

Regaining Tolerance to a Self-antigen by the Modified Vaccination Technique

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Abstract Autoimmune diseases are initiated and maintained by complex immunopathological processes in environmental and genetic factor predisposed patients. In certain autoimmune diseases, the etiologies and pathogenesis of the conditions are quite well understood; yet in others, controversy surrounds as to why and how auto-injurious processes start. Clinical and laboratory examinations reasonably well define the state of progression/remission of an autoimmune disease and allow treatment according to observed findings. However, none of the presently employed treatment options are specific. In fact, they are all nonspecific in their actions and have undesirable side effects. Over the years, experiments carried out in animals have shed light on the complex immunopathological processes which contribute to disease development and progression. At least one experimental autoimmune kidney disease—which we shall describe—helps to understand how pathogenic autoimmune responses can be terminated specifically, without side effects. Since the new vaccination method—that we call modified vaccination technique—was successfully implemented in an experimental autoimmune disease model called slowly progressive Heymann nephritis for the termination of pathogenic immune responses by a target antigen-specific treatment modality, we shall highlight its use in providing insight to physicians and autoimmunologists for its future implementation in human autoimmune diseases.

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Abbreviations

aab	Autoantibody
aag	Autoantigen
ab	Antibody
ag	Antigen
BB	Brush border
GBM	Glomerular basement membrane
GN	Glomerulonephritis
IC	Immune complex
ICGN	Immune complex glomerulonephritis
MGN	Membranous glomerulonephritis
MVT	Modified vaccination technique
MW	Molecular weight
rKF3	Rat kidney fraction 3
rarKF3	Rat anti-rat kidney fraction 3
SPHN	Slowly progressive Heymann nephritis
IgG	Immunoglobulin G
IgM	Immunoglobulin M

Introduction

Antigen (ag)-specific termination of autoimmune diseases is believed to be possible [1]. However, to accomplish this seemingly impossible task, a vaccination technique, other than the ones presently used, should be implemented. In the meantime, autoimmune diseases are treated by non-ag-specific treatment options [1–7] which do not terminate the disease and cause side effects.

We believe that normal tissue components, on their own, cannot produce autoimmune disease-causing immune responses [8–10]. Autoantigens (aags) have to be modified

[8, 11–18] chemically or structurally into hapten–self-protein conjugates before the cells of the immune system recognize them as foreign ags and mount pathogenic immune responses against them. As long as the cells of the immune system are exposed to modified self-ags, pathogenic immune-mediated (cellular/humoral) events will continue [8] and cause targeted tissue damage. It is also believed by some researchers that long-lived plasma cells, after initiation of a pathogenic immune response against self, will continuously produce pathogenic immunoglobulin G (IgG) autoantibodies (aabs) and maintain the autoimmune disease [3, 6, 7].

Present treatment options of autoimmune diseases show beneficial effects in clinical signs and symptoms, e.g., when tumor necrosis factor is targeted in rheumatoid arthritis and multiple sclerosis [1], or when CD20 is targeted by rituximab (an anti-CD20 antibody (ab)) in rheumatoid arthritis, systemic lupus erythematosus, and multiple sclerosis [3, 6, 19]. Nevertheless, neither approach is able to terminate autoimmune diseases.

We shall describe and illustrate, as an example, how immune events initiate and maintain an experimental autoimmune kidney disease called slowly progressive Heymann nephritis (SPHN) in rats by pathogenic IgG aabs directed against the brush border (BB) ag of the renal proximal convoluted tubules, and how immunopathological responses are responsible for a secondary immune-mediated event that results in immune complex glomerulonephritis (ICGN) [20–29]. In this typical autoimmune disease, we have shown that autoimmune kidney disease-causing events can be prevented [30], and when the disease was established it could be terminated [31, 32] by an ag-specific treatment option utilizing a new vaccination method that was introduced by us called modified vaccination technique (MVT) [33, 34].

General Background to Autoimmunity

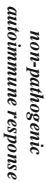
Over the years, it was learnt and stated that the word “autoimmunity” encompasses four possible immune responses against self: two beneficial and two harmful ones [35, 36]. During normal physiological conditions, one expects beneficial aspects of the immune response to dominate against self [37, 38]. One of the beneficial responses against self-ags is manifested by the immune system’s ability to remove from the circulation, released intracytoplasmic ags from cells by specific immunoglobulin M (IgM) aabs and mononuclear cells, thereby keeping the internal environment of the host free of floating nonfunctional cell debris [37, 39–44]. The other beneficial response is manifested by the elimination of those intact cancer cells which emerge from a clone of cells with cancer-specific ag cell surface markers [35]. Unfortunately, there are harmful immune events

against self as well. One of the harmful immune responses against self is manifested in autoimmune diseases [16, 45–47] and the other one is due to the inability of the immune system to recognize and eliminate cancer cells [35, 48] (Fig. 1).

