Review

Autoimmune diseases: Understanding the mechanisms and therapeutic strategies for treating autoimmunity

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ABSTRACT

Autoimmune diseases are a broad class of disorders that are characterised by the irregular response of immune cells creating self-reactive antibodies that target its own cells and tissues. The primary cause for the development of autoimmunity is yet to be known. However, current research suggests that increased genetic susceptibility combined with multitude of triggering elements such as environmental influences and infection are some of the most significant causative factors leading to autoimmunity. Using the above-mentioned factors, till date, researchers have proposed several theories in an attempt to explain the underlying mechanisms and complexities of how autoimmunity occurs. Some of the most widely accepted theories include cryptic determinants, molecular mimicry, altered glycan theory, and the hygiene hypothesis as well as the interaction of B and T lymphocytic cells. Understanding these molecular mechanisms of autoimmune diseases is key for the development of future preventative therapies, as currently there is no therapeutic strategy to cure these conditions. The traditional concept of T cell-mediated and autoantibody-mediated autoimmune diseases should be adjusted to reflect the new understanding of the interaction of different immune cells in autoimmune pathogenesis. Recognition of B cell contribution to the pathogenesis of autoimmune diseases

(traditionally thought to be mediated by T cells) has led to promising new therapies.

1. Introduction

Autoimmune diseases include a diverse range of chronic conditions that are characterised by the development of an irregular response by the immune cells, which produce self-reactive antibodies that target the cells and tissues within the host body [1]. Although, autoimmune diseases include a broad range of disorders, the incidence of these conditions is relatively rare, as it affects roughly 8.5% of the world population. Thyroid-hashimoto's disease and rheumatoid arthritis are the most common conditions associated with autoimmunity. Autoimmune disease can be further classified into systemic or organ-specific conditions, in which tissue damage occurs through mechanisms of both the innate and adaptive immune response. Activation of these immune systems can lead to inflammation and formation of antigen-specific autoantibodies that attack healthy cells, thereby resulting in symptoms such as pain, swelling, fatigue, fever and rashes. Increased secretion of cytokines along with other mechanisms such as formation of immune complexes phagocytosis and cytolysis of the target cells could be some of the key mechanisms leading to tissue damage in autoimmune diseases. The underlying cause of autoimmunity towards a specific cell type is still

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unknown, which is often considered as one of the primary reasons that make this disease difficult to treat [2, 1]. Several studies have now confirmed that the pathogenesis of autoimmune diseases is multifactorial and can be caused by an interaction between genetic and environmental factors. Single gene mutations or mutations in multiple genes that control immune function and auto-reactivity can increase the risk of developing the disease. Recent studies have shown that most autoimmune diseases are multigene and till date researchers have identified up to 25 genes that are associated with the development of autoimmune diseases. In genetically susceptible individuals a number of etiological agents such as infections, environmental triggers and possible drug-induced factors can initiate auto reactivity, thereby leading to conditions such as celiac disease, type 1 diabetes, Graves' disease, multiple sclerosis, psoriasis, rheumatoid arthritis, and lupus [2-5].

Lymphocytes are part of the immune system of the human body, and are known to play a key role in autoimmune conditions. Lymphocytes are broadly classified into T and B lymphocytes. In regular immune response, antigens are taken up by antigen-presenting cells and processed into peptides and taken up by the major histocompatibility complex molecules (MHCs) for presentation to T cells *via* the T cell receptor (TCR) [3]. T helper cells may elicit direct effects by releasing specific cytokines or can activate macrophages, monocytes and B cells. The TCR on helper T cells binds to antigen complexes and MHC molecules on the surface of B cells leading to T cell activation [3]. After receiving the signal from the helper T cell, the B cell will create an antibody specific for the antigen and bind to its target [3]. This crucial role of B cells in autoimmune diseases is now being recognized, despite autoimmune diseases being traditionally viewed as to be mediated by T cells. New research is now looking to further the understanding of these pathogenic B cells and novel therapies are aimed towards selectively targeting them. This paper will discuss some of the theories behind autoimmune diseases as well as the role of B cells in autoimmune diseases.

