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Modified self-antigen Caused Autoimmune Disease and its Reversal by a new Vaccination Technique

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Abstract

Autoimmunity represents four possible aspects of immune responses against self-components. Two of the immune responses are beneficial and two are not. We are most familiar with those aspects of autoimmunity, which are harmful to the individual and cause disease, such as they are manifested in autoimmune diseases. While the study of autoimmune diseases are important, it is equally important to know the entire spectrum of autoimmunity in order to fully understand the etiological, physiological, pathological etc. aspects of immune responses that are harmful and/or beneficial. Only by fully understanding the entire spectrum can we design appropriate interventions for treating mishaps, which can occur. Since, most of the immune events, which cause autoimmune disorders, are not yet fully unravelled, autoimmune diseases are treated non-specifically e.g. with immunosuppressive agents.

One the beneficial aspects of autoimmunity is manifested in the clearance of native and modified cellular breakdown products by specific non-pathogenic IgM autoantibodies; and the other beneficial aspect manifests in the recognition and elimination of emerging cancer cells. Without these beneficial aspects of autoimmunity, life as we know could not exist.

There are two harmful aspects of autoimmunity as well that manifest in autoimmune disorders: autoimmune diseases and cancer.

In recent years, Barabas and colleagues have developed a new way of vaccinating that allows prevention and when present termination of an experimental autoimmune kidney disease. It is believed that the new vaccination technique with appropriate modifications will be applicable for many of the presently drug only treatable endogenous disorders, such as autoimmune diseases and cancer.

Keywords: Self-antigen; Autoimmune disease; rKF3; Vaccine

Abbreviations:

aab: Autoantibody; aag: Autoantigen; ab: Antibody; ag: Antigen; BB: Brush Border; FCA: Freund's Complete Adjuvant; GBM: Glomerular Basement Membrane; HN: Heymann Nephritis; IC: Immune Complex; ICGN: Immune Complex Glomerulonephritis; MVT: Modified Vaccination Technique; rKF3: Rat Kidney Fraction 3; rarKF3: Rat Anti-rat Kidney Fraction 3; SPHN: Slowly Progressive Heymann Nephritis

Introduction

The subject of autoimmunity encompasses a very broad aspect of immunity dealing with the maintenance of tolerance to self and at times with the loss of tolerance to self (Figure 1). Since this short communication will mainly deal with two aspects of autoimmunity, namely, with an autoimmune disease and with normal functioning immune system to clear cell debris, our comments will be directed to those areas of interest [1]. It was observed in experimental animals (i.e., rats) that injected 'normal' cellular components (e.g. a nephritogenic antigen [ag] derived from normal rat kidneys) will only produce naturally occurring specific non-pathogenic IgM autoantibodies (aabs) [1,2] and not pathogenic kidney damaging IgG aabs. However, the same injected ag initiated circulating pathogenic IgG aabs when it was chemically modified [3,4] or incorporated into adjuvants like Alum [5] or Freund's complete adjuvant (FCA) [6]. It is safe to conclude that only 'modified' self ags [3-6] are able to initiate and maintain the production of pathogenic IgG aabs which in turn are responsible for the development of autoimmune diseases such as they occur in Heymann nephritis (HN) [7] and slowly progressive Heymann nephritis (SPHN) [5].

Shoenfeld et al. have implicated several modifying agents like: smoking, alcohol, UV light, drugs, chemicals, infectious agents, toxins etc., [8-11] that can contribute to the development of a wide range of autoimmune diseases in humans. Knowing that certain agents can influence the initiation and progression of autoimmune diseases gives us a chance of eliminating them from the internal environments of patients and achieve cure. Since in most instances the implicating factors are not known, humans with autoimmune diseases are treated with immunosuppressive agents [12-14], which are non-specific in their actions and have numerous side effects of which infection related

complications are the worst. We shall describe how the implementation of the modified vaccination technique (MVT), with suitable immune inducing components, was able to terminate an experimental autoimmune kidney disease specifically and without observable side effects. The same immunization technique with appropriate modifications could also help humans to recover from certain autoimmune diseases.

