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Molecular recognition theory and sense-antisense interaction: therapeutic applications in autoimmunity

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1. ABSTRACT

Perhaps behind only the understanding of the genetic code in importance is the comprehension of protein sequence and structure in its effect on modern scientific investigation. How proteins are structured and interact dictates a considerable amount of the body's processes in maintaining homeostasis. Unfortunately, in diseases of autoimmunity, these processes are directed against the body itself and most of the current clinical responses are severely lacking. This review addresses current therapeutics involved in the treatment of various autoimmune diseases and details potential future therapeutics designed with a more targeted approach. Detailed in this manuscript is the concept of utilizing peptides possessing an inverse hydropathy to the immunogenic region of proteins to generate anti-idiotypic (anti-Id) and anti-clonotypic T cell receptor (TCR) antibodies (Abs). Theoretically, the anti-Id Abs cross react with Id Abs and negate the powerful machinery of the adaptive immune response with little to no side effects. A series of studies by a number of groups have shown this to be an exciting and intriguing concept that will likely play a role in the future treatment of autoimmune diseases.

2. INTRODUCTION

There are many instances where the nature of peptide-peptide interaction plays a critical role in the maintenance of homeostasis in humans. Ligand/receptor, Ab/antigen, protein production and folding are all processes dependant upon specific and coordinated peptide/peptide interaction. Perhaps nowhere is this more readily apparent than in the case of autoimmune disease. Autoimmunity is a condition that has been reported to afflict 1 in 31 people in the United States alone (1). While there are low level amounts of self-reactive T cells and auto-Abs detected in the healthy population, they are held in check by a system of regulatory T cells (T_{reg}) and both Id and anti-Id Abs (2-4). It is when there is a dysregulation of this system of T_{reg} cells and Abs that autoimmunity occurs. The most obvious culprit for the initiation of autoimmunity is a genetic factor although it is unknown to what extent environmental components come in to play (5, 6). This review will discuss the current treatment modalities for various autoimmune diseases, the potential for vaccines and/or treatments designed on peptide-peptide interactions, and briefly discuss other areas outside autoimmunity where a more

complete knowledge of peptide interaction(s) is making an impact.

3. CURRENT TREATMENT MODALITIES IN AUTOIMMUNE DISEASES

3.1. Graves' disease

Graves'disease, or Graves' hyperthyroidism, is caused by IgG auto-Abs that bind and activate the thyrotropin receptor of thyroid cells (7). Graves' is characterized by thyroid hypertrophy with the possible formation of a goiter, ophthalmopathy, and weight loss with increased appetite (8). The most attractive treatment for this condition would obviously be to ablate the auto-Abs present and restore natural thyroid function; unfortunately the current therapies are much less sophisticated. Standard clinical treatment today consists mainly of reducing hypertrophy of the thyroid through anti-thyroid medications, radio-isotopes of iodine, or finally, surgery (9, 10). Sadly, these treatments are limited by only indirectly addressing the disease, similar to cancer, the disease is never said to be "cured," a patient can merely reach "remission" a state that they will fight to maintain for the rest of their lives.

3.2. Multiple sclerosis

Multiple sclerosis (MS) is neurodegenerative disorder caused by incorrect recognition of the myelin sheathes of the central nervous system (CNS) by the immune system (11). Unlike Graves' disease, the clinical approach in MS focuses more on the immune system itself. Interferon-beta (IFN-beta), a cytokine is one of the most common therapies used in the treatment of MS. IFN-beta treatment has been shown to reduce MS exacerbation frequency, although the specific mechanism of action remains unclear (12). Copaxone, or glatiramer acetate, is a polypeptide mimetic of myelin sheath proteins, and is believed to reduce the available auto-Abs (13, 14). Unfortunately, both of these treatments are not conducive to high quality of life due to the frequency of injection required and unsure efficacy.

