Preventative and therapeutic vaccination to combat an experimental autoimmune kidney disease

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Abstract: We describe a new vaccination method called modified vaccination technique (MVT). The technique is able to achieve downregulation of pathogenic autoimmune events leading to a chronic progressive disorder in rats called slowly progressive Heymann nephritis. Downregulation of immunopathological events is achieved by injections of immune complex (IC) made up of the target native antigen (ag) and specific naturally occurring immunoglobulin M (IgM) antibody (ab) directed against it. Repeated injections of IC maintain high levels of specific circulating IgM autoantibodies (aabs) against the kidney ag. The developing physiologic IgM aabs assist in the catabolism of both modified and unmodified renal ags from the circulation. No disease-causing renal ags in the circulation results in no stimulation of pathogenic immunoglobulin G aab producing cell lines. Such specific targeted therapy leads to termination of disease-causing processes and reestablishment of tolerance. The MVT can be employed both prophylactically and therapeutically with equal effectiveness. A redirected immune response is achieved by specifically stimulating the animals' own IgM-producing cell lines with the injected ICs, resulting in a natural cure. Such ICs are nontoxic and nonirritant and cause no side effects. We surmise that the MVT, employing the appropriate components in each instance, can also be used to treat human ailments.

Keywords: antibody information transfer; autoimmune disease; immune complex; modified vaccination technique; prophylactic; therapeutic

Introduction

The reason why we cannot specifically treat experimental autoimmune disorders and naturally occurring autoimmune diseases in humans is that we still do not fully understand the autoimmune events that take place and contribute to the maintenance or loss of tolerance to self (Weigle et al 1967; Weir 1969; Tung 1994; Drakesmith et al 2000; Manz et al 2002). Hence autoimmune diseases are still not treated specifically, but rather with immunosuppressive agents. Not only are immunosuppressive agents nonspecific in action, most often resulting in serious side effects, but they also fail to cure the disease, since the underlying pathogenic immune events can continue despite the control of symptoms (Ben Yehuda et al 1988; Golbus and McCune 1994).

It should be acknowledged that not every autoimmune process is harmful. In effect, most of the autoimmune process related events occurring throughout life are physiologic (Grabar 1965, 1983; Weir et al 1966; Weir 1966; Casali and Notkins 1989; Nawata et al 1990; Chen et al 1995). Physiologic autoimmune events contribute in a major way towards the catabolism of intracytoplazmic components released into the circulation from cells at the end of their life span. In a physiological sense, we are not per se "tolerant" to our intracytoplazmic components (Weir and Elson 1969), since specific immunoglobulin M (IgM) autoantibodies (aabs) are designated from birth to react with

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these components and assist in their removal once they are released into the intravascular space (Solvason et al 1992). Such events prevent toxic accumulation of tissue breakdown products and/or their chemical modification by intrinsic or foreign agents (Yung et al 1995). Chemically modified autoantigens (aags) can initiate pathogenic autoimmune disease-causing responses (Totoritis and Rubin 1985).

The development of an autoimmune disease therefore results in most instances not from some malfunctioning of the immune system against normal self components but from abnormal presentation of self or self-like molecules to the cells of the immune system (ie, as modified self or by molecular mimicry) (Barabas and Lannigan 1969; Fujinami and Oldstone 1985; Wilson et al 2000; Lenz et al 2001; Barabas et al 2004c). This thesis presumes that normal intracytoplazmic components will not produce autoimmune disease per se but in the meantime does not preclude their participation in lesion development. The following explanation will help to clarify these statements.

Issues relating to altered self antigen initiated events

If a native antigen (ag) from the target organ is exposed and becomes modified, eg, by a chemical agent (Schoen and Trentham 1981; Totoritis and Rubin 1985; Yung et al 1995; Rich 1996) in the intravascular space, or if a modified self-like ag is administered repeatedly (Barabas et al 2003, 2004c), then the following events can occur:

- If the modified ag initiated events are short-lived, then a limited pathogenic autoimmune disease process will result in minimal functional and morphological alterations in the target organ (Totoritis and Rubin 1985).

- If the modified ag initiated events are maintained, then a progressive autoimmune disease process will ensue by the developing pathogenic immunoglobulin G (IgG) aabs and cause major morphological and functional change in the target organ resulting in a diagnosable autoimmune disease (Heymann et al 1959; Mendrick et al 1980).

