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Contaminations and Immune System Infections

Tejaswi Chaudhary and Amit Nayak*

Department of School of Medical and Allied Sciences, GD Goenka University, Haryana. India

Corresponding e-mail: choudharytejaswi@gmail.com

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ABSTRACT

The considerable prevalence of disease-discordant pairs among monozygotic twins underscores the pivotal role of environmental factors in the development of autoimmune diseases. Initial efforts were focused on identifying triggering factors, which have been found to include infections in animal models. For instance, the Coxsackie B4 virus has been linked to type I diabetes, while the encephalomyocarditis virus is associated with autoimmune myositis. In these models, viruses are thought to increase the immunogenicity of autoantigens by inducing local inflammation. In addition, there are cases of mimicry between microbial and human antigens. For instance, the induction of Guillaine-Barre syndrome in rabbits through immunization with a peptide derived from Campylobacter jejuni is explained by the similarity between C. jejuni antigens and peripheral nerve axonal antigens. In other models, chemical modification of autoantigens triggers autoimmune responses, such as in the case of iodine-induced autoimmune thyroiditis. Although these mechanisms have limited clinical counterparts, unknown viruses may be responsible for several chronic autoimmune diseases, including type I diabetes and multiple sclerosis. However, infections can also offer protection against autoimmune diseases. Western countries are currently witnessing a disturbing increase in the incidence of immune disorders, including autoimmune and allergic diseases, inflammatory bowel diseases, and some lymphocyte malignancies. This increase is believed to be linked to the improved socio-economic status of these countries, which raises the question of the causal relationship and the nature of the link.

The hygiene hypothesis, which posits that the decrease in infections observed over the last three decades is the main cause of the rise in immune disorders, is supported by epidemiological and clinical data. This hypothesis does not rule out the possibility of a specific etiological role for certain pathogens in some immune disorders, such as inflammatory bowel diseases. Even in these cases, infections may still have a non-specific protective effect. Numerous questions remain regarding the mechanisms of protection and the nature of infectious agents that confer protection. Four orders of mechanisms are being explored, including antigenic competition and immunoregulation. The former hypothesis proposes that immune responses against pathogens compete with autoimmune and allergic responses, while the latter suggests that infectious agents stimulate various regulatory cells whose effects extend to other specificities. Toll receptors and TIM proteins present in Th cells may also play a role.

The final proof of principle will be derived from therapeutic trials, where immune disorders will be prevented or cured using products derived from protective infectious agents. Several experimental data are already available in various models, with preliminary results in atopic dermatitis using bacterial extracts and probiotics.

Keywords: Immune System, Infections, Antigen

INTRODUCTION

The conspicuous role of environmental factors in the development of autoimmune diseases cannot be denied, as evidenced by the disease discordance rate among monozygotic twins, with more than 50% and sometimes up to 80% being affected differently. The fact that twins share a similar environment during childhood makes this discordance even more striking. Countless studies have been conducted to identify environmental factors that control the onset of autoimmune diseases, with a particular focus on triggering factors such as drugs or iodine nutritional supplements [1]. Infectious agents have also been extensively researched, with some evidence pointing toward their etiological role in certain autoimmune diseases. However, in most cases, the link between infections and autoimmune diseases remains indirect. Surprisingly, it has also become apparent that infections may offer protection against autoimmune diseases, by the hygiene hypothesis. This manuscript aims to provide a brief overview of the contrasting effects of infectious agents on the development of autoimmune diseases, independent of genetic factors, although their expression depends on the interplay between infections and genes predisposing to or protecting against autoimmune diseases [2].

LITERATURE REVIEW

Infections Triggering Role

Introduction: Autoreactive B and T cells are an intrinsic part of the immune system and are present in all healthy individuals. However, their specific repertoire and prevalence are still not well-defined, especially in the case of T cells, which undergo intrathymic negative selection to eliminate autoreactive T cells with high-affinity receptors for autoantigens expressed in the thymus. Despite this, peripheral autoreactive T cells can recognize a wide range of major autoantigens distributed across different organs, which are often implicated in various autoimmune disorders [3].