Epidemiological evidence suggests that there is consistent growth of autoimmune diseases around Western societies over the past few decades [6].

According to the Australasian Society of Clinical Immunology and Allergy, diseases such as thyroiditis, rheumatoid arthritis, and diabetes affect more than 1% of the Australian and New Zealand population and are more common among the Indigenous Australians, Polynesians and individuals who are descendants from Southeast Asia [7]. These conditions are known to affect approximately 5% of the populations in Australia and New Zealand with women being more commonly affected than men [7].

The current treatments of many of the above-mentioned autoimmune conditions aim to suppress the symptoms [8]. Traditional therapies for autoimmune diseases have relied on immunosuppressive medications that dampen immune responses within the body [8]. Depending on the severity of the condition, nonsteroidal anti-inflammatory drugs (NSAIDs), corticosteroid drugs, and immunoglobulin replacement therapy are often used [8, 1]. Due to the fact that autoimmune diseases are not curable, the patients are often on immunosuppressants for long periods of time, thus leaving them defenceless against opportunistic pathogens. Therefore, in order to reduce the risk of systemic immune suppression for improving drug tolerance, there has been a push to develop more specific strategies for treatment [8]. Recent advances in research suggest that maintaining a balance of effector and regulatory immune function is critical for avoiding autoimmunity. New therapeutic targets such as co-stimulation blockade, regulatory T-cell therapy, antigen-specific immunotherapy, and manipulating the interleukin-2 pathway look to restore the balance of effector and regulatory immune function, aiding patients suffering from autoimmune disease, and refrain from the use of immunosuppressive techniques thus avoiding its negative effects [8].

2. The theories

There are many theories as to how an autoimmune disease state arises. Some common ones are listed below.

2.1. Cryptic determinants

During the maturation of immune cells, the body's antigens are presented to the immune cells at certain 'check points' to ensure auto-reactivity

does not occur; however, it is impossible to induce tolerance to all aspects of auto-antigen [9]. This is because under normal conditions, some regions of these antigens are not expressed to a sufficient level to induce tolerance. This is known as the "cryptic determinants" and is one theory relating to why autoimmunity may occur [9, 10].

2.2. Molecular mimicry

The concept of molecular mimicry describes a situation where a foreign antigen shares sequence of structures similar to autoantigens in the host, which can initiate an immune response in which a T or B cell component will mount an immune response to self [11]. There are many mechanisms by which infection in the human host by pathogens can lead to the development of autoantibodies. Several pathogens have elements and surface antigens that are very similar to the self-antigens of a human host in their amino acid sequences or structures [3]. For example, it has been suggested that molecular mimicry resulting in immunological cross reactivity might be the primary cause for the development of autoantibodies in individuals following an infection from gram-negative bacteria such as *Klebsiella pneumonia* and *Campylobacter jejuni*. Infection with *K. pneumonia* or *C. jejuni* has also been seen to lead to the production of self-antibodies [11]. Antigens are taken up by antigen-presenting cells and processed into peptides, and pathogens have the potential to 'mimic' and appear as self-antigenic ones [3]. T or B cells which are activated in response to a causative agent are also cross-reactive to self, and cause direct damage and further activation of other cells of the immune system [3].

2.3. Bacterial DNA

Human beings or *Homo sapiens* who previously were considered as a product of a single genome, are now considered as superorganisms with a plethora of bacterial genomes that exist in concert with our own human metagenome. Previously, Proal AD and colleagues in their review article have suggested that an estimated 90% of the cells in *Homo sapiens* are of microbial but not human origin. Furthermore, it was also suggested that these microbes and their metabolites can alter the expression of several genes that are associated with the development of autoimmune conditions