Pathogenic autoimmune disease-causing events can take place because the pathogenic aab (resulting from the stimulation of IgG aab producing cell lines by the modified native ag) is able to cross-react with both native and modified aags present in the circulation and in the target organ (eg, in the kidney it reacts with fixed glomerular kidney ags and forms immune complexes (ICs) during the course of the autoimmune disease).

Genetic predisposition can also affect autoimmune disease development. Certain patients are unable to respond

with sufficiently strong immune responses to bacterial or viral infections. Under such circumstances, bacterial or viral breakdown products linger on at the site of infection, and sustained tissue damage occurs whereby cells are injured and intracytoplazmic components are released. In this local milieu the ideal conditions are thus created for the modification of self ags. If a low-grade chronic infection persists, then pathogenic IgG aab production (occurring alongside IgM aab production) can commence. If such events are sufficiently prolonged then serious morphologic and functional alterations can take place in the target organ and lead to a chronic progressive autoimmune disease (Wucherpfennig 2001).

Genetic susceptibility could also be due to physiologic immune response deficiency where an infection is not involved. For example, an individual's immune system might be unable to produce sufficient amounts of specific IgM aabs to clear released intracytoplazmic ags from the intravascular space; under such conditions aags can become modified by agents (chemicals, drugs, toxic compounds, etc) present in the circulation and initiate pathogenic IgG aab response against the modified self. If pathogenic IgG aabs are continuously produced then damage to a target organ can cause a low-grade slowly progressive autoimmune disease.

Issues relating to normal self ag initiated events

Although normal aags will not themselves produce an autoimmune disease, they can contribute to disease establishment and progression for two reasons. First, the normal aags within an organ can become the primary targets of pathogenic autoimmune processes (Barabas et al 2004a), and second, they can contribute to IC deposits in affected organs (eg, in the glomeruli) (Barabas et al 2003).

In our studies we found that the physiologic IgM aabs and pathogenic IgG aabs cross-react with both normal and modified ags (Barabas et al 2004b):

- Pathogenic aabs reacting with normal aags in the target organ cause autoimmune disease (Barabas et al 2003), and when reacting with modified aags in the circulation, maintain increased pathogenic IgG aab production.

- Nonpathogenic IgM aabs also react with both native and modified ags in the circulation and assist in their catabolism.

Heightened IgM aab production is maintained alongside IgG aab production during an autoimmune disease state both by native aags per se that are released into the intravascular space (Barabas et al 2003) and by developing ICs (made up

of native aags and specific IgM aabs). Thus, while pathogenic IgG aab production attempts to increase the severity of insult against a target, there is a concurrent attempt by the IgM aabs to slow down pathogenic autoimmune processes (Barabas et al 2006c).

Despite the normal functioning of the IgM mechanism, as long as the modified ag is present and maintains pathogenic IgG aab production, tissue damage will proceed towards chronic progressive changes that result in morphological and functional alterations. But tipping the balance in favor of increased IgM aab production, in order to neutralize the circulating modified and native ags that contribute to pathogenesis, can halt the autoimmune disease altogether (Barabas and Lafreniere 2005).

Recent attempts to treat autoimmune disorders

So far research scientists have not come up with a specific immune-inducing technique that could prevent or treat endogenous source ag derived chronic ailments (such as autoimmune disorders and cancer). This might be due to the very complex science that describes autoimmune related diseases. Indeed, consensus as to the etiology and pathogenesis of autoimmune diseases still has not been reached (Tung 1994; Theofilopoulos 1995; Garza et al 2000; Lernmark 2001; Ludewig et al 2001; Sherman 2001; Lafaille and Mathis 2002). Consequently, diverse opinions and research efforts continue to contribute to the probative and problem-solving work to find a cure. Under these circumstances the use of immunosuppressive agents is still advocated to treat patients with chronic ailments. In recent years treatment with monoclonal abs has achieved approval but most of such products are not specific in their action and cause side effects. Another treatment modality, the oral presentation of tissue-derived ags, has in experimental animals and even in humans with autoimmune disorders had a degree of beneficial influence on autoimmune disease-causing events, but has not resulted in a cure (Ramiya et al 1997; Weiner 1997, 2000; Faria and Weiner 1999; Bilsborough and Viney 2002).