To better understand the paradox of how these autoreactive cells attack their target organs and trigger autoimmune diseases, researchers have developed a double transgenic mouse model, in which transgenic mice expressing large amounts of the Lymphocytic Choriomeningitis Virus (LCMV) glycoprotein on the b cells of the islets of Langerhans were hybridized with transgenic mice harboring a majority of CD8 T cells specific to the LCMV glycoprotein. These mice represent an extreme expression of physiological autoreactivity since they possess a defined autoantigen on their b cells, yet do not develop diabetes unless infected by LCMV.

This model suggests that infection-induced activation of glycoprotein-specific T cells could lead to the lysis of b cells and subsequent induction of diabetes. This represents an example of virus-induced autoimmune disease, although it is a special case since the target viral protein is transgenically expressed on the b cells.

It is still unclear how dormant autoreactive T cells are activated in patients with autoimmune diseases in whom the viral protein is not an autoantigen, as its expression only appears after infection. Several mechanisms have been proposed to explain the modalities of T cell activation necessary to break down the aforementioned indifference [4].

Mechanism

There are 3 possible mechanisms.

Polyclonal lymphocyte activation: Polyclonal lymphocyte activation refers to the activation of multiple types of lymphocytes, including both B cells and T cells, by a non-specific stimulus such as an infection, vaccination, or exposure to a foreign antigen. This results in the production of a wide variety of antibodies that can recognize and bind to a diverse range of antigens.

In polyclonal lymphocyte activation, the immune system responds to the presence of foreign antigens by activating a large number of lymphocytes. This can result in the production of a wide range of antibodies that recognize and bind to different parts of the antigen. This is in contrast to monoclonal lymphocyte activation, where a single type of lymphocyte is activated, resulting in the production of a single type of antibody that recognizes a specific antigen.

Polyclonal lymphocyte activation can be beneficial in fighting infections, as it provides a diverse range of antibodies that can target different parts of the pathogen. However, it can also result in the production of autoantibodies that recognize and attack the body's tissues, leading to autoimmune diseases [5,6].

Antigen cloning: There has been an observation that the protein sequence of certain bacterial or viral proteins shares homology with autoantigen sequences [7,8]. This includes a significant homology between the Coxsackie B4 virus

protein and the glutamic acid decarboxylase sequence, as well as between the hepatitis B virus polymerase sequence and a segment of myelin-basic protein which has been implicated in the development of multiple sclerosis [9,10]. This list of homologies is lengthy. However, it is important to note that the consideration of such homologies often does not provide definitive evidence for a possible role of shared antigenic determinants between the infectious agent and the autoantigen.

Bioinformatics-based searches for homologies reveal the existence of a large number of medium-length homologies, the relevance of which is elusive. Therefore, it is crucial to collect more direct evidence on the responsibility of the shared epitope in question. Such evidence has only been obtained in a limited number of diseases, and we will discuss the two best-documented cases, namely rheumatic fever and Guillaine-Barre syndrome.

Rheumatic fever is often associated with heart involvement, preceded by acute polyarthritis in a large percentage of cases. The disease is secondary to streptococcal infections. Epidemiological studies indicate that the onset of carditis usually appears after repeated streptococcal infections, some of which may have been clinically latent. Common antigenic determinants have been evidenced between streptococcal proteins and heart autoantigens, but their precise chemical nature has not yet been analyzed in depth. It is postulated that the strong hyper-immune response to these determinants, helped by the T cell response to unshared determinants, leads to the appearance of anti-heart autoimmunity. Heart-specific cross-reactive T cells were extracted from heart specimens of rheumatic fever patients obtained after surgery [11,12].

