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Review Article

A Review on the Current Treatment Therapies for Autoimmune Disorder

Emmanuel Osei Mensah[1]* and Christiana Agbo[2]

[1]*School of Biotechnology, Cell glycobiology, Jiangnan University, Wuxi, Jiangsu, China*

[2]*School of Applied Science and Arts, Cape Coast Technical University, Cape Coast, Ghana*

***Corresponding Author:** Emmanuel Osei Mensah, School of Biotechnology, Jiangnan University, Wuxi, Jiangsu, China.

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Abstract

Autoimmune disorders are diseases in which the body produces antibodies that attack its tissues, leading to the deterioration of such tissues. Rheumatoid arthritis (RA) and Nephrotoxic-nephritis (NTN) are among the common autoimmune disorders. The pathogenesis of these autoimmune disorders is complex and includes many cell types, including both adaptive and innate immune cells, synoviocytes and epithelial cells. Various treatment therapies are available for RA and NTN, but the gene and immune therapies are the least expensive and commonly used although the mechanisms underlying their dysregulation in this disease remains unknown. Again, other treatments can be given to patients, but they might not necessarily cure the disease. However, it could usually attenuate the disease's progression. In this review, current gene and immune treatment therapies for autoimmune disorders are discussed.

Keywords: Autoimmune Disorders; Rheumatoid Arthritis; Nephrotoxic Nephritis; Gene Therapy; Immune Therapy

Abbreviations

HLA-DRB1: Human leukocyte antigens- DRB1; SIGN-R1: Specific intracellular adhesion molecule-grabbing nonintegrin R1; FcγR: Fcγ Receptor; DC-SIGN: Human dendritic cell-specific ICAM3-grabbing non-integrin; IVIG: Intravenous Immunoglobin G; IgG: Immunoglobin G; HAdV5: Human Adenovirus Type 5; GPS: Goodpasture Syndrome; NTN: Nephrotoxic Nephritis; FLS: Fibroblast-Like Synoviocytes; Ag: Antigen; Ab: Antibody.

Introduction

Autoimmune disorders are common, incurable and often challenging to treat. Over 80 different types of autoimmune diseases have been recorded and tend affecting nearly any part of the body [1]. These diseases arise from an abnormal immune response to a healthy body part. Although there are common symptoms such as tiredness and fever, the cause of the disease is generally unknown [2]. Genetic and environmental factors instigate some autoimmune disorders. Most often than not, the treatments are dependent on the type and severity of the disorder. Medications can be given to patients but might not necessarily cure the disease although it could usually attenuate or reduce the disease's progression (severity and symptoms) [3].

Recombinant therapeutic proteins are becoming significant pharmaceutical agents for treating intractable diseases such as cancer and autoimmune diseases [4]. Although the leading cause of these disorders is not known, various treatment therapies are employed in controlling RA and other autoimmune disorders. This review seeks to address the issues of autoimmune disorders with the main focus on Rheumatoid arthritis and Nephrotoxic-nephritis (NTN) and their treatment therapies.

Autoimmune disorders

The body's immune system functions as a defense against infections and invaders. On the other hand, in cases where the body's immune system attacks and destroys healthy body tissue by mistake, it leads to the occurrence of autoimmune disorders [1,5]. In this case, the immune system is unable to differentiate between healthy tissue and antigens. As a result, the body initiates a reaction that destroys normal tissues [2]. Blood cells in the body's immune system assist in protecting the body against harmful substances such as bacteria, viruses, toxins, and cancer cells as well as blood and tissue from outside the body. These substances are contained with antigens, and the immune system produces antibodies against these antigens; thus, enabling it to destroy these harmful substances [2,6].