The form of presentation of the target aag in producing (and also in preventing and treating) an autoimmune disorder can influence outcomes even to the extent of determining final states of disease or no disease. A detailed schematic of the events involved is given in Figures 1 and 2. Under certain circumstances native aags and injected disease-related ags can start or worsen disease progression (Peakman and Dayan 2001), for example when an aag released from the intracytoplazmic environment or an injected disease-related ag is modified by a modifying agent present in the individual's intravascular space (Figure 3). Such modifying agents can be drugs (Yung and Richardson 1994) or their metabolic products, or toxic agents derived from infectious microbes etc (Guilherme and Kalil 2004). Peptides of microbial proteins, exhibiting sequence similarity or identity to self peptides through molecular mimicry (Wucherpfennig 2001), can also activate autoreactive T-cells and cause autoimmune disease. Under these unusual circumstances autoimmune disease-initiating processes can take place; however, under normal circumstances "native" intracytoplazmic ags liberated into the circulation will not cause pathogenic IgG aab response.

A new vaccination technique for the prevention and treatment of an experimental autoimmune kidney disease

Heymann nephritis (HN) and slowly progressive Heymann nephritis (SPHN) are pathogenic IgG aab initiated and mediated autoimmune diseases (Heymann et al 1959; Barabas et al 2004c). Classical HN is established in susceptible strains of rats by repeated IP injections of nephritogenic ags incorporated into Freund's complete adjuvant [FCA] (Barabas and Lannigan 1969). After two to four injections of the preparation, progressive proteinuria, severe morphological changes in the kidney, and in the circulation pathogenic IgG aab against the brush-border region of the renal proximal convoluted tubules commences. Attempts to treat HN by various agents before or after the induction of the disease have proved to be unsuccessful (Barabas et al 1969, 1970; Kupor et al 1976; Cattran 1988; Matsukawa et al 1992; Penny et al 1998; Yokoyama et al 1999; Hasegawa et al 2001;). The futility of these attempts to downregulate immunopathological events has been due to at least two factors:

- Kidney ag injected in FCA established an irreversibly progressive disease process with the development of pathogenic IgG aabs (Andres et al 1986).
- Agents used to circumvent disease development or treat the progressive disease did not act specifically to achieve downregulation or termination of the ab-mediated response against kidney-directed immune insults (Barabas et al 1969, 1970; Baker et al 1989; Penny et al 1998; Hasegawa et al 2001; Spicer et al 2001).