The case of Guillaine-Barre´s syndrome is even more clear-cut. There is well-documented evidence of a temporal relationship between various infections or vaccinations and the onset of the syndrome, an acute polyradiculoneuritis. Particular attention has been drawn to intestinal infections by Campylobacter jejuni. Antibodies cross-reacting with C. jejuni and peripheral nerve gangliosides are detected in the serum of GBS patients [13]. Recently, a strong homology was found between lipo-oligosaccharides present in C. jejuni and in ganglioside GM1. The etiological role of this lipo-oligosaccharide was strongly supported by the induction of clinically overt GBS in rabbits repeatedly immunized with the lipo-oligosaccharide.

In summary, while it has been noted that there are homologies between certain bacterial or viral proteins and autoantigen sequences, these homologies do not always provide conclusive evidence for the existence of shared antigenic determinants between the infectious agent and the autoantigen. More direct evidence is necessary to establish a causal relationship between these homologies and autoimmune diseases. However, in the cases of rheumatic fever and Guillaine-Barre syndrome, there is clear-cut evidence of a temporal relationship between infections and the onset of these diseases, and common antigenic determinants between the infectious agent and the autoantigen.

Expanded immunogenicity of organ autoantigens auxiliary to disease-intervened irritation: Localized inflammation of the target organ is induced by several infectious agents, including a broad spectrum of viruses. This may trigger an organ-specific autoimmune response, which can intensify and perpetuate the inflammation. The mechanism is illustrated by two experimental models. In Theiler's disease, infection initially leads to virus-specific encephalomyelitis, associated with T cell reactivity to viral proteins. Within a few weeks, however, the virus-specific immune response is replaced by a genuine autoimmune response, characterized by T cell reactivity to myelin-basic protein and proteolipid protein. This autoimmune response is responsible for the chronicity of the disease. Similarly, infection of mice with the Coxsackie B3 virus induces long-term cardiomyocytes that develop in two phases: the first viral and the second autoimmune [8,9].

It is hypothesized that in these models, the initial virus-induced inflammation causes an overexpression of molecules that participate in the recognition of autoantigens by T cells. These molecules include MHC molecules (class one and class two), as well as costimulatory and adhesion molecules. Interestingly, blocking the B7 CD28 costimulatory pathway inhibits the onset of the autoimmune phase of Theiler’s disease [10].

The role of inflammation in triggering autoimmune disease is also supported by data obtained using the Coxsackie B4 (CB4) virus in Non-Obese Diabetic (NOD) mice. CB4 is associated with the etiology of human type 1 diabetes and is an enterovirus with clear pancreatotropism. Infection with CB4 can induce diabetes in non-autoimmune-prone mouse strains and accelerate diabetes onset in diabetes-prone NOD mice. The fact that diabetes acceleration is also observed in BDC 2.5 transgenic NOD mice expressing an islet-specific TCR derived from a diabetogenic T cell clone suggests

that the diabetogenic effect of the virus is mediated by inflammation, rather than by antigen-mimicry, which is unlikely to be a significant factor in mice showing a highly skewed T cell repertoire [11].

It is tempting to speculate that human counterparts of such experimental models may explain some of the infection-associated autoimmune diseases. However, it should be noted that no direct demonstration of such a mechanism has been made in human autoimmune diseases, possibly due to the difficulties encountered in identifying etiological viruses, as discussed below.

Quest for Etiological Irresistible Specialists

Over the past few decades, there has been a significant focus on identifying the exact infectious agent that triggers major autoimmune diseases. Despite extensive research, the quest for a definitive etiological infectious agent in autoimmune diseases has been largely unsuccessful. However, there have been some notable exceptions, such as the identification of group A beta-hemolytic streptococci in rheumatic fever and Campylobacter jejuni in Guillain-Barré syndrome, both of which are acute diseases.

In contrast, other autoimmune diseases, which are typically chronic, have yielded limited and controversial data regarding their etiological infectious agents. For example, despite decades of research, the underlying cause of type 1 diabetes and multiple sclerosis remains unknown. The situation is even more complicated for rheumatoid arthritis and systemic lupus erythematosus, as the etiology of these diseases is not well understood and is likely multifactorial [12,13].