Although the precise cause of autoimmune disorders is unknown, theories have it that some microorganisms such as bacteria or viruses and some drugs may activate changes that confuse the immune system [7]. Also, this is most likely to occur in people who have genes that make them more prone to autoimmune disorders [8]. This disorder may destroy body tissues, cause abdominal growth of an organ as well as changes in organ function. Areas frequently hit by autoimmune disorders may include connective tissues such as the pancreas, joints, red blood cells, blood vessels, and the skin. Some common autoimmune disorders include type 1 diabetes, rheumatoid arthritis, systemic lupus, inflammatory bowel disease, multiple sclerosis, and nephrotoxic nephritis among others [1]. Research has found some underlying causes of autoimmune diseases which include leaky gut [5], gluten, toxins, infections, and stress.

Rheumatoid arthritis

Rheumatoid arthritis (RA) is a chronic auto-immune disease that symmetrically affects most joints. It is associated with progressive disability, systemic complications, early death, and socioeconomic costs. RA is of 1% prevalence owing to the less awareness of this connective tissue degenerative disorder [9]. RA is a heterogeneous disease, varying from slowly progressive symptoms to severely destructive inexorable disease associated with nodules and systemic inflammation [10]. It is well recognized that striking pathogenic similarities exist between periodontitis and RA [11]. RA is genetically associated with MHC class II molecules that contain the shared epitope [12]. By the selective binding of arthritogenic peptides for presentation to autoreactive CD4+ T cells. MHC molecules may participate in disease pathogenesis.

On the other hand, the nature of the arthritogenic antigen, Ag is unknown, but some current studies have recognized post-translationally modified proteins containing citrulline (deiminated arginine) as some specific targets of the IgG Ab response in RA patients [13]. Hill., *et al*. came out with a more unobstructed view of how citrulline might evoke an autoimmune reaction [13]. In their study, they analyzed how T cell response to citrulline-containing peptides in HLA-DRB1*0401 transgenic (DR4-IE tg) mice. Also, they elaborated on the conversion of arginine to citrulline at the peptide side-chain position interacting with the shared epitope which significantly increases peptide- MHC affinity leading to the activation CD4 T cells in DR4-IE tg mice — hence disclosing how DRB1 alleles with the shared epitope could initiate an autoimmune response to citrullinated self-Ags in RA patients [13].

RA is mostly characterized by synovial inflammation and pannus formation as well as hyperplasia, which can lead to cartilage and bone degradation or damage, joint destruction and deformation [14] in almost all cases. It is also characterized by systemic features, including cardiovascular, pulmonary, psychological, and skeletal disorders. However, genetic susceptibility to this disease in most populations is associated with MHC class II molecules that comprise an amino acid motif known as the shared epitope [12]. Moreover, these clinical features raise concerns on what genetic-environmental interactions must occur to facilitate autoimmunity and why does synovial inflammation perpetuate and finally, what drives local destruction leading to joint dysfunction [15]. Although various autoantigens have been investigated, an RA-specific Ag targeted by both the CD4 T cell and B cell immune response has not been identified yet. However, recent studies have identified a subset of IgG autoantibodies that are both sensitive and specific (90%) diagnostic marker of RA [16]. Inflammation in the case of rheumatoid arthritis also affects the brain (fatigue and reduced cognitive function), liver, lungs, exocrine glands, muscles (sarcopenia). Osteoporosis affects the axial, bones (osteoporosis) and appendicular skeleton, with only a modest elevation of the acute-phase response or subclinical inflammation, and perhaps occurs before the onset of articular disease [17]. On the other hand, effective anti-inflammatory treatment has a high tendency of retarding bone loss and also suppresses the high rate of systemic bone resorption, as measured with the use of bone-turnover biomarkers [18].

Fibroblast-Like Synoviocytes (FLS)

Fibroblast-like synoviocytes (FLS), also known as synovial fibroblasts or type B synoviocytes, are the predominant cell type including the structure of the synovial intima. Specialized cell type such as Fibroblast-like synoviocytes (FLS) located inside joints in the synovium is reported to play a vital function in the pathogenesis of chronic inflammatory diseases, such as rheumatoid arthritis [9].