In the present communication, we shall emphasize how an autoimmune disease emerges [20, 22, 29, 49–51] and how it can be terminated specifically without side effects, relying on the immune system’s ability to respond to corrective information [31, 32, 52–54].

Throughout life, there is an inbuilt protective mechanism which, in animals and humans, prevents pathogenic immune responses to occur against self-ags [39, 40]. Broken-down cellular components, released from intact cells, as a consequence of aging or from cells having been damaged by toxic agents, e.g., by smoking, alcohol, infectious agents, chemicals, drugs, UV light, vaccines, etc. [8, 11, 15], are assisted in their removal from the system by specific nonpathogenic IgM aabs [53] and degraded into small molecular weight (MW) peptides by mononuclear cells. These simple yet effective immune-mediated processes prevent toxic accumulation of cellular breakdown products and their possible chemical or structural modification that could lead to a modified self-ag-initiated autoimmune disease [8, 18, 46]. Through this process, broken-down cellular components are reutilized and become available for functional and structural proteins.

Unfortunately, this normally functioning physiological process can be disrupted and released aags can be modified into hapten–self-protein conjugates [8]. Hapten–self-proteins, being not quite self-ags, are recognized by the immune system as foreign proteins and an immune response against them evokes a pathogenic IgG aab-mediated event that results in a targeted attack on the organ where the native aags reside [8]. In SPHN, the primary damage occurs to the BB-associated nephritogenic ag of the renal proximal convoluted tubules [54, 55]. During the course of investigating immunopathological events in SPHN, it was learnt that both specific nonpathogenic IgM aabs and pathogenic tissue-damaging specific IgG aabs are present in the circulation [8, 31, 49, 56], and that they are both cross-reactive. That is to say, specific nonpathogenic IgM aabs are not only able to react with the released native aags from damaged cells, but also with the same modified native aags. In this way, they assist in the elimination/neutralization of both released normal and modified self-ags. Similarly, the specific pathogenic IgG aabs are not only able to react with the hapten–self-proteins which initiated their production, but also with the native aags which reside in the organ of origin. The reaction of the specific pathogenic aabs with the native aag within an organ leads to damage, and if the damage is continuous, it will lead to a chronic progressive autoimmune disease.



*pathogenic
autoimmune response*

57], and if such events become chronic in nature, an autoimmune disease will manifest itself in clinical signs and symptoms. Such immune events are not beneficial to the host, and if they are maintained for a prolonged period of time, then serious structural and functional disturbances could occur in the target organ [14, 49]. Tolerance to self, in such an instance, can only be regained if the inciting agent (which modified the self-ag, driving the pathogenic immune response against the self-ag) is removed from the system. Even if the immune response is halted, the resulting tissue damage could compromise the functional and structural integrity of the affected part(s). The only time when a pathogenic autoimmune response against self is beneficial to the host is when it is directed against cancer-specific ag markers for cancer cell recognition and elimination. If such a pathogenic immune response is completed, then tolerance to self is regained. However, if such a pathogenic aab response is not directed against cancer-specific ags found on cancer cell surfaces then cancer will prevail.

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Tolerance to self is a balancing act throughout life, and the immune system's ability to correct and maintain "normal" functioning organs, tissues, and cells are called upon continuously. For this reason, it is wise not to expose the cells of the immune system to chemically or structurally modified self-aags that can cause autoimmune diseases or to agents that are carcinogenic and cause cancer [58].