3.3. Guillain-Barre Syndrome

Guillain-Barre Syndrome (GBS) is another neurodegenerative demyelinating disease caused by auto-reactive Abs. GBS is a disease of the peripheral nervous system, however, and is characterized by ascending paralysis and typically associated with an acute infection (15). At least 25% of patients with GBS will undergo ventilation during the acute phase and with 3.5-12% of patients dying of complications in this phase. Once the patient is stabilized, maintenance therapy begins, with plasmapheresis and intravenous immunoglobulin (IVIg) being the most common. While these provide a reduction in frequency and length of hospital stay, they are by no means curative and many patients have chronic fatigue associated with the disease (16).

3.4. Myasthenia gravis

Myasthenia gravis (MG) is caused by auto-reactive Abs to the alpha-chain of the nicotinic acetylcholine receptor (nAChR), resulting in ptosis, fatigue, and possible pulmonary impairment (17, 18). Broad immunosuppressive therapies such as; steroid treatment, thymectomy, and acetylcholinesterase inhibitors can be effective but are accompanied by a variety of deleterious side effects (19). Additionally, the efficacy of the therapeutics used to treat MG decreases over time, resulting in increasing relapsing/remitting cycles of symptomatic disease.

4. DESIGN OF FUTURE THERAPEUTICS

4.1. Optimum treatment and roadblocks

The optimal treatment for any autoimmune disease would be the ablation of the recognition of self, and a return to normal homeostasis. There are, unfortunately, several factors that make this extremely difficult to achieve. Perhaps the most important impediment to immunomodulation is the fact that the vast majority of auto-Ab reactions and auto-reactive T cell responses are polyclonal in nature, making a treatment designed against a single Ab Id or TCR irrelevant. Additionally, as has been previously described the presence of epitope spreading – in which cross reaction with a single portion of an antigen induces further cross reaction of Ab with more epitopes of the same antigen and increase the immune response (20-22). Perhaps the most therapeutic idea is one that has been gaining ground for the last several decades, and is rapidly being utilized in several of the diseases discussed above: antigen receptor mimetic (ARM) induced anti-Id response.

4.2. Molecular recognition theory and sense/anti-sense interaction

The molecular recognition theory (MRT) was initially proposed by Blalock and Smith based upon the concept that complementary strands of DNA would encode peptides that would exhibit inverse hydropathic signatures (23). The idea being that due to the inverse hydropathy and subsequent mirror image of tertiary structure, the sense (5'-3') and anti-sense (3'-5') peptides would bind in specific and predictable manner (24, 25). It has been well established that almost regardless of amino acid identity, the tertiary structure of a protein can be reliably predicted through analysis of the pattern of hydrophobic and hydrophilic residues in the primary amino acid sequence (20). Indeed, the initial system used to test this theory was the binding of corticotrophin (ACTH) and a reverse-engineered synthetic peptide representing a 5'-3' or 3'-5' translation of the antisense RNA for ACTH, dubbed HTCA (26). ACTH and HTCA bound in a high affinity and titratable fashion. Through this and other work it was determined that the tertiary structure of a protein could be predicted based on its hydropathic profile. Hydrophobic residues tend to arrange themselves towards the interior of the protein, and hydrophilic amino acids reside outwardly. It is because of this natural arrangement that the external "landscape" of the sense peptide/protein, and its complement would be able to interact. There are various computer programs that are capable of designing complementary peptides based on the coding strand of DNA or the resultant amino acid sequence. In fact, Blalock *et al.* (23) elucidated that the primary determining factor in the hydropathic nature of an amino acid was the central

base in a tri-nucleotide codon. The resultant generalizations are that A in the central position results in a hydrophilic amino acid with U leading to a hydrophobic one, while C and G foster the production of slightly polar or neutral residues, such as glycine. This work has been repeated and confirmed by a variety of researchers in a number of systems over the last few decades. The Fassina group (27) showed that increased hydropathic complementarity positively correlated with improved binding of a glycoprotein. Indeed, since the early studies by Blalock and coll. (23, 26), there have been several systems in which complementary peptides have been produced and employed; fibrinogen, laminin receptor, angiotensin II, arginine vasopressin, beta-endorphin, growth hormone releasing peptide, and acetyl choline receptor, among others (28-35). In 2002, Goicoechea *et al.* (36) utilized the concept of inverse hydropathy to demonstrate that the interaction between thrombospondin and cell surface calreticulin was due to opposite hydropathic profiles between multiple peptide sequences in the proteins. The Tzioufas group (37-40) has published multiple papers discussing both T cell and B cell mediated immunity in the context of complementary peptide interaction. Finally, the Johnson's laboratory at the University of Florida (41, 42) has performed several studies detailing the use of a suppressor of cytokine signaling-1 (SOCS1) mimetic peptide to protect against experimental allergic encephalomyelitis (EAE) and the complementary peptide approach was used in the design of this mimetic. However, autoimmunity is not the only area where the MRT has been shown to be applicable, studies investigating the toxin specificity of *Bacillus thuringiensis* and *Heliothis virenscens* also made use of this algorithm (43, 44). There has been some controversy due to the occasional inability to repeat some of these studies, but in general it has been a widely successful field of research and discovery (45-47).