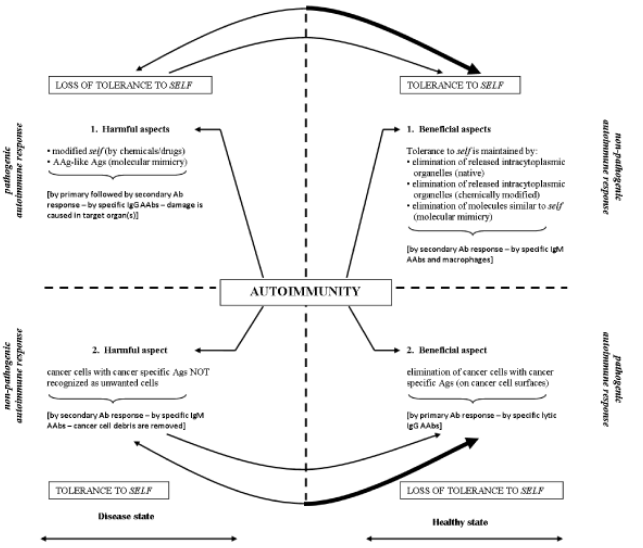

Figure 1: Two beneficial and two harmful aspects of autoimmunity. The diagram depicts how regained health from autoimmune disorders can be achieved. This can be attained either by the immune system's natural ability to evoke corrective immune responses or by appropriate application of the MVT. [Figure reproduced by permission from BioProcessing Journal, 2007 Winter; 6(4):12-18].

General Background

While numerous external agents (i.e., bacteria, viruses etc.) can cause infectious and contagious diseases, they can be prevented by active immunization programs or treated by antibiotics when the occur; endogenous ag induced autoimmune diseases cannot be prevented or treated by an immune mediated corrective immune response in humans to date. To fully understand what happens to released intracytoplasmic ags from damaged or dying cells, one must know that in a physiological sense we are not tolerant to our own intracytoplasmic components [15-17]. If cells are damaged or come to the end of their life spans, then released intracytoplasmic ags have to be somehow processed/moved out of the system in order to prevent toxic accumulation or possible modifications of cell debris that could initiate a pathogenic immune response leading to an autoimmune disease. The released endogenous ags are assisted in their removal by specific non-pathogenic IgM aabs [2,18-21] prior to being digested by mononuclear cells [21-24]. Mononuclear cells break down the intracytoplasmic antigenic material into small molecular weight peptides. The peptides subsequently can be part of functional and structural protein synthesis. In this manner, there is very little wastage and simple building blocks can be part of complex protein production.

However, if there is interference with the natural cellular break down process, as it can happen when:

specific non-pathogenic IgM aab production is insufficient to assist in the removal of cellular breakdown products [25]; specific non-pathogenic IgM aab production is overwhelmed e.g. by sudden unusual breakdown of cells in a certain organ e.g. as it occurs in HN [6] and SPHN following injections of a modified nephritogenic ag [3]; during the chain of events mononuclear cells are unable to degrade cellular breakdown products sufficiently etc.; then unprocessed cellular breakdown products floating around could become modified by modifying agents [8-11] into hapten-protein conjugates, which are strictly speaking are no longer 'self' components. The cells of the immune system view these conjugates as foreign even though they are mainly 'self.' Not being 'self,' they evoke the production of pathogenic IgG aabs [3,5]. These cross reactive aabs will not only react with the modified self ag which initiated their production but also with the target ag e.g. as it does in HN and SPHN, attacking the brush border (BB) related nephritogenic ag of the renal proximal convoluted tubules [5] and cause an autoimmune disease.

Production of an experimental autoimmune kidney disease in rats

Administration of a modified nephritogenic ag – as it occurs e.g. when rat kidney fraction 3 (rKF3) ag is injected intraperitoneally in FCA [7] or Alum [5] or in a chemically modified form [3] – into rats will produce an autoimmune kidney disease in conjunction with contributing to immune complex (IC) depositions in the glomeruli and proteinuria. The injected nephritogenic ag in a modified state is able to evoke the production of pathogenic IgG aabs [5]. These aabs are primarily directed against the injected modified nephritogenic ag but they are also able to cross react with the native BB associated nephritogenic ag in the renal proximal convoluted tubules and cause damage that results in an autoimmune kidney disease [5,26,27]. Liberated nephritogenic ag – as a result of rat anti-rat kidney fraction 3 (rarKF3) pathogenic IgG aab reacting with the BB associated ag – will get into the urine and the circulation [28,29].