Despite the challenges, significant efforts continue to be made to identify the underlying cause of autoimmune diseases. Researchers are exploring various avenues, such as examining genetic and environmental factors, as well as the role of the immune system in these diseases. Despite the relative lack of progress in identifying the exact infectious agents that trigger autoimmune diseases, the research being conducted is increasing our understanding of these complex diseases and bringing us closer to effective treatments and potential cures.

The instance of type 1 diabetes: For decades, viruses have been considered major potential candidates for the development of Type 1 Diabetes (T1D). The viral hypothesis initially emerged due to the temporal relationship between specific viral infections and the onset of overt diabetes. Coxsackie B4 virus was particularly noted in this regard. However, this argument is not very strong because T cell-mediated islet aggression most likely begins many years before the clinical onset of diabetes in most patients. Therefore, the incriminated infection could only exacerbate the anti-islet response and accelerate disease onset, rather than being the sole cause of the disease. Additionally, there has been a lack of serological evidence, such as the detection of antiviral antibodies in T1D patients, and the episodic claims of virus isolation from pancreatic tissue have also not been very convincing [14].

Recently, interest in enteroviruses has been renewed due to a set of observations. However, even at the experimental level, there are limited data. For instance, the encephalomyocarditis virus has been reported to induce T1D in rodents, but the T1D is of the cytopathic type without much immunological involvement. The Coxsackie B4 virus can induce diabetes in mice with some features of autoimmune T1D, but it is still unclear whether disease pathogenesis involves a direct cytopathic effect or an immune b cell attack secondary to virus-induced inflammation [4].

Other interesting data have been derived from the RIPLCMV transgenic mice, which develop T1D after LCMV infection according to a hit-and-run mechanism. The viral infection stimulates the induction of LCMVgp-specific CD8 cytotoxic T lymphocytes which cause the disease, even though the virus is rapidly cleared through the action of such CTLs.

Collectively, these data provide some support for a viral etiology for T1D, even though the diabetogenic virus is still unidentified. The etiological infection may take place many years before clinical onset, which could explain the difficulty in identifying the diabetogenic viruses, which might not be unique.

Another very strong indirect indication for viruses in the etiology of T1D comes from the recent demonstration of the important role of interferon-a in the pathogenesis of the autoimmune disease. Interferon-a is known to play a crucial role in the immune response against viral infections. Therefore, its involvement in the development of autoimmune diseases suggests that viral infections might be a significant trigger for these diseases.

In conclusion, although the evidence for a viral etiology of T1D is not very robust, the available data suggest that it might play a role in disease development, possibly through a hit-and-run mechanism. Further research is needed to identify the diabetogenic virus and determine its exact role in the pathogenesis of T1D.

The reasons why etiological infections have not been identified: Identifying the etiological infections in human autoimmune diseases is a complex issue, and various explanations can be proposed to understand the difficulties faced in doing so. One possible hypothesis is that the triggering infection occurs many years before the clinical onset of the autoimmune disease. It is plausible that the triggering infection resolves rapidly, and its virological and serological traces disappear by the time of clinical onset. Even if antibodies to the pathogen are present, their specificity to the autoimmune disease may be uncertain, especially if the infection in question is common in the general population. The genetic predisposition to react unfavorably to the infectious agent is what causes the disease. It is worth noting that healthy individuals can also be infected by the pathogen without showing any signs of autoimmunity. This hypothesis is consistent with the mechanisms discussed above, such as the virus-mediated two-phase disease, as seen in cases like Theiler's disease and cardiomyocytes. This idea is also supported by extensive studies conducted in RIP-LCMV mice, where infection with LCMV triggers diabetes through hit-and-run mechanisms.

Another possible explanation is that several viruses could cause a particular autoimmune disease. In the context of the inflammation-mediated mechanism, what is important is the tropism of the etiological virus for the target organ. It is conceivable that several viruses, which show a tropism for the same organ, could trigger an autoimmune response specific to that organ.