We realized that in order to influence immunopathological events we needed to establish a new model of HN that was
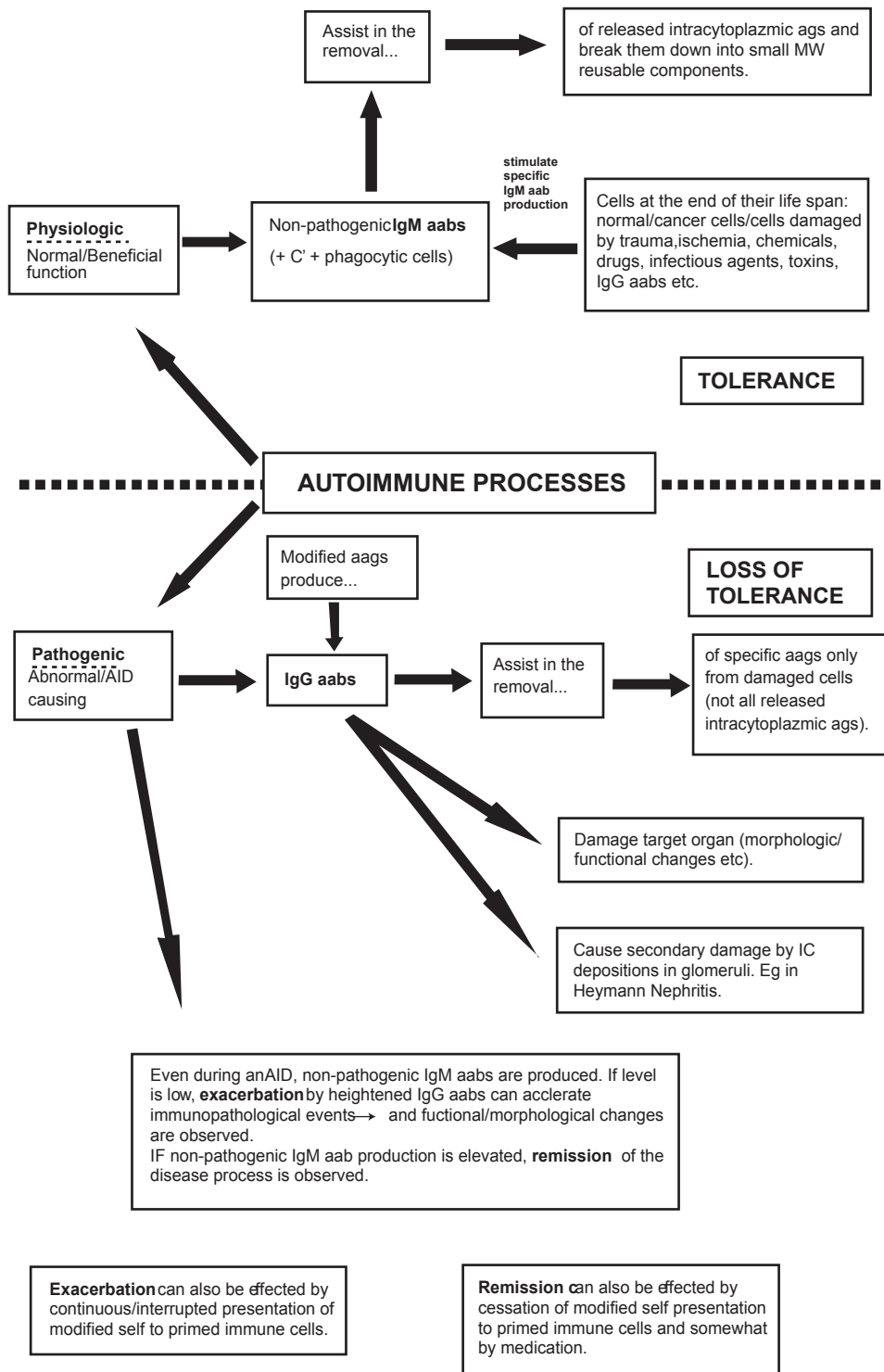
Figure 1 Autoimmune processes initiated and maintained by native and modified autologous antigens.

Note: Autoimmune disease is initiated by pathogenic IgG aabs against modified self (or by molecular mimicry). The cells of the individual's immune system see the modified self or self-like ags as exogenous (foreign-like) ags and respond accordingly to eliminate them with the developing IgG aabs. In the process of eliminating a particular aag major damage can occur by the pathogenic IgG aabs reacting with antigenic components in the target organ resulting in organ failure (brought about by morphological and functional changes) and even death. In order to reverse pathogenic autoimmune disease-causing events the following must take place:

1. Removal of the inciting agent that modifies the autologous ags, if it can be identified (it could be a drug, infectious agent etc);
2. Increase in the specific IgM aab response against the target ags capable of removing both modified and native ags from the circulation; or
3. Preferably both 1 & 2.

"Native" aags initiate and maintain physiologic IgM aab response throughout life, assisting in the removal of intracytoplasmic aags released into the intravascular space.