4.3. MRT and design of antibodies

Perhaps the field of research most ripe for the implementation of the MRT is immunology, more specifically autoimmunity. In using a peptide specifically designed to have a hydropathy pattern inverted to known proteins' epitopes as an immunogen, an Ab will be produced that will bind that protein of interest's receptor, allowing for the purification and isolation of receptors or other proteins that interact with the target protein (48, 49). To extend this concept further into the field of Ab research, if two complementary peptides were used as antigens, they would produce Abs capable of binding each other (50). This was demonstrated initially by Blalock and Bost (51), using an algorithm they developed specifically for this purpose. As previously mentioned, there are multiple computer programs available today that are capable of designing a complementary peptide. The algorithm is based upon the calculation that amino acids with positive hydropathic assignations are mirrored by residues with equally negative hydropathic scores in the complementary peptide such that the sum total approaches zero. What is important to note however, is that the anti-sense peptides need only to maintain inverse hydropathy, exact inverse sequence homology is not required.

4.4. Complementary peptides vaccines

It is with all of this in mind that we begin to discuss the concept of peptide based vaccines for diseases of autoimmunity. Blalock *et al.* (35) initially described this concept in a rat model of myasthenia gravis. MG in humans is most often due to IgG Abs directed against amino acid residues 61-76 of the AChR, the main immunogenic region (MIR), that leads to decreased receptor concentrations at the neuromuscular junction and symptomatic disease. In the rat model, when immunized with purified AChR rats developed fatigability and muscle weakness, characteristic of myasthenia gravis. Referencing Jerne's network theory that disease manifestation could be modulated by shifting the Id anti-AChR Ab and an anti-Id Ab, Blalock and colleagues (52) tested this concept using complementary peptides. Employing a peptide hydropathically complementary to the MIR of AChR, they immunized rats with experimental autoimmune myasthenia gravis (EAMG). The group was able to demonstrate that rat anti-sera to the complementary peptide blocked anti-AChR Ab binding with the receptor and lead to decreased disease severity in the affected animals (35). Not only was this approach effective in inducing an anti-Id Ab response but was also useful in addressing the T-cell component of the disease (53, 54). By using a complementary peptide to the dominant T-cell epitope of the AChR and inoculating rats, the group was able to induce the production of an anti-TCR Ab against T-cells reactive with AChR *in vivo* and further abrogate the effects of the EAMG (55). This approach was able to both prevent disease when administered prior to induction of EAMG and decrease the disease incidence and severity when delivered after disease onset, further paving the way for anti-sense complementary peptides to be used in a clinical setting.

Perhaps the most important study involved in the treatment of MG using a complementary peptide vaccine was published by Galin *et al.* in 2007 (56). Unlike previous studies the animal subjects were dogs that spontaneously developed the disease, it was not induced as before in the rats. It is because of this spontaneous pathology, similar to humans that any success with the complementary peptide vaccine would carry more weight than any previous successful outcomes. Indeed, when peptide mimetics of T cell and B cell antigen receptors were administered, the percentage of remitted dogs increased from 17% to 75%, as determined by both auto-Ab titer and clinical improvements. Additionally, there was a three fold decrease in the amount of time to remission compared to that of spontaneously remitting animals.