and their progression [12]. Based on the above-mentioned theory, it can now no longer be assumed that autoantibodies are generated purely against *Homo sapiens* metagenome. Furthermore, research has shown that bacteria can significantly alter the expression of several genes within the human body, thereby affecting the progression of autoimmune diseases. For example, an infection from *Mycobacterium tuberculosis* has shown to change the expression of up to 463 different human genes. Notable examples of microbiota changing gene expression, thereby altering the progression of autoimmune disease include, increased levels of protein tyrosine phosphate, non-receptor type 22 (also known as PTPN22), a protein regulated by the *PTPN22* gene in humans. Increased PTPN22 protein levels are associated with an increased risk of diabetes mellitus, lupus and rheumatoid arthritis. Up-regulation of PTPN22 activity and increased PTPN22 levels were observed in individuals following an infection from mycobacteria. Although in autoimmunity, the autoantibodies are created against self, there may be evidence that the immune system is therefore not attacking itself, but instead protecting the body from these bacteria, which it does not consider as part of self [12].

2.4. Altered glycan theory

Glycans along with lipids, proteins and nucleic acids are fundamental to all living systems. Glycans are molecules that are made of numerous monosaccharides that are linked glycosidically. It is widely believed that glycans play a crucial role in the etiology of all diseases. In the immune system glycans act as protein markers, and aid the immune system in cell recognition and eliciting a response. Like in most cells, surface-localized immune-receptors are glycoproteins, including the pattern recognition receptor such as toll-like receptors, major histocompatibility complex proteins, chemokine receptors and T and B cell receptors [13]. The role of each glycan in these receptors can vary significantly, which allows these receptors to interact with other immune system components such as glycan-binding proteins or lectins. The binding of lectins contributes to the immune response [13]. Glycocalyx can dictate the migration pattern of immune cells, and dictate the effector function of immunoglobulins and

humoral components of the immune system [14]. According to this theory, individuals with autoimmunity show alterations in their glycosylation profile such that pro-inflammatory immune response is favoured. In addition, individuals with autoimmune diseases are hypothesized to have unique glycan signatures [14]. Since the discovery of altered IgG glycosylation in patients with rheumatoid arthritis, there has been mounting evidence favouring the role of glycans in the pathophysiology of autoimmunity [14].

2.5. Hygiene hypothesis

According to the "hygiene hypothesis", the decreasing incidence of infections in western countries could be the underlying cause of the increasing incidences of autoimmune diseases [15]. According to this theory, it has been hypothesised that individuals migrating from an area of low incidence of/exposure to symbiotic microbes and pathogens to an area of high incidence/exposure may acquire the immune disorders with a high incidence at the first generation [15]. Exposure to fewer antigens at a younger age could relate to factors such as difference in immunoregulation, involving various regulatory T cells and Toll-like receptor stimulations, triggering the immune system to become overactive and more likely to elicit an inappropriate response to self-antigens to cause autoimmune conditions such as asthma [15].

2.6. Natural antibodies

Antibodies present in the serum of healthy individuals, without the deliberate stimulation of immunization or any antigens are called natural antibodies [16]. The majority of natural antibodies react with one or more self-antigens and are therefore termed natural autoantibodies. These natural autoantibodies are usually directed against self and alter self-components [16, 17]. Naturally produced autoantibodies have low-titer, low-affinity, and interact with self-antigens. Furthermore, these autoantibodies play an important role in immune homeostasis and can participate in a variety of physiological functions such as regulation of the immune function, repertoire selection and developing resistance to infection [18, 17]. The importance of natural autoantibodies in immunomodulation has long been neglected, as

antibodies which are self-reactive are deleted or rendered functionally inactive through deletion of auto-reactive clones, as proposed in the clonal selection theory. However, autoantibodies have been found in healthy individuals and these naturally occurring autoantibodies are thought to be independent of any exogenous antigen stimulation [18, 16].