Abbreviations: aab, autoantibody; aag, autoantigen; ag, antigen; AID, autoimmune disease; C, complement; IC, immune complex; IgG, immunoglobulin G; IgM, immunoglobulin M; MW, molecular weight.
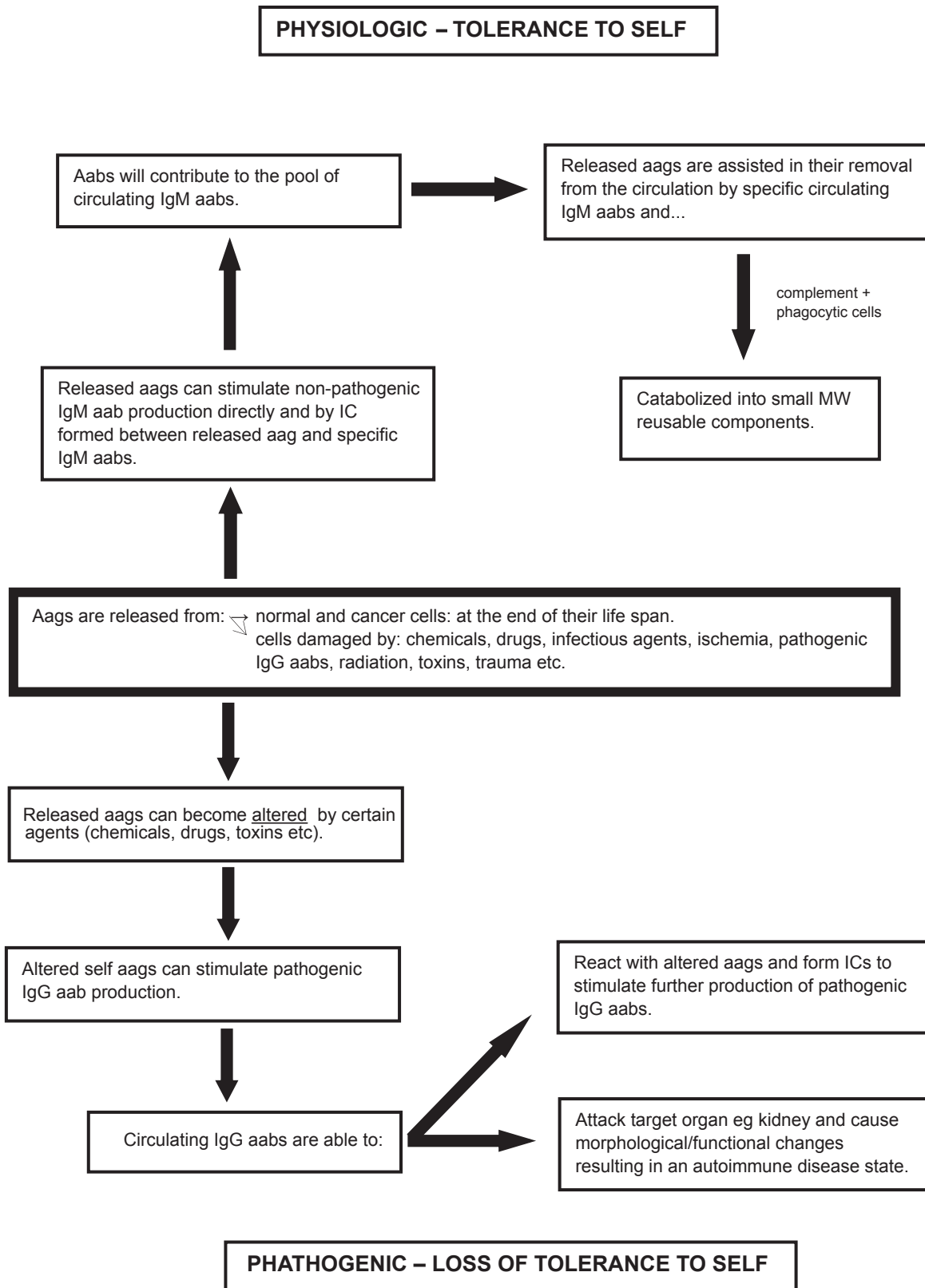
PHYSIOLOGIC – TOLERANCE TO SELF

Aabs will contribute to the pool of circulating IgM aabs.

→

Released aags are assisted in their removal from the circulation by specific circulating IgM aabs and...

complement + phagocytic cells

Catabolized into small MW reusable components.

Released aags can stimulate non-pathogenic IgM aab production directly and by IC formed between released aag and specific IgM aabs.

Aags are released from: normal and cancer cells: at the end of their life span.
cells damaged by: chemicals, drugs, infectious agents, ischemia, pathogenic IgG aabs, radiation, toxins, trauma etc.

Released aags can become <u>altered</u> by certain agents (chemicals, drugs, toxins etc).

Altered self aags can stimulate pathogenic IgG aab production.

React with altered aags and form ICs to stimulate further production of pathogenic IgG aabs.

Circulating IgG aabs are able to:

Attack target organ eg kidney and cause morphological/functional changes resulting in an autoimmune disease state.