Lastly, it is essential to recognize that the methods presently used to incriminate a given infectious agent in disease are difficult to interpret in the absence of a clear-cut temporal relationship or disease prevention by vaccination. As mentioned above, the specificity of serological data is usually insufficient in the absence of IGM antibodies that suggest a recent infection. Direct virus identification is complicated by the challenges involved in obtaining relevant organ specimens. Clinical epidemiology is also confronted by the frequency of latent infections and the common lack of specificity in clinical signs. Therefore, a combination of multiple approaches, including serology, virus identification, and epidemiology, may be necessary to identify the etiological agent of autoimmune diseases accurately [15].

Defensive Impact of Contaminations on Immune System Infections

General introduction: As per the evidence accumulated from various sources, it seems that the Western countries' rise in autoimmune diseases can be attributed to a decrease in infectious diseases and an improvement in hygiene. This theory, which was initially developed for allergic diseases, applies to most autoimmune diseases, but not necessarily all of them. This notion has been reviewed in several recent papers.

There has been a concurrent increase in autoimmune diseases and a decline in infectious diseases in Western countries. In North America and Europe, the incidence of most autoimmune diseases has been steadily increasing over the past thirty years. This trend is particularly noticeable in type 1 diabetes, inflammatory bowel disease, and multiple sclerosis. However, for the latter disease, it appears that a plateau has been reached. In the case of type 1 diabetes, the rise in incidence is alarming due to the decrease in age of onset, with young children (less than 2 years-3 years old) being frequently affected. This epidemic is not observed in less developed countries, and within developed countries, it is more common in northern than southern regions. Although genetic differences are not the primary explanation for this discrepancy, children from families that recently migrated from low-incidence to high-incidence countries have developed the disease with a high incidence, as shown for multiple sclerosis and type 1 diabetes. For example, Pakistani families who immigrated to the UK developed a higher frequency of type 1 diabetes.

In developed countries, the incidence of major infectious diseases has decreased, despite the persistence of some serious infections and the emergence of new ones such as AIDS. In this context, special attention should be given to gastrointestinal infections, which are prevalent in underdeveloped countries and relatively rare in Western countries. The dramatic improvement in the quality of drinking water and food, particularly in young children, has contributed to this trend in Western countries.

The correlation between the decline in infections and the rise in autoimmune diseases is further supported by the relationship between socioeconomic levels (including sanitation quality) and the frequency of major autoimmune diseases, whether considering whole countries or individual patients. Additionally, the frequency of type 1 diabetes is higher in firstborns of multiplex families than in other children, which may be due to lower exposure of firstborns than siblings to infections.

Animal models: Scientific studies conducted on animals have shown that reduced exposure to infections can increase the risk of autoimmune diseases. This has been particularly demonstrated in NOD mice that are bred in conventional facilities, as a simple decontamination process leads to a significant increase in the frequency of diabetes. Conversely, when NOD mice are deliberately infected with various bacteria, viruses, or parasites at an early age, the onset of diabetes can be completely prevented. Similar findings have been reported for experimentally induced autoimmune diseases, such as mycobacteria in experimental allergic encephalomyelitis [4,21,22].
However, it is important to note that the protective role of infections is not a general rule. In specific pathogen-free animals, autoimmune diseases may develop under certain conditions, such as the presence of transgenic T cell receptors or depletion of regulatory cells. Additionally, for some autoimmune diseases like arthritis in the SKG mouse model and inflammatory bowel disease, infections may be required for disease development. Interestingly, in the case of inflammatory bowel disease, the disease can be prevented by administering non-pathogenic lactobacilli.
These animal studies provide strong evidence that exposure to infections plays an important role in the development of autoimmune diseases. However, it is important to note that not all autoimmune diseases follow the same pattern and that the relationship between infections and autoimmune diseases is complex. Further research is needed to fully understand the mechanisms behind the relationship between infections and autoimmune diseases [21,22].