Lessons Learnt from Immune Events that Can Initiate and Maintain Autoimmune Diseases

Experimental counterparts of human autoimmune diseases provide useful information for the etiology and pathogenesis of autoimmune diseases [8, 10, 22, 24, 26]. By knowing what immunological processes are taking place, we are closer finding answers as to how to interfere and perhaps even terminate undesirable immune events against self. For years, we have investigated an experimental autoimmune disease which is morphologically and functionally similar to membranous glomerulonephritis (MGN) [49, 59]. The autoimmune disease model is represented by SPHN, an autoimmune kidney disease of rats. It is initiated and maintained by repeated injections of a nephritogenic ag in alum [49]. It develops into a chronic disease slower than Heymann nephritis, but in its advanced state, it is similar in every aspect to its counterpart [8, 49] and to MGN of humans. Because of its slower onset and development into a chronic progressive glomerulonephritis (GN), there is enough time to study the various aspects of the immune response against the kidney and find ways to downregulate harmful immune events [31, 32, 53]. The injected adjuvanted nephritogenic ag causes the production of pathogenic IgG aabs against the nephritogenic ag [32, 53]. The developing pathogenic IgG aabs' main target is the BB localized and produced nephritogenic ag [22, 29, 60], and its continuous bombardment results in the autoimmune kidney disease [21, 26]. The pathogenic antinephritogenic ag IgG aabs' secondary target is the glomerular basement membrane (GBM)-localized nephritogenic ag, causing ICGN [23–25, 27].

Till recently, the injury to the GBM was considered to be due to an autoimmune kidney disease-causing event by pathogenic IgG aabs for the following reasons: It was shown that the developing pathogenic IgG aabs reacted with the glomerular fixed and glomerular epithelial cell-produced nephritogenic ags [23, 61] causing the initial deposition and formation of immune complexes (ICs) in the presence of complement. Chronic progressive GN resulted from the continuously produced nephritogenic ag by the epithelial cells of the GBM and the continuously produced pathogenic antinephritogenic ag IgG aabs depositing and forming large ICs on the epithelial side of the GBM in the presence of complement [23]. If this was true, then the GBM-produced

lesion could also be considered to be due to an autoimmune disease-causing immune event. However, Barabas et al. conclusively demonstrated that the GBM-localized nephritogenic ag is present on its epithelial aspect by ICs made up of: [nephritogenic ag $\times$ autologous anti-autologous nephritogenic ag IgM aab] [62]. Presumably, these ICs—sparsely present in the glomeruli (and more abundantly in the mesangium)—are located temporarily without causing harm at these anatomical sites because of their physicochemical properties. To these ICs, the developing pathogenic IgG aabs (directed against the nephritogenic ag portion of the ICs) joined, followed by nephritogenic ags released from the BB zone of cells of the renal proximal convoluted tubules joining to free antigenic sites of the pathogenic IgG aabs which were directed against the nephritogenic ag in the presence of complement, and so on. Through this process, ICs increase in size causing secondary injury to the GBM, resulting in ICGN (similar to MGN of humans) [63–67].

It is a possibility that MGN in humans is also initiated by pathogenic IgG aabs directed against nonpathogenic temporarily anchored molecules on the epithelial side of the GBM which are in the form of IC such as: (endogenous ag $\times$ human antihuman endogenous ag IgM aab). To these ICs, cross-reactive pathogenic IgG aabs (produced, e.g., against chemically modified endogenous ags) joined to the endogenous ag portion of the IC starting an immunopathological process. Layered deposition of the following components could ensue on the epithelial side of the GBM composed of the endogenous ag, pathogenic IgG aab against the endogenous ag, and complement components. The autoimmune disease-causing immune response could continue as long as the modified endogenous ag is present in the system producing pathogenic IgG aabs, which in turn, could damage the target organ where the native aag resides and incidentally could maintain the insult in the kidney, resulting in MGN.

Immune Events that Maintain Nonpathogenic Immune-Mediated Responses Against Self to Prevent Autoimmune Diseases

In a physiological sense, we are not tolerant to our intracytoplasmic ags within normal intact functioning cells [10]. Once intracytoplasmic ags are released from cells, specific nonpathogenic IgM aabs assist their clearance prior to being digested and degraded into reusable peptide and polypeptide fragments in the presence of complement in enzyme-rich mononuclear cells [38, 40, 42, 68–72]. In this way, toxic accumulation and possible chemical/structural modification of aags are prevented throughout life. During normal physiological condition, this aspect of autoimmunity against normal-released self-ags is highly beneficial in maintaining tolerance to self.