Antibodies that bind to a variety of exogenous antigens such as those on bacteria, viruses, and fungi, as well as self-antigens account for a significant proportion of immunoglobulins in healthy individuals [19]. Most natural autoantibodies are IgM and may be polyreactive with moderate intrinsic affinity and have protective functions [19]. One of these functions is the clearance of apoptotic cells [20]. The lack of secreted IgM was shown to correlate with increased pathogenic IgG autoantibodies and autoimmune diseases, presumably due to the absence of apoptotic cell depletion [20].

Antibodies are produced by B cells and play an important role in autoimmune diseases [19]. Natural autoantibodies are predominantly produced by (CD5 +) B-1 cells. The lymphocytic B-1 cells are highly effective in antigen presentation and can play an important role in the production of pathogenic autoantibodies in several autoimmune diseases, including systemic lupus, Sjögren's syndrome, and rheumatoid arthritis [19]. Traditionally, autoimmune diseases have been viewed as autoantibody-mediated or are classified as T cell-mediated due to the autoantigen presentation and interactions with T cells to initiate response. However, the interactive roles of T cells and B cells with the adaptive immune response and B-cell help in CD4+ T-cell activation are increasingly recognized [8]. Most conventional autoantibody-mediated diseases have IgG isotype and carry somatic mutation, which strongly suggested the help of T cells in autoimmune B cell response [20].

2.7. Predisposing factors to autoantibody production

Production of pathogenic autoantibodies signifies a serious breach in tolerance to self-antigens [19]. It is estimated that 50% to 75% of newly formed human B cells are self-reactive and should be

eliminated by several mechanisms [20]. B cell tolerance is established at several checkpoints in the development of B cells both in bone marrow and periphery. The main mechanisms of elimination are receptor editing, clone deletion and functional inactivation (anergy) [20]. Despite physiologic elimination (negative selection) or anergy, self-reactive T and B lymphocytes in the thymus and bone marrow persist [19]. In patients with chronic rheumatoid arthritis, systemic lupus erythematosus and type 1 diabetes, this early tolerance induction checkpoints were observed to be defective [20].

Alterations in molecules that promote the abnormal survival of autoreactive lymphocytes are well described, particularly in the Fas-dependant apoptosis of lymphocytes [19]. Interaction between Fas (a member of the tumour necrosis factor receptor family) and its Fas ligand (FasL) causes apoptosis after recurrent activation triggering of TCR to maintain homeostasis and regulate lymphocytes [21]. Fas/FasL activates Fas-associated death domain (FADD) which activates caspase-8 which initiates the apoptotic cascade. This induced apoptosis is important for lymphocyte homeostasis as shown in Fas-deficient (*lpr*) mice [21]. Furthermore, it is proposed that Fas/Fas ligand (FasL) acts as an activation inhibitor of recurrently stimulated T cells, and that its disruption causes overexpression and overproduction of $CD4^+$ and $CD8^+$ T cells (as well as double-negative TCR+CD4−CD8−B220+ T cells) [21].

Recently, Balomenos D *et al*. (2017) have defined that the underlying mechanism of this Fas/FasL effect could resolve the phenotype of *lpr* mice and lead to the development of therapeutics for related human syndromes [21]. The overexpression of the B-cell stimulator (BLyS) has also been linked to the survival of these cells as shown by Rodríguez-Carrio and his colleagues [22]. In addition Anstee *et al*. have shown the possibility of the overexpression of the antiapoptotic regulator Bcl-2 in 'Overexpression of Mcl-1 exacerbates lymphocyte accumulation and autoimmune kidney disease in *lpr* mice' [23].