PHATHOGENIC – LOSS OF TOLERANCE TO SELF

Figure 2 Possible fate of released autoantigens.
Note: Most of the time intracytoplazmic components released from damaged cells will be catabolized by physiological processes involving specific IgM aabs. However, when aags are altered, modified aags can initiate and maintain disease-causing pathogenic aab production.
Abbreviations: aab, autoantibody; aag, autoantigen; IC, immune complex; IgG, immunoglobulin G; IgM, immunoglobulin M; MW, molecular weight.
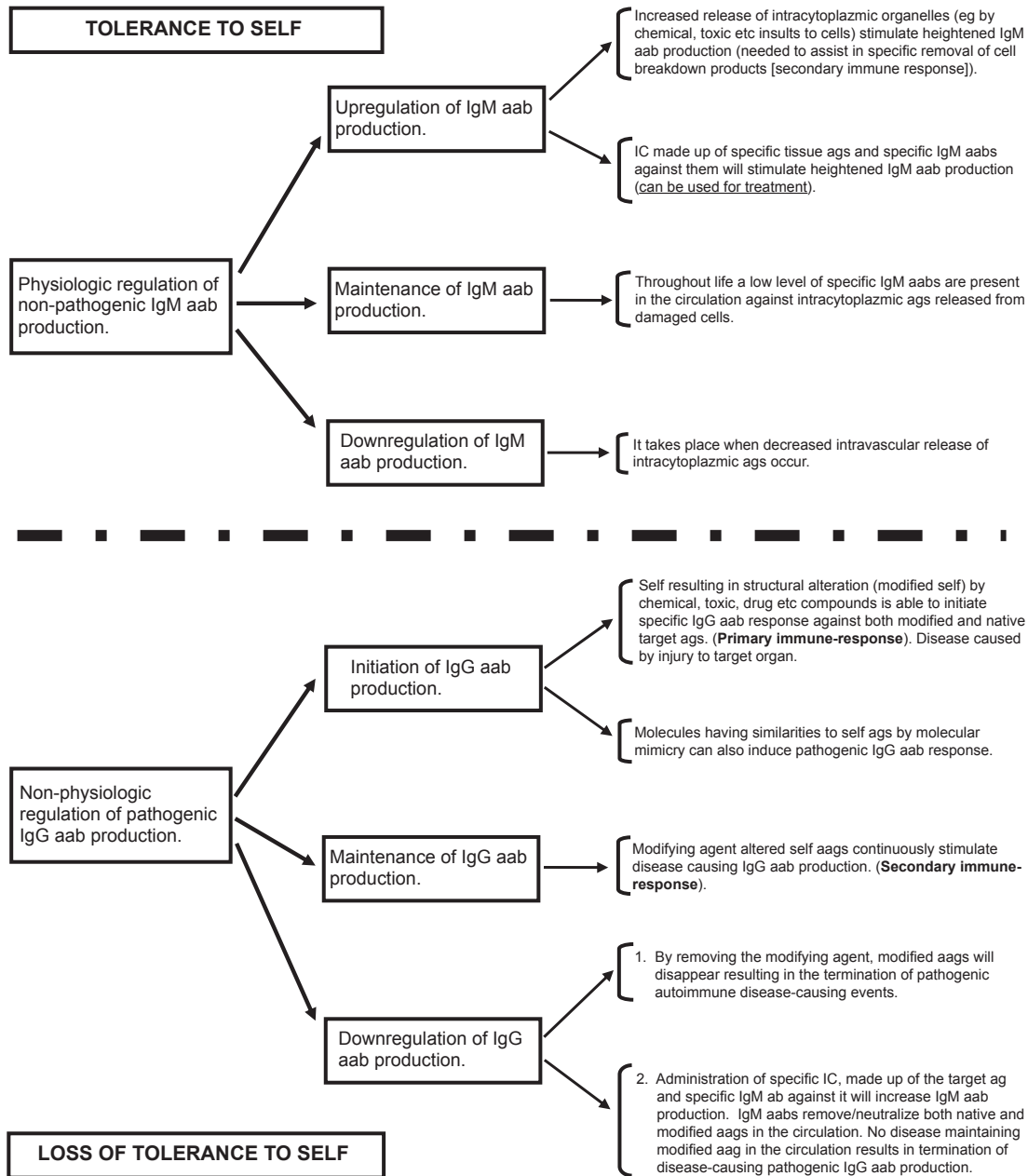
Figure 3 Downregulation/upregulation of nonpathogenic and pathogenic autoimmune processes.
Note: Both physiologic and pathogenic autoimmune initiated and maintained events are regulated by the presentation of native and altered self-aags to the cells of the immune system. As shown, autoimmune disease-causing events can be accelerated as well as terminated by appropriate presentation of native aags.
Abbreviations: aab, autoantibody; ag, antigen; IC, immune complex; IgG, immunoglobulin G; IgM, immunoglobulin M; MW, molecular weight.

slowly progressive. We established two models of SPHN. One was produced by using alum instead of FCA as the adjuvant in the injected renal ag (Barabas et al 2003). The other, which perhaps mimics most closely the development of a slowly progressive autoimmune disease in humans, was established by repeated injections of a chemically modified renal ag preparation (Barabas et al 2004c). The two SPHN models illustrate the process by which immunological

mishaps result in pathogenic autoimmune events that cause harm in target organs and lead to morphological and functional changes.