The normally functioning immune system is occasionally overwhelmed by aags that are released from damaged cells and subsequently modified. These modified aags can be considered hapten–self-ag conjugates and, being not quite self-ag, can have the following fate:

- If the immune system is not compromised and fully functional, then it is able to—by increased production of specific cross-reactive nonpathogenic IgM aabs—assist in the removal of both released native and hapten–self-protein ag conjugates and become digested in mononuclear cells. Through this process, an autoimmune disease is averted.
- If the immune system is overwhelmed, then the insufficiently produced specific cross-reactive nonpathogenic IgM aabs will be unable to assist in the complete removal of hapten–self-protein ag conjugates from the system. Under such circumstances, the hapten–self-protein ags will initiate a pathogenic IgG aab response against the target ag and cause injury, resulting in an autoimmune disease.

Once the modifying agent is reduced or no longer present in the system, the production of the disease-causing pathogenic immune response will subside [53, 73] and the continuously produced nonpathogenic IgM aabs clear the circulation from modified and native aags.

It is observed that the nonpathogenic cross-reactive IgM aab response—against native and modified native aags—is operational throughout life, and if it is not overwhelmed by modified aags [11, 15–17, 74, 75], then it will fulfill its physiological role in maintaining tolerance to self.

Reasons Why an Autoimmune Disease Can Be Initiated and Why It Can Also Be Terminated

Reasons why an autoimmune disease can be established in experimental animals may be due to a number of influences, among them, genetic and environmental factors being the most obvious ones [51]. The same influences can also play a part in the occurrence of autoimmune diseases in humans [11, 15–17, 47, 51, 76]. Normal tissue components, whether they are part of an organ or released into the circulation, do not initiate pathogenic immune responses [8–10] that could lead to autoimmune diseases. Animal experiments and observations proved that aags, homologous cellular components, or aag-like aags [77–80] (molecular mimicry) must be introduced in modified forms [8, 49] (not quite self-ag, e.g., as hapten–self-protein conjugates) to the cells of the immune system to evoke a pathogenic tissue-damaging immune response. The developing pathogenic IgG aabs, e.g., in SPHN, are cross-reactive [81]. They are able to react with the ag, i.e., the modified self that initiated its production and

equally with the normal target ag that resides in the BB zone of cells of the renal proximal convoluted tubules. Coming into contact with the nephritogenic ag in the BB, the pathogenic IgG aab will initiate and maintain tissue injury leading to the autoimmune disease [8, 49], and reacting with the GBM localized nephritogenic ag, will cause ICGN similar in morphological appearance to MGN in humans [66, 67]. As long as the modifying agent is present in the system and able to modify and retain the modified self-ag in the circulation, pathogenic immune responses will continue.

The only way one could terminate autoimmune diseases is by removing the inciting agent(s) from the internal environment of the host that modified the self-ag or by preventing additional modified self-nephritogenic aags entering into the system. However, the fastest way to achieve results is by applying the MVT [31, 32, 52, 53]. Injecting ICs made up of: (endogenous ag $\times$ antihomologous endogenous ag IgM ab) at ag excess, increases the specific nonpathogenic IgM aabs against the endogenous ag in the circulation. IgM aabs, like that of IgG aabs, are cross-reactive and are able to assist in the removal of both native (lesion contributing) and modified (disease causing/maintaining) aags from the circulation. In the absence of both aags in the circulation, immunopathological processes are terminated and tolerance to self is regained. It is inferred that the same control mechanism exists in humans as well, and for that reason, appropriate implementation of the MVT could terminate those autoimmune disease initiated and maintained immunopathological processes that caused the disease. Nevertheless, memory to the modified aag is retained; therefore, patients have to be followed up to be certain that tolerance, i.e., an autoimmune disease-free state is maintained. In certain cases, the MVT may have to be reapplied to maintain health.

MVT for the Prevention and Termination of an Autoimmune Disease

It is well known that only an ag-specific treatment option could terminate autoimmune disease-causing events [1]. However, such a treatment option in humans has not been achieved by scientists due to technical difficulties, e.g., how to administer the target ag without causing further complications by pathogenic immune responses. For this reason, immunosuppressive agents were/are employed to treat naturally occurring autoimmune diseases of humans [4, 5], and recently monoclonal abs, especially rituximab [3, 6, 7, 19], to reduce the number of ab producing cells which make the pathogenic IgG aabs. These treatment options are nonspecific, have side effects, and do not terminate the disease.