- **Fundamental mechanisms:** There is evidence to suggest that infections can have a protective effect on autoimmune diseases, but the exact mechanisms behind this effect are complex and not yet fully understood. Studies conducted on animal models have shown that infections can prevent the onset of autoimmune diseases, such as diabetes, in some cases. Interestingly, this protective effect appears to apply to both TH1-mediated autoimmune diseases and TH2-mediated allergic diseases, despite initial theories that the protective effect of infections was exclusive to TH1-mediated diseases. Additionally, there seems to be a growing trend of individuals experiencing both allergic and autoimmune diseases simultaneously.
  Three possible mechanisms could explain the protective effect of infections on autoimmune diseases: competition, regulation, and stimulation of innate immunity. These mechanisms are not mutually exclusive, nor are they independent of each other. More research is needed to fully understand the complex relationship between infections and autoimmune diseases [23].
- **Competition:** Antigenic competition refers to the phenomenon where the immune response to a single antigen is stronger than the response to the same antigen given in conjunction with other antigens. Various mechanisms explain this, including the pre-emption effect on macrophages, competition for cytokines or growth factors, and competition for peptide binding to MHC molecules. With recent advances in understanding lymphocyte homeostasis, it has become clear that lymphocyte proliferation and survival depend on several homeostatic signals, such as cytokines like IL-7 and self-peptide MHC recognition.
  The strong immune responses elicited by infectious agents may compete with immune responses against weaker antigens, such as autoantigens and allergens, for these homeostatic signals. This idea is supported by recent studies using the NOD mouse model, which showed that Complete Freund's adjuvant has an anti-homeostatic effect.
  This competition can have implications for the development of autoimmune and allergic diseases. It is postulated that in situations where the immune system is exposed to strong antigenic stimuli, such as infections, the immune response against weaker antigens may be suppressed due to competition for homeostatic signals. This could explain the increased incidence of concomitant occurrence of autoimmune and allergic diseases in single individuals.

Therefore, the mechanisms of antigenic competition are neither mutually exclusive nor independent and may include competition, regulation, and stimulation of innate immunity. Further research is needed to fully understand the complex interplay between these mechanisms in the development of autoimmune and allergic diseases [24].

- **Regulation:** Research has demonstrated that immune responses to one antigen can also have a suppressive effect on immune responses to other antigens, a phenomenon known as bystander suppression. Infectious agents may stimulate regulatory cells that dampen autoimmune responses through this mechanism. While limited data is supporting the involvement of TH2 cells, studies conducted on NOD mice in our laboratory have revealed that TGF-b plays a critical role in situations where TH2 cytokines are not at play. Further research has shown that NKT cells could also play a role, as CD1D-deficient NOD mice, which lack NKT cells, displayed reduced protection from diabetes after being treated with a Gram-positive bacterial extract compared to wild-type mice [25].
- **Innate immunity:** Recent studies have highlighted the significance of Toll-like receptors in the activation of autoimmune responses. This concept has been supported by research conducted on RIP-LCMV mice, which revealed that TLR3 stimulation and the consequent production of IFN-a are essential for virus-induced autoimmune diabetes. Interestingly, it has also been observed that TLR stimulation could have a protective effect against autoimmune diseases. The administration of various TLR agonists (such as TLR2, 3, 4, and 9) in young NOD mice has been shown to prevent the onset of diabetes. It has been suggested that this protection is linked to the TLR-dependent production of IL-10 and TGF-b, as confirmed by both in vitro and in vivo studies [26,27].

CONCLUSION

Autoimmune diseases are influenced by a variety of environmental factors, including infections, which can have both positive and negative effects. The mechanisms by which infections modulate autoimmune disease development are complex and may vary depending on the pathogen involved. Investigating these mechanisms and their correlation with gene polymorphisms predisposing to or protecting against autoimmune diseases could provide valuable insights. For instance, recent research has linked gene polymorphisms of TLR2, TLR4, and TLR10 to asthma, potentially implicating a range of genes coding for various cytokines and receptors, including virus receptors. At the therapeutic level, these findings may lead to new approaches for preventing or treating infections or using immunostimulation to safely replicate the protective effects of infections.

DECLARATIONS

Conflict of Interest

The authors declared no potential conflicts of interest concerning the research, authorship, and/or publication of this article.

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