2.8. Genetic factors

Genetic studies in humans show that full-fledged clinical autoimmune diseases are caused by multiple genetic changes that can be affected by environmental factors [19]. Despite the polygenicity of the human autoimmune disorder, knockout and overexpression of a single gene in a mouse model have been identified to be particularly instructive to help identifying several important pathways leading to autoimmunity related to the production of autoantibodies [23]. Predisposition to several autoimmune diseases due to genetic factors has been seen *via* several proven gene regions associated with regulating immune system and antibody production. Gene duplication along with a significant degree of overlap between genetic loci has been observed in autoimmune diseases. One of the most well-known examples of genetic overlap of loci leading to autoimmune disease can be observed in the association of human leukocyte antigen (HLA) region, and several other loci such as *TNFAIP3, IL2RA* and *IL23R* with several autoimmune diseases [24]. However, the genetic inheritability of autoimmune conditions is diverse, as seen in highly heritable conditions such as Crohn's disease or systemic sclerosis [24]. Several rare family clusters are known to have a common genetic basis leading to autoimmune phenotypes [25]. Rheumatoid arthritis (RA [MIM 180300]), autoimmune thyroid disease (AITD) (especially Hashimoto thyroiditis [MIM 140300]), and type 1 diabetes (T1D [MIM 222100]) show these familial autoimmune disease clustering [25].

2.9. Generation of autoantibodies

Organ-specific autoimmune diseases such as thyroiditis and type 1 diabetes mellitus strongly suggest that autoantibodies are stimulated by inflammation in the target organ, although, as previously discussed theories of cross-reactivity and molecular mimicry cannot be excluded [19]. On the contrary to organ-specific autoimmune diseases, it is unclear about how autoantibodies in systemic autoimmune diseases are generated and cause damage to several organs. Some of possible mechanisms associated with the production of autoantibodies in systemic autoimmune diseases include mutations in the genes that are primarily associated with the production of antibodies long with survival of abnormal B and T lymphocytes [26]. Post-translationally modified autoantigens have been linked to autoantibody production and are highly specific and have a significant prognostic value [19].

Natural IgM antibodies secreted from a subset of B cells bind to epitopes, specifically those expressed on apoptotic cells, to clear them [20]. As discussed above, the cleavage performed by a number of intracellular nucleases and proteases during apoptosis of certain pathogens sections the molecules in such a way that it can lead to the formation of neoepitopes [19]. These neoepitopes are often recognised as foreign by the immune system and uses them to trigger an immune response. Under normal conditions, epitopes generated in the thymus and bone marrow play a crucial role in the maturation of B and T cells in a process known as negative selection. During this process, epitopes resembling the self MHC molecules are presented to the immature lymphocytes. Immature lymphocytes that do not bind to these self-epitopes proceed through the maturation process having gained tolerance to the autoantigens; however lymphocytes that are capable of strongly binding with the "self" MHC peptides will be removed. In individuals with greater susceptibility of developing an autoimmune disease, due to factors such as increased inflammation, UV damage or environmental agents, the antigens expressed on cells can be alterd, causing our immune system to recognise them as forigen and thus stimulate an autoimmune response to self-antigens [19].

Antibodies may also form when natural IgM antibodies undergo somatic hyper-mutation or class switching. Somatic hyper-mutation inserts point mutations into the genes of the antibody variable regions [19]. Class switching occurs in the constant region by recombination upstream, and therefore the antibody then has a new and more diverse effect. Somatically mutated and class-switched IgG and/or IgA autoantibodies are characteristic of autoimmune states, in particular autoimmune states associated with proliferation of B-1 cells [19].

Autoimmune diseases are characterized by the appearance of autoantibodies, but autoantibodies have also been found in healthy people, most of which were of the IgM isotype [27, 28]. Autoantibodies obtained from studies in patients with autoimmune diseases such as systemic lupus erythematous and in lupus-prone mice confirmed these multi-specific binding IgM isotypes [27, 28].

The data from these studies clearly suggests that lymphocytes that make autoantibodies are common and are part of the normal repertoire of B cells that are encoded in the germline genes. However, the regulation, activation and function of these lymphocytes that produce autoantibodies *in vivo* are yet to be fully understood. Furthermore, it is yet to be found, if certain factors such as viruses, genetic or environmental, play a role in enhancing the production of autoimmunity [27].

