to, and therefore the specific equivalent of, the host's target ag (native aag) (Kerjaschki, 2000a; Kerjaschki & Farquhar, 1982);
- For application in a chronic infection: ag derived from the causative organism, prepared *ex vivo*.

6.2 Ab against the disease causing/contributing target ag

- For application in an autoimmune disease: homologous non-pathogenic IgM ab directed against the target ag(s), prepared *ex vivo* by monoclonal ab technology;
- For application in a chronic infection: homologous pathogenic neutralizing IgG ab against target ags on the surface of infectious agents, prepared *ex vivo*.

The modified vaccine is composed of an IC mixture made up of the target ag and ab against the target ag in slight ag excess. E.g. in an experimental autoimmune kidney disease (Barabas et al., 2003; Barabas et al., 2004b; Barabas et al., 2006c; Barabas et al., 2006b) it was observed that:

- immunization with suitable IC (rat kidney fraction 3 X rat anti-rat kidney fraction 3 IgM ab) at slight ag excess prior and subsequent to disease-inducing inoculation prevented

the occurrence of the autoimmune kidney disease (Barabas et al., 2004b; Barabas et al., 2006b) (prophylactic vaccination);

- immunization post-disease-induction with the same IC, when the autoimmune disease was in its chronic progressive phase, terminated the disease causing immune events (Barabas et al., 2004b; Barabas et al., 2006b) (increased levels of specific IgM aabs removed both the pathogenic immune response inducing modified ag and the disease contributing native aag from the system, thereby terminating pathogenic immune response; therapeutic vaccination);
- corrective immune response induction was immediate (similar to secondary ab response);
- there was no need for adjuvant application as immune response was quick, specific, and powerful;
- the MVT was not a mere supplementary therapeutic option for prevention or treatment of the endogenous ag induced disorder; rather, it was key; by ab information transfer, utilizing the immune system's natural abilities. We achieved production in the vaccinated host of the same ab (i.e., the corrective immune response), with the same specificity against the target ag, as was present in the injected IC; and
- tolerance to self was accomplished specifically and without side effects (utilizing the MVT) by downregulating and terminating pathogenic immune events.

7. Conclusion

There are several reasons why up to now chronic disorders have been mainly treated with drugs and not by immune intervention. Perhaps the most important reason was that we were unable to present the offending ag(s) (i.e., the antigenic information) to the cells of the immune system in a suitable form to elicit corrective immune response outcomes. However, we have learned how to prepare and present exogenous ags such as bacterial/viral products to the body in attenuated or inactivated forms – usually in adjuvants – to elicit protective immune responses.

We have developed a new vaccination methodology called MVT that is able to downregulate immunopathological events in an experimental autoimmune kidney disease in animals and is also able to upregulate immune responses against an exogenous ag. This method, which is the third method of vaccination to be developed, has the potential not only to prevent but with equal effectiveness cure certain autoimmune diseases and chronic infections in humans.

Autoimmunity encompasses four possible immunological events against self, two beneficial and two harmful aspects (Figure 2). The two beneficial aspects of autoimmunity function throughout life to preserve the internal integrity of the organism by maintaining tolerance to normal self while preventing corrupted self from taking hold. The maintenance of antigenic homeostasis is the most important function of the autoimmune system.

The autoimmune system achieves its aim on one hand (the first beneficial aspect of autoimmunity) by degrading cellular debris – from cells damaged by various agents (e.g. chemicals, drugs, smoke, toxins, etc.) and from cells which have come to the end of their lifespan – into reusable small MW peptides. The efficient clearance of cellular waste is assisted by non-pathogenic IgM aabs prior to their degradation by phagocytic cells. These specific IgM aabs are the main agents of the maintenance of tolerance to self, and fulfill a

continuous physiological role throughout life. In a physiological sense, we are not *per se* tolerant to normal self components within cells.

On the other hand (the second beneficial aspect of autoimmunity) the autoimmune system works to eliminate abnormal cell lines that emerge as a result of external (e.g. drugs, radiation, smoking, etc.) and internal (e.g. genetic) influences. Emerging cancer cells are recognized and eliminated by NK cells. In addition, cancer specific ags can stimulate a pathogenic lytic IgG aab response, particularly when presented to the system with an adjuvant. These aabs may lyse cancer cells in the presence of complement and eliminate them from the system.

The two harmful aspects of autoimmunity, i.e., autoimmune disease and cancer, will manifest only if external (e.g. carcinogens, chemicals, infectious agents, UV irradiation, drugs, smoking) or internal (e.g. genetic) influences cause changes in the structural makeup of cells or cell products containing native ags. Such changes could result in harmful immune events leading to functional disturbance of the affected cells, tissues and organs.

Taking advantage of recent insight into the workings of the immune system, our MVT has proved itself to be effective in preventing the development of an experimental autoimmune kidney disease, and when the disease was in its progressive phase, in terminating it altogether, by halting immunopathological events that were causing the symptomatic, morphological and functional changes.

The immune system has a natural ability to correct immunological mishaps and restore the body to normalcy, provided the right information is presented to it for processing. The MVT is a way of presenting that information, in the form of specific ICs, and triggering or enhancing the body's own ability to counteract autoimmune disease, cancer, and chronic infection. We have observed that by injecting ICs – made up of a given endogenous or exogenous ag and a specific ab against it at slight ag excess – into experimental animals, the recipient's immune system produced the same ab, with the same specificity against the target ag, as was present in the IC (ab information transfer).

We have shown in experimental situations that corrective immune responses can be induced by the application of the MVT. We remain convinced that by the proper application of the MVT in humans, chronic diseases such as cancer, autoimmune disease, and chronic infections will be prevented and cured as well.

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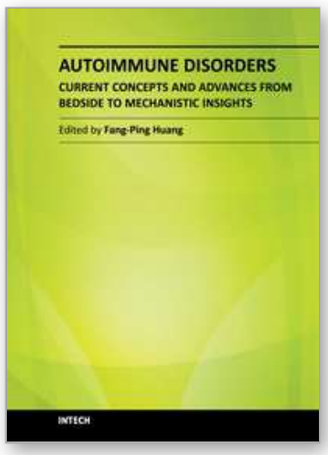

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Autoimmune disorders are caused due to break down of the immune system, which consequently fails in its ability to differentiate "self" from "non-self" in the context of immunology. The diseases are intriguing, both clinically and immunologically, for their diversified clinical phenotypes and complex underlying immunological mechanisms. This book offers cutting-edge information on some of the specific autoimmune disease phenotypes, respective diagnostic and prognostic measures, classical and new therapeutic options currently available, pathogenesis and underlying mechanisms potentially involved, and beyond. In the form of Open Access, such information is made freely available to clinicians, basic scientists and many others who will be interested regarding current advances in the areas. Its potential readers will find many of the chapters containing in-depth analysis, interesting discussions and various thought-provoking novel ideas.

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