While developing a disease focused treatment for MG is important, it is hardly a widespread disease (incidence of 1 case/100,000 births). By expanding the concept of the MRT to produce therapies for other autoimmune conditions different groups have shown that using complementary peptides to induce an anti-idiotypic response is a viable approach for the treatment of some autoimmune conditions. Pendergraft and colleagues (57) demonstrated that in autoimmune necrotizing systemic vasculitis associated with anti-neutrophil cytoplasmic Ab, there is a high titer of anti proteinase-3 Ab in the human.

They went on to show that this could be recapitulated in the mouse using an inverse hydropathy peptide vaccine similar to those discussed above. The mice demonstrated the same idiotypic/anti-idiotypic profile observed in the human. There has been some controversy about this of late, but studies are on-going to determine the accuracy of the initial findings by Pendergraft *et al.* (58).

Additionally, some work has been done avoiding the complexities of the Ab response altogether, by designing direct antagonists based on the hydropathy algorithm described above. Heal *et al.* (59) described the effectiveness of complementary peptides as selective inhibitors of the cytokine interleukin-1 (IL-1). The peptides they designed and produced interact directly with IL-1 and act as "mini-receptor inhibitors" of the pro-inflammatory cytokine. Williams *et al.* have described a semaphorin/neurophilin complementary peptide antagonist that is specific to semaphorin 3A but has no effect on semaphorin 3F, components of the central nervous system that play an important role in both axonal growth and neuronal apoptosis *in vitro* (60). This system has also been extended to other cytokines, including interleukin-18 (IL-18) (61).

The MRT has also been vital in creating potential therapeutics for the autoimmune conditions previously described; GBS and MS. Experimental autoimmune neuritis (EAN) is the animal model of GBS and is caused by creating an immunogenic response to a myelin protein P2 (62). In a similar manner to that described above, Araga *et al.* (63) created a complementary peptide to the P2 epitope responsible for the immune response, immunized the rats and demonstrated a dramatic *in vivo* response. The vaccine caused a significant ablation of disease phenotype and was also protective to animals when pretreatment with vaccine occurred. Both human and animal models of MS have a significant T-cell component to the disease and thus are ripe for attempts to use the MRT to address the condition. In a Lewis rat model of MS (experimental autoimmune encephalomyelitis (EAE)), inverse hydropathy peptide administration and the subsequent anti-Id response reduced severity of disease, and frequency of relapse (64). Finally, there have been recent studies showing the effectiveness of a complementary peptide to La/SSB, the main auto-antigen in both systemic lupus erythematosus and Sjogren's syndrome (4, 65).

5. SUMMARY AND FUTURE DIRECTIONS

The purpose of this review is not to propose complementary peptide-based therapies as the sole solution for autoimmune diseases, but rather to summarize the science that has been done to bring the field to where it is now; on the cusp of producing targeted, disease specific therapeutics in multiple autoimmune conditions. Perhaps the overriding benefit to several of the studies previously mentioned is the lack of side effects of the treatment. Unlike iodine irradiation, or surgery for Graves' disease, or repeated cytokine treatment for relapsing remitting MS, anti-sense inverse hydropathy vaccines and related therapies utilize the incredible complexity and specificity of the body's immune system to assist in disease resolution.

Although this review has focused on the use of the Molecular Recognition Theory in dealing with autoimmune disease, there are several other fields of research that can be positively impacted by understanding the forces in play. The identification of orphan receptors, through the use of peptide mimetics of proteins has already yielded interesting results. Herrera and Ruiz-Opazo (66) were able to describe a previously unknown arginine-vasopressin receptor. The possibilities for the usage of the MRT are wide and varied.

With the implementation of genomic and proteomic work it only becomes more likely that more and more naturally occurring peptides will be shown to interact in an anti-sense hydropathically inverse manner. Additionally, due to the increasing utilization and sophistication of computer programs it has become much more facile to design and test a peptide *in silico* prior to using physical resources to investigate a hypothesis. It is through the combination of all of the techniques, in concert with the extraordinary capacity of high-throughput screening that major advancements in research and treatment of chronic, debilitation autoimmune diseases will occur. Anyone interested in further reading on this topic can obtain a complete bibliography of the subject via email request (blalock@uab.edu).

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