In humans, the antibodies consist of two heavy and two light immunoglobulin chains, which join together to produce a "Y" shaped molecule. The variable region of an antibody is located on the upper branches of the Y shaped molecule and act as the antigen-binding sites of the antibody. Increasing the complexity and variability of the antigen-biding sites is crucial to regulating immune system homeostasis and preventing self-reactivity. Therefore, for increased complexity of immunoglobulin variable region the genes that code for the heavy chains, which consist of about 1000 segments of germline genes, are randomly combined to generate unique antibodies with greater diversity for antigen binding [29]. Approximately 50,000 different variable regions form only 1015 germline gene segments, and as each of these segments are linked recombinantly, additional nucleotide variability is introduced so that at each binding site there are at least three additional amino acids that increase this diversity by a factor of 10 and can result in nearly half a million different structures [29]. Somatic mutations provide an infinite repertoire of variable region structures that can act against any antigenic challenge. The organization of the V_H locus is particularly interesting as it falls into 'families' of genes. Families are identified as being approximately 80% homologous at the nucleotide level. Several genes are found between them, and antibodies of a particular specificity are often found only in a single gene family [29]. The immune response strongly depends on the genes of the major histocompatibility complex. Large amounts of experimental data indicate that other genes also control the immune response. It has been seen in mouse models that variations in the immune response can be represented in the variable regions of the heavy and light chain polypeptide chains [30, 29]. The locus of the T cell can

also be affected by the disease. There are presently a wide range of experimental works available from the literature explaining the relationship between human T cell and T cell receptor polymorphism in rheumatoid arthritis, autoimmune thyroiditis, insulin-dependent diabetes mellitus and myasthenia gravis [29].

Several papers have been published describing the genetic links to autoantibodies which are cross-idiotypes, particularly between human autoantibodies, specifically, cold agglutinins and monoclonal rheumatoid factors [30, 29]. Many studies have examined rheumatoid arthritis and found that the majority of rheumatoid factors have serologic markers of V_KIIIb light chains. These results, in turn, indicate that the V_H gene used for this particular autoantibody is most likely germline encoded, and that these autoreactive V_H genes are expressed early in the development of the B cell repertoire [29]. The V_H and V_L genes, which are used for many autoantibodies obtained from relatively small gene families, can prove to be of importance to understanding the mechanisms autoimmune disease. All of these factors, along with MHC products and environmental factors can interact to increase the number of autoimmune patients, whereas in normal people these clones are present, but down regulated and are not aggressive, and relatively 'benign' [29].

3. How do autoantibodies cause disease?

In many systemic autoimmune diseases, autoantibodies seem to directly cause damage following deposition in tissue and amplify inflammation and perpetuate autoantibody production by engaging Toll-like receptor [19]. Autoantibodies can react with free molecules, phospholipids or cell surfaces to form antibody-antigen immune complexes. For organ-specific autoimmune diseases such as myasthenia gravis, autoantibodies bind directly to target organs and cause damage [19]. These autoantibodies damage tissues and organs by activating FcγR of the complement system and initiating internalization and activation of Toll-like receptors. Antigen-antibody complexes are known to cause vasculitis and glomerulonephritis. Activation of intracellular Toll-like receptor in dendritic cells results in interferon type I production, whereas stimulating intracellular Toll-like receptors on antigen-presenting cells activates the productions of other inflammatory cytokines and thus the immune complex can persist the positive feedback response and enhance the inflammatory response [19].

In systemic autoimmune diseases, many autoantibodies cause damage by direct deposition within the tissues; they can increase inflammation and stimulate further production of autoantibodies [19]. Fc gamma receptor (FcγR) is a receptor for the Fc portion of IgG, and in mouse models it has been shown that mice lacking FcγRγ are protected from nephritis, which indicates an important role of FcγRs in tissue inflammation. In contrast, mice with FcγRIIb knocked out spontaneously develop lupus-like disease [19]. Antibodies of different isotypes have varying affinity for the four FcγRs. IgG2a has high affinity, causing inflammation, whereas IgG1 selectively engages FcγRIIb, which inhibits inflammation. A similar relationship is found in human FcγRs and the ability to inhibit or induce inflammation is believed to depend on autoantibodies and the FcγR engaged [19].