The fate of released nephritogenic ag into the circulation is as follows:

some will be catabolized. Specific naturally occurring non-pathogenic IgM aabs [2,19,20] will assist in the removal of the nephritogenic ag prior to being engulfed and degraded into reusable peptides by mononuclear cells [18,21,23,30,31].;

some will settle into the glomeruli and become part of layered deposition of ICs on the epithelial side of the glomerular basement membrane (GBM), composed of [18,32]:

1. the starting ICs made up of (even in normal rat kidneys) [nephritogenic ag X rat anti-rat nephritogenic ag non-pathogenic Ig Maab] [26];
2. the pathogenic IgG aab reacting with the nephritogenic ag portion of starting ICs [26];
3. the liberated nephritogenic ag reacting with the pathogenic IgG aab described in 2 above in the presence of complement [18,33];

during the chronic progressive phase of HN and SPHN the liberated nephritogenic ag could also contribute to the production of pathogenic IgG aab against the nephritogenic ag by ICs made up of [rKF3 ag X rarKF3 ag pathogenic IgG aab] [18]. Note: native

nephritogenic ag to be involved in pathogenic IgG aab production can only occur during the chronic phase of the disease;

As long as pathogenic IgG aabs are produced:

damage to the nephritogenic ag, localized in the BB region of the renal proximal convoluted tubules (primary insult to the kidney causing the autoimmune disease) will occur [27]; and

released nephritogenic ags contribute with circulating pathogenic IgG aabs , in the presence of complement, to layered depositions of ICs in the glomeruli (secondary insult to the kidney resulting in immune complex glomerulonephritis [ICGN]) will commence [18].

MVT for the prevention and when present termination of an experimental autoimmune kidney disease

Treatment of autoimmune diseases are presently undertaken by immunosuppressive agents [12-14,34]. They are non-specific in their actions, have undesirable side effects and will not terminate those immunopathological processes which are responsible for the disease. The ultimate aim is to eliminate from the system those inciting agents which are able to modify self ags, and those native autoantigens which are already modified, to terminate immunopathological processes [35-37] that cause and maintain progressive disorders.

The vaccination technique we have developed and call MVT is able to prevent and when present terminate an experimental autoimmune kidney disease called SPHN [1,15,38-43]. The MVT is the third vaccination method after active and passive immunizations; and the only one which is able to initiate preventative and therapeutic responses. The MVT is based on administering – to the vaccinated host – ICs composed of the target ag and a desired antibody (ab) against it. E.g. in SPHN where the immunopathological events are maintained by the continually produced cross reactive pathogenic IgG aabs against the modified and native nephritogenic ags, the aim was to remove from the circulation both modified and native nephritogenic ags; in order to prevent:

further production of pathogenic IgG aabs which could continue to damage the BB region of the renal proximal convoluted tubules; and

glomerular lesion advancement;

In SPHN rats, autoimmune kidney disease prevention or when the disease was present termination of it was achieved by injections of ICs composed of [rKF3 ag X rarKF3 ag non-pathogenic IgM ab] in ag excess. The injected IC produced the same elevated ab response in the injected host that was present in the IC, namely, rarKF3 ag non-pathogenic IgM aabs. The elevated ab response was achieved by ab information transfer by specifically evoking the production of those naturally occurring non-pathogenic IgM aabs which were responsible for initiating the catabolism process of both native and modified nephritogenic ags. Once both modified and native nephritogenic ags were removed from the circulation the production of the pathogenic IgG aabs ceased [1,44] and disease causing immunopathological processes came to a halt.

Discussion

HN and its variant SPHN were extensively studied by us over the years [1,5,7,44] and allowed us:

to decipher those immunopathological processes which were responsible for the autoimmune kidney disease [26,27] and the glomerular lesion [26]; and

to find ways for preventing/terminating the disease processes [1,38,39,44];

We have shown that only modified nephritogenic ags, injected into rats in adjuvants [6,7] or in a chemically modified state [3], can induce the production of pathogenic IgG aabs which are responsible for the autoimmune kidney disease after coming into contact with and damaging the BB region of the renal proximal convoluted tubules [27,45] where the nephritogenic ag resides (primary insult to the kidney causing the autoimmune kidney disease.)

We have demonstrated that rats injected with normal nephritogenic ag containing rKF3 ag produced elevated levels of naturally occurring specific non-pathogenic IgM aabs [5] which were responsible for clearing released nephritogenic ags from the circulation [1,44] prior to being digested by mononuclear cells [18,20,21].