The next challenge was to find a way to correct such immunological mishaps. To do so we have developed a new vaccination technique, and have successfully employed it in both SPHN models, before and after the initiation of the disease. This modified vaccination technique (MVT), which

is a hybrid of active and passive immunization programs, has proven itself capable of redirecting immune responses (Barabas et al 2004b, 2006b, 2006c).

In our SPHN experimental autoimmune disorder models, the MVT achieved specific downregulation of disease initiating and maintaining events (Figure 3). We produced specific ICs made up of the disease-causing native kidney tubular ag and specific IgM abs directed against it at slight ag excess (Barabas et al 2004b, 2006b, 2006c). Injections of these ICs at weekly intervals maintained high levels of circulating nonpathogenic IgM aabs. The increased production of IgM aabs neutralized both modified and native ags by removing them from the circulation and preventing them from playing a part in pathogenic autoimmune events. Since the modified ag was no longer available to stimulate pathogenic IgG aab production, the pathogenic IgG aab producing cell lines were silenced. The unmodified (native) ag, normally located in the glomeruli of the kidney (Kerjaschki and Farquhar 1983; Cornish et al 1984) and also present in the circulation (Makker and Singh 1982; Singh and Makker 1986; Singh and Schwartz 1986), did not remain a target of pathogenic aabs or a contributor to further deposition of IC. The absence of altered or native ags in the circulation meant downregulation of pathogenic autoimmune events (Figure 3).

We maintain that such downregulation of pathogenic autoimmune events can only be achieved with our MVT. The MVT is effective in both pre- and post-treatment protocols, ie, both in preventing autoimmune disease development (Barabas et al 2006b) and in terminating ongoing auto-immune disease processes (Barabas et al 2004b, 2006c). The MVT, via the injection of ICs with predetermined immune inducing components, produces the same class of immunoglobulin (in our case specific IgM aabs directed against the nephritogenic ags both modified and native) with the same specificity against the target ag as resides in the inoculum. The technique provides a specific redirected immune response without influencing normal immune events in any way. The ICs are nontoxic and nonirritant in both short- and long-term applications. The technique achieves total downregulation of pathogenic autoimmune events resulting in regained tolerance. However, since memory cells are retained for pathogenic aab production, pathogenic autoimmune events could start up again if modified ags are reintroduced.

Summary and concluding remarks

Vaccination over the last 200 years has prevented the occurrence and spread of often lethal infectious and contagious diseases (diphtheria, small pox) in our population. However, in spite of vaccination's development, many diseases initiated and maintained by exogenous ags (HIV/AIDS, malaria, TB) and all of those caused by endogenous ags (autoimmune diseases, cancer) are still not controlled or treated either by prophylactic or therapeutic vaccination programs. Numerous attempts, especially within the last few years, attest to the desire to come up with effective vaccinations to deal with chronic ailments (Peakman and Dayan 2001; Schijns 2001; Andre 2003; Reed and Campos-Neto 2003; Slingluff, Jr. and Speiser 2005; Tang and Bluestone 2006). The fact that we still have not come up with specific vaccination technologies, despite enormous investments of money, manpower, government resources, etc, confirms that the search for a cure is not easy. However, we are inching towards solutions. Lately there have been many publications that provide hope, not only for better drugs, but also for other treatment methods able to influence immune response outcomes (Peakman and Dayan 2001; Stauss 2001; Maloney et al 2002; Melief et al 2002; Morris et al 2003; Clynes 2005; Polakis 2005). We have substantial evidence demonstrating that a normally functioning immune system can exert protective immune responses against exogenous source ags (bacteria, viruses, etc) but often not so protective immune responses against harmful endogenous source ags. Sorting out physiologic and pathogenic immune activity against endogenous source ags – ie, events that can maintain, break, or reestablish tolerance – would provide us the chance to understand how to manipulate immune responses, eg, for tolerance reestablishment in an autoimmune disease. (In cancer, we would require the opposite. We would want a specific immune response against cells bearing cancer-specific ags, for the elimination of these cancer cells from the host's internal environment).