The complement system is an important part of the innate immune system, which plays an important role in clearing apoptotic cells and pathogens when activated [31]. It is well known that IgG and IgM can activate complement *via* the classical pathway by binding of C1q to the Fc-region of these antibodies [31]. Mouse models have shown that autoantibodies can also activate these pathways and induce cell lysis and tissue damage, and play a role in many diseases, particularly vascular diseases [31].

4. Current and future therapies for the treatment of autoimmunity

4.1. Traditional treatment of autoimmune disorders

As autoimmune diseases, at this point in time, are not curable, the goals of treatment are to reduce symptoms, control the auto-reactivity, and maintain the body's physiological ability to fight the disease [7]. Treatments that are currently available depend on the specific disease and its severity. Immunosuppressive medications such as corticosteroids and nonsteroid drugs such as azathioprine, cyclophosphamide, mycophenolate,

sirolimus, or tacrolimus, and immunoglobulin replacement therapy are often used [7, 8].

Disease-modifying anti-rheumatic drugs (DMARDs) are a category of drugs, which are defined by their use in rheumatoid arthritis to delay the progression of disease [32]. This term is often used in contrast to non-steroidal anti-inflammatory drugs and steroids. DMARDs were first used in the treatment of rheumatoid arthritis; however it has since been expanded and used in the treatment of other conditions such as Crohn's disease, lupus erythematosus, Sjogren's syndrome, and many others [32].

The type of treatment used varies on a case-to-case basis and depends on the specific disease and symptoms and hence treatments may include supplementing patients with hormone or vitamin replacements if the body is lacking [33]. Lifestyle modifications can be implemented to minimize flares of the disease, for example protection from light for patients suffering from Lupus, or dietary changes such as a gluten-free diet for patients with coeliac disease can be implemented to help manage the symptoms. Most autoimmune diseases are chronic, but many of them can be controlled by treatment. Haematopoietic stem cell transplantation represents a possible therapeutic strategy for autoimmune diseases resistant to available treatments [33].

Depletion of B cells by rituximab can effectively eliminate target-specific B cells because the drug targets B cells expressing surface CD20 receptor. Treatment with rituximab has previously shown to reduce the number of mature and memory CD20+CD27+ B cells in blood and primary lymphoid organs. However, rituximab treatment appears be ineffective with circulating IgG levels, while reducing the level of circulating IgM [20]. Several courses of Rituximab are often associated with progressive decreases in circulating levels of IgM and IgG [34]. However, long-term effects of using the anti-CD20-mediated B cell depletion therapy such as rutaximab administration have shown to induce immunodeficiency in individuals, thus raising the risk of infection.

New therapeutic targets such as costimulation blockade, regulatory T-cell therapy, antigen-specific immunotherapy, and manipulating the interleukin-2 pathway look to restore the balance of effector and regulatory immune function, aiding patients suffering from autoimmune disease, and refrain from the use of immunosuppressive techniques thus avoiding its negative effects [8].

4.2. Emerging therapeutic strategies for treating autoimmune conditions

Novel studies are still emerging, looking at a variety of different factors to move away from the immunosuppressive route of treatment. Study by Dwyer *et al.* in 2016 looked at autoimmune diseases such as type 1 diabetes and the possibility of using low dose of interleukin-2 [35]. The genetic risk of type 1 diabetes is associated with the IL-2 and IL-2R signalling pathways leading to the destruction of the self-tolerance mechanism primarily due to T cell regulatory functions and changes in homeostasis [35]. In an attempt to remedy such drawbacks, therapeutic administration of IL-2 at low doses attracted attention due to its ability to stimulate T cells without undesirable stimulation of effector T cells. The results show that low-dose IL-2 therapy corresponds to a new class of immunotherapy [35].