It was observed that injected or released intracytoplasmic aags into the circulation produced nonpathogenic IgM aabs in the rat [8, 9, 38]. The role of these IgM aabs is to assist in

the removal of released intracytoplasmic ags from damaged cells, thereby keeping the system free of ags which no longer play a role in normal cellular events. However, if the same ags are introduced in modified forms, e.g., as hapten–self-protein conjugates, then the immune response will manifest in pathogenic IgG aab production against the target ags [8, 49]. Barabas et al. have noted that during the course of experimental autoimmune diseases, both pathogenic tissue-damaging IgG aabs and nonpathogenic IgM aabs are present in the circulation [31, 32, 53]. The modified self-ags stimulate the production of pathogenic IgG aabs, and certain portions of the released native target ags from damaged cells stimulate the production of nonpathogenic IgM aabs.

It is well known how to increase the production of pathogenic IgG aabs in experimental animals, e.g., by repeated administration of the “modified” hapten–self-ag conjugates [8, 26]. Such an exposure stimulates the pathogenic aab cell lines to produce a high aab-titered response. The pathogenic IgG aab titer against the target ag must be zero before termination of the autoimmune disease is achieved [53]. Various experimental results have revealed to us that specific IgM aabs, against the native nephritogenic ag in SPHN, must be elevated in order to remove both modified and native circulating ags from the system, which cause and contribute to disease development and progression [31, 32, 53]. This can be achieved by the third immunization method, after active and passive immunizations, called MVT [30, 31, 34, 35, 48]. We have shown that injecting ICs into rats, composed of the native nephritogenic ag (i.e., rat kidney fraction 3 (rKF3) ag) and a homologous anti-native nephritogenic ag IgM ab (i.e., rat anti-rat kidney fraction 3 (rarKF3) ag IgM ab) in slight ag excess [31, 32, 53], will stimulate the cells of the immune system to produce elevated IgM aabs against the nephritogenic ag.

We have applied the new vaccination technique in rats *prophylactically* by injecting ICs (rKF3 ag $\times$ rarKF3 ag IgM ab) in ag excess, prior to inducing SPHN and at regular intervals thereafter, and found that most rats with elevated IgM aabs against the nephritogenic ag did not develop the disease [34, 82]. We also used the MVT *therapeutically* in established SPHN rats. When the same ICs were used as above, it was observed that the pathogenic IgG aab response against the target nephritogenic ag in the renal proximal convoluted tubule’s BB, rapidly subsided and the autoimmune disease-causing immunopathological processes were terminated [31, 34, 52, 53, 82].

The MVT was employed in several experiments and it was found that its appropriate application can upregulate an immune response against an exogenous target ag [83, 84] and equally it can also downregulate an immune response against an endogenous ag [31, 32, 52, 53]. The MVT works on the principle of ab information transfer [82]. The injected IC produces the same ab with the same specificity against

the target ag that resides in the IC. The predetermined immune response is specific and can be applied both prophylactically and therapeutically. Since it evokes an immune response without side effects in downregulating/terminating the experimental autoimmune disease SPHN, it promises to provide the same ag-specific treatment option for naturally occurring autoimmune diseases of humans as well. Though the MVT could be applied for the prevention of autoimmune diseases in humans, it is envisaged that it will be employed predominantly for terminating immunopathological processes that damage organ-related target ags.

Summary

Throughout life, there is an inbuilt mechanism which, in animals and humans, prevents pathogenic immune responses to occur against normal self-ags [10, 38]. Broken-down cellular components released from intact cells as a consequence of their aging or from cells damaged by toxic agents, e.g., smoking, alcohol, infectious agents, drugs, chemicals, UV light, vaccines, etc. [8, 11, 15, 18], are assisted in their removal from the system by specific nonpathogenic cross-reactive IgM aabs [9, 40, 42, 44, 85], prior to being degraded into small MW peptides by mononuclear cells [39, 41, 43, 69]. These simple yet efficient immune-mediated processes prevent toxic accumulation of cellular breakdown products and their possible chemical and/or structural modifications that could lead to modified self-ag-induced autoimmune diseases. Unfortunately, this normally functioning physiological process can become compromised and released aags can be modified into hapten–self-protein conjugates by modifying agents. Hapten–self-proteins, being not quite self-ags, are recognized by the immune system as foreign proteins and an immune event against them evokes a pathogenic IgG aab response that causes a targeted attack on the organ where the aag resides. In the case of SPHN, it primarily damages the BB region-associated nephritogenic ag of the renal proximal convoluted tubules and causes an autoimmune disease. Secondly, it injures the GBM, where the temporarily deposited nephritogenic ags [62] (in the form of ICs (rKF3 ag $\times$ rarKF3 ag IgM aab)) allow the pathogenic IgG aabs to initiate, and as the disease progresses, maintain a chronic ICGN.