So far autoimmune diseases have been generally treated with immunosuppressive agents (Barabas et al 1969, 1970; Bolton et al 1974; Cattran 1988). These medications nonspecifically suppress immune functions and predispose patients to infections. The aim in the last few years has been to find better solutions or techniques to downregulate autoimmune disease-causing immune events. By observing the "natural" and "pathogenic" events that take place in normal and experimental autoimmune disease induced animals, one can investigate physiologic and pathogenic autoimmune responses in health and in disease. Extensive literature documents how aags released from the intracellular environment are assisted in their removal by specific IgM aabs (Weir et al 1966; Elson and Weir 1967;

Casali and Notkins 1989; Avrameas 1991; Chen et al 1995; Coutinho et al 1995; Barabas et al 2003). These aabs are physiologic and specific in their action against native and corresponding modified native aags. Weir and associates have shown that specific naturally occurring IgM aabs play a significant role in the catabolism of intracytoplazmic ags released from normal cells (Pinckard and Weir 1966; Weir et al 1966) at the end of their lifespan and following injury by cytotoxic and infectious agents, burns, hypoxia, trauma, etc. Such observations led naturally to the suggestion that these aabs played a role in the maintenance of tolerance to self ags (Weir and Elson 1969), ie, by efficiently removing intracytoplazmic waste.

Several experiments have revealed promptly increased IgM aab production (since animals/humans are not per se "tolerant" to escaped intracytoplazmic cell components) following massive release of aags from the intracellular environment [secondary ab response] (Pinckard and Weir 1966; Weir 1966; Barabas et al 2003). The elevated level of circulating IgM aabs assist in the removal of released aags. However, if the circulating released aags are not efficiently cleared in the shortest possible time, they can become modified by agents present in the circulation such as drugs or their breakdown products, toxic agents, etc. In order to prevent toxic or modified-self aag accumulation in the intravascular space, we can increase IgM aab production more effectively (ie, not relying on IgM aab stimulation by released aags alone) by administering ICs made up of aags and specific IgM abs directed against them at slight ag excess. These ICs, as mentioned above, will enhance the production of the same class of immunoglobulin with the same specificity against the target ag as resides in the inoculum.

The implementation of our MVT is most appropriate during a pathogenic autoimmune event, such as in our experimental autoimmune kidney disease (Barabas et al 2004b, 2006a, 2006b, 2006c), for the following reasons:

- During an autoimmune disease process both pathogenic IgG aabs and nonpathogenic IgM aabs are produced. Pathogenic aabs cause harm and nonpathogenic aabs attempt to remove both native and modified self ags thereby aiming to terminate autoimmune disease-causing events.
- The pathogenic IgG aab production is maintained by modified self-like ags.
- The nonpathogenic IgM aab production is maintained by native aags.
- Tipping the balance between IgG aab and nonpathogenic IgM aab production in favor of IgM aab response is

achieved by injections of suitably assembled ICs made up of the target ag and specific IgM ab against it. The resulting increase in IgM aab in the circulation assists in the removal of both native and modified ags and prevents further production of pathogenic IgG aabs.

- In certain autoimmune diseases the inciting agent also has to be removed to achieve termination of pathogenic aab production.

We have shown that by redirecting an immune response we can prevent an experimental autoimmune kidney disease-causing process from beginning (Barabas et al 2006b) and also terminate it with equal effectiveness when the disease is established (Barabas et al 2004b, 2006c). This solution is achieved by the MVT that we have developed. The vaccination technique can evoke a specific predetermined immune response of our choosing by stimulating appropriate ab-producing cell lines, as long as the appropriate vaccine components are present. The injected components are nontoxic and nonirritant and do not cause any disturbance in the normal functioning of the immune system. The MVT achieves by ab information transfer the production in the vaccinated recipients of the same class of immunoglobulin (ie, ab) with the same specificity against the target ag as resides in the inoculum. According to our assessment, the immune system should be able to correct any mishaps that might occur (associated, eg, with autoimmune diseases, cancer, chronic infections, etc) provided the cells of the immune system are afforded the right presentation of the offending ag.

We predict that this MVT will in time be the vaccination technique of choice for both the prevention and with equal effectiveness the treatment of most of the presently untreatable diseases caused by exogenous and endogenous source ags.

Acknowledgments

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