In another study in 2016 conducted by Zhang *et al.*, a new approach took into account antibodies, in particular antibodies against CD20 with a multimerized Fc domain [36]. Recombinant protein for CD20 called GB4542 was created which not only preferentially bound with $CD20^+$ cells but also helped in the recognition of $CD20^-Fc\gamma R^+$ PBMCs. In contrast, the control mAb containing the same Fab region, GB 4500, was unable to bind to $CD20-Fc\gamma R^+$ PBMC [36]. At low concentrations, GB4542 showed enhanced antibody-dependent cytotoxicity, antibody-dependent cellular phagocytosis and complementary cytotoxicity compared to GB4500. This data demonstrates that GB4542 may be a useful tool in treating autoimmune diseases by combining both mAb-mediated B cell depletion and multimerized Fc-mediated tolerogenic effects [36].

Integrin $\alpha 9\beta 1$ has been identified as an important receptor involved in the onset of autoimmune diseases. However, the detailed mechanism of the binding of integrin $\alpha 9\beta 1$ and its ligand is unknown [37]. Matsumoto *et al.*, in their study, have introduced XCL1/Lymphotactin, a member

of the chemokine family, as a novel ligand for α integrin. Using α9 integrin-overexpressing NIH3T3 cells and human rhabdomyosarcoma cells, expressing endogenous α9 integrin, the interaction with XCL1 and α integrin was confirmed by pull-down analysis assay, thereby providing evidence *in vitro* and *in vivo* that the interaction between XCL1 and α9 integrin plays an important role in autoimmune diseases and possible avenues for treatments [37].

Brandsma *et al.* investigated the effects of single nucleotide polymorphisms (SNPs) of the high affinity IgG receptor FcγRI on the FcγRI immune complex binding and downstream effector functions [38]. This novel study performed in 2017 addresses the physiological consequences of SNPs in the high affinity FcγR and shows a reduction in various FcγRI functions, which hold the potential to alter the efficacy of therapeutic antibodies [38]. Binding of IgG antibodies to the FcγR receptors on immune cells can result in the FcγR crosslinking, thereby leading to activation of cellular functions such as phagocytosis, antibody-dependent cellular cytotoxicity and cytokine release [38]. However, low-affinity polymorphisms seem to be associated with the avidity of IgG, which can decrease the outcome of multimodular therapy. In this study, three nonsynonymous SNPs for FcγRI receptors with high affinity for IgG were investigated and it was found that SNP 'V391' in the extracellular domain of FcγRI reduced immune-complex binding [38].

5. Conclusion

Autoimmune diseases are a complex class of disorders, in which the body's immune system targets and damages its own cells and tissues. The underlying causes of autoimmunity are unknown, and therefore, treating these conditions poses a significant challenge as currently there is no therapeutic strategy to cure these conditions. A number of etiological factors such as genetic predisposition along with environmental influences have been speculated to be causative agents leading to autoimmunity. The traditional concept of T cell-mediated and autoantibody- mediated autoimmune diseases should be adjusted to reflect the new understanding of the interaction of different immune cells in autoimmune

pathogenesis. Recognition of B cell contribution to the pathogenesis of autoimmune diseases (traditionally thought to be mediated by T cells) has led to promising new therapies.

The formation of autoantibody specificity, in general, includes high-affinity IgG autoantibodies that have undergone somatic hypermutation and class switching, reflecting a pathologic process and resulting in tissue damage through IgG Fc direct activation but also by uptake of immune complexes by cells, leading to activation of Toll-like receptor. Treatment aims to reduce the symptoms and control the autoimmune process as autoimmune disease is not curable.

Current treatments for autoimmune conditions depend on the specific disease and consist of immunosuppressive medications. New therapeutic targets such as regulatory T-cell therapy, antigen-specific immunotherapy, and manipulating the interleukin-2 pathway look to restore the balance of effector and regulatory immune function, aiding patients suffering from autoimmune disease, and refrain from the use of immunosuppressive techniques thus avoiding its negative effects.

CONFLICT OF INTEREST STATEMENT

The authors have no conflicts of interest to declare.

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