According to some observations, once an autoimmune disease is initiated, it will be maintained by pathogenic IgG aabs that are produced by long-lived plasma cells [3, 86] against the target ag. Would this be the case, treatment of autoimmune diseases would only be possible—to a limited extent—by immunosuppressive agents, since secondary immune responses cannot be satisfactorily suppressed. Besides, immunosuppression is nonspecific, does not terminate progressive autoimmune diseases, and the side effects immunosuppressive agents cause are quite often severe.

A more factual explanation—based on experimental findings—of the etiology, pathogenesis, prevention, and termination of an experimental autoimmune kidney disease called SPHN was provided by Barabas et al. [8, 31, 32, 49, 52, 53]. It is likely that human autoimmune diseases have the same starting triggers and immunopathological processes and have the same opportunities to be successfully terminated as experimentally induced autoimmune diseases. As long as the modifying agent is in the system, modified self-aggs will be produced, and if they are not removed by specific non-pathogenic cross-reactive IgM aabs and not digested by mononuclear cells [39, 41, 43, 69], then they will initiate/maintain the production of pathogenic IgG aabs, hence continuance of the autoimmune disease. If the modifying agent(s) could be removed completely from the system, then pathogenic IgG aab production would cease. However, most often it is not known what the modifying agent is, and even if it would be known, it would be difficult, if not impossible to exclude it from the external/internal environments. In such instances, it would appear that the continuous production of pathogenic IgG aabs is by long-lived plasma cells. However, it was conclusively proven that for the continuous production of pathogenic IgG aabs, the presence of modified aags are needed per se [26, 53] or ICs at ag excess. During the chronic progressive phase of the disease, native aags can also contribute to pathogenic IgG aab production in the form of ICs (e.g., rKF3 ag × rarKF3 ag IgG aab) at ag excess, but not in its native form alone [81].

To clear those ags which are present in the circulation—and able to stimulate continuous pathogenic IgG aab production and also able to contribute to IC depositions in the glomeruli as it occurs in SPHN—specific cross-reactive nonpathogenic IgM aabs targeting the nephritogenic ag have to be present in the system with a very high aab concentration. Only high concentrations of IgM aabs [53] can assist the efficient clearance of pathogenic IgG aab-stimulating aags. Specific IgM aabs—produced by native nephritogenic ags stimulating the IgM aab-producing cell lines—are present with an elevated concentration in the circulation during an autoimmune disease [53], yet most often not sufficiently elevated to terminate the disease. It is likely that without the presence of circulating high-titered cross-reactive IgM aabs—directed against the target ags in their native and modified forms—human autoimmune diseases would also progress.

The vaccination technique Barabas et al. have developed, called MVT, was able to prevent the autoimmune kidney disease SPHN in rats and, when the disease was in its progressive phase, was able to terminate it specifically and without side effects by the increased production of IgM aabs [30, 31, 34, 35, 48]. To achieve prevention or termination of SPHN, rats were injected at regular intervals with ICs made up of: (rKF3 ag × rarKF3 ag IgM ab) at ag excess [53]. The ICs, directly stimulating the IgM aab-producing cell lines,

produced excessive amounts of IgM aabs against the nephritogenic ag. The developing abs were specific cross-reactive IgM aabs and were able to assist the removal of both modified and native nephritogenic aags, and those ICs which were present containing modified and native aags in conjunction with pathogenic IgG aabs in the circulation. In the absence of pathogenic IgG aab-producing ags in the circulation, the level of pathogenic IgG aabs rapidly declined [26, 53], and in their absence, the autoimmune disease-causing immunological processes halted, and tolerance to self was regained. To ensure that tolerance to self is maintained, regular retesting and revaccination using the MVT is recommended to assure that there are no pathogenic IgG aabs in the circulation against the target ag.

This review article described events that were documented in experimental and human autoimmune diseases; nevertheless, the most relevant observations were derived from data obtained from animal experiments, e.g., up until now, no experimental evidence was available on how to regain tolerance to a certain autoimmune disease causing ag. Notwithstanding, it is clearly envisaged by the present contributors of this review paper that the MVT will be able to terminate endogenous ag-caused immunopathological disorders in humans specifically and without side effects by the immune system's ability to respond to corrective information.

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