We have also documented that glomeruli which were not open to the circulation had no nephritogenic ags [26,46] while those which were open had small ICs composed of: [nephritogenic ag X rat anti-rat nephritogenic ag non-pathogenic IgM aabs] [26]. These findings have shown that the nephritogenic ag is not produced by the epithelial cells of the glomeruli, as it was demonstrated earlier by others [47,48], but rather derived from the circulation [28,29,49] after being released from the renal proximal convoluted tubules' BB related regions.

The secondary insult to the kidney's glomeruli – by the developing pathogenic IgG aabs, directed against the nephritogenic ag – starts by the pathogenic IgG aabs reacting with free antigenic sites of the IC [nephritogenic ag X rat anti-rat nephritogenic ag non-pathogenic IgM aab] containing nephritogenic ags [26,33,45]. The insult continues as layered deposition of ICs form on the epithelial side of the GBM in the presence of complement composed of: the continually released nephritogenic ag from the renal proximal convoluted tubules and the pathogenic IgG aab directed against the nephritogenic ag [18,50]. The resulting lesion in the glomeruli can be referred to as ICGN or membranous glomerulonephritis.

Characteristic tubular [27] and glomerular [6] lesions develop – following administration of chemically [3] or otherwise altered nephritogenic ags [1,44] – when cross reactive pathogenic IgG aabs are produced [18] with the ability to react with the injected altered ag but with the tissue localized native normal self ag as well [27].

Throughout life physiologic specific non-pathogenic IgM aabs [2,51] are produced for assisting in the clearance of cellular debris which are released from cells damaged or cells coming to the end of their life spans. These IgM aabs are also able to clear those intracytoplasmic debris – since they are also cross reactive – which became modified by various agents such as drugs, toxins, alcohol, chemicals etc [8-11]. Utilizing the immune system's natural abilities to clear cellular debris (native and modified), we designed experiments where specific increased non-pathogenic IgM aab levels were achieved in rats by injections of ICs containing [rKF3 ag X rarKF3 ag non-pathogenic IgM ab] prior to [1,44] and during the progressive phase of SPHN. We have noticed that animals pre-immunized and continued to be immunized did not develop the typical disease characterized by renal tubular and glomerular lesions [1,44]; and those immunized during the chronic progressive phase of the disease stopped producing pathogenic disease maintaining IgG aabs within a very short time [1].

It was achieved by injections of ICs made up of: rKF3 ag (the target ag rich in the nephritogenic ag) and rarKF3 ag non-pathogenic IgM ab (IgM ab raised in normal rats against the target nephritogenic ag). The IC [rKF3 ag X rarKF3 ag non-pathogenic IgM ab] injected into pre-disease induced rats and those with chronic progressive autoimmune kidney disease, produced elevated specific IgM aabs against the nephritogenic ag, which prevented/terminated the immunopathological processes responsible for the disease [1,44]. The successful prevention and cure of the autoimmune disease were due to ICs producing in a predetermined fashion the same ab with the same specificity against the target organ ag that resided in the IC, in our case, rat anti-rat nephritogenic ag non-pathogenic IgM aab. Elevated cross reactive IgM aab levels by clearing the circulation from both native and modified nephritogenic ags prevented/terminated further production of disease causing pathogenic IgG aabs and hence terminated the disease [1,44].

Initiation of elevated ab response in experimental animals by injections of ICs is well documented; this method of introducing the ag is more effective than administration of the same ag in an aqueous solution [52-56]. This information is not new nor is the fact that ICs can be used to vaccinate animals to achieve better protective immune responses [57-59].

However, to redirect immune events specifically using the immune system's natural abilities to deal with e.g. acceleration/downregulation of immune responses against a self ag – as it occurs in an autoimmune disease – has not been achieved by others to date, using specifically formulated ICs, except by us [1,43,44,57-59].

It was eloquently expressed by Feldmann and Steinman in one of their publications, where they correctly stated:

"although several attempts in the past decade have failed, we are optimistic that eventually, the molecular understanding of tolerance and immunity will progress, and the *holy grail* of autoimmunity – long term antigen-specific therapy – will be reached." [35].

We firmly believe that the MVT that we have developed [1,42-44]– the third method of immunizing – will achieve prevention/ termination of autoimmune disorders (i.e., autoimmune disease and cancer).

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