Figure 1 illustrates the normal physiology of the joint and also the diseased state of the joint when affected by the autoimmune disorder. In non-diseased tissue, the physiological function of synovial fibroblasts (SFs) is to deliver the joint cavity and the adjacent cartilage with nutritive plasma proteins and lubricating molecules such as hyaluronic acid [19]. Due to the alterations in the proliferative process, the total number of cells increases in the synovium and significantly increases the number of fibroblast-like synoviocytes [20]. Eventually, these cells, coupled with other immune cells

such as macrophages, lymphocytes, neutrophils, dendritic cells, and platelets, additionally creates an inflammatory environment in the synovium. This, in turn, attracts more immune cells to the damaged area and hence contribute to the joint destruction [21].

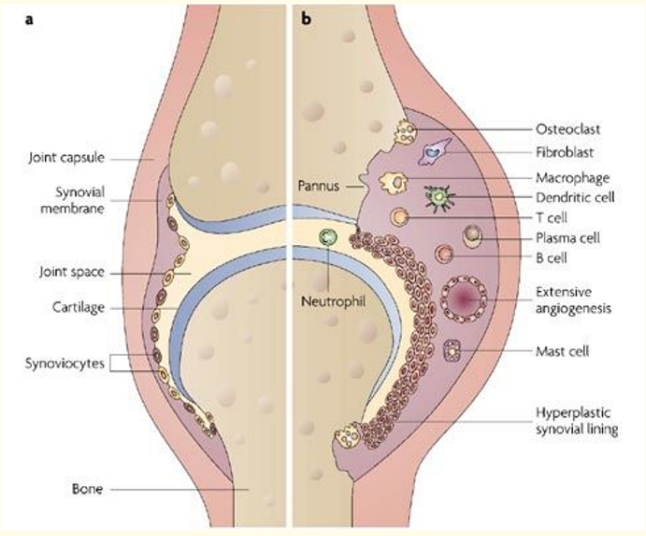


Figure 1: Normal healthy joint (a) and rheumatoid arthritis joint (b) [23].

FLS present in the synovium during rheumatoid arthritis display altered phenotype compared to the cells present in normal tissues. There is a loss of contact inhibition and the growth dependency on adhesive surfaces [9,15]. These phenomena add to the increase in the number of fibroblast-like synoviocytes in the inflammatory tissue and are characteristic for the growth of cancerous cells. Also, these cells can produce some pro-inflammatory signaling molecules, particularly Interleukin-6 and 8 (IL-6 and IL-8), matrix metalloproteinases (MMPs) and prostanoids, which may directly affect other cells and also contribute in the inflammation enhancement [22]. These progressions are influenced by microvesicles derived from platelets and further contributes to the activation of fibroblast-like synoviocytes through secretion of IL.

Pathogenesis of RA

Though the cause of rheumatoid arthritis is unknown, and the prognosis is guarded, developments in understanding that the pathogenesis of the disease has raised the development of new therapeutics, with enhanced upshots [24]. The current treatment strategy is to initiate aggressive therapy soon after diagnosis and to strengthen the treatment, guided by an assessment of disease activity, in pursuit of clinical remission [15]. On the other hand, several unmet needs remain. Some new conventional and biologic disease-modifying therapies sometimes fail or produce only partial responses while other reliable predictive biomarkers of prognosis, therapeutic response, and toxicity are also lacking [25]. Rheumatoid arthritis involves a multifaceted interplay among genotype, environmental triggers, and chance [15].

Risk factors

PAD4, genetic and environmental factors

Rheumatoid arthritis involves an intricate interaction among genotype, environmental triggers, and chance [15]. Peptidylarginine deiminase 4 (PAD4) has arisen as a key contributor in the pathogenesis of rheumatoid arthritis (RA). PADs catalyze the post-translational deimination of peptidyl-arginine to citrulline, generating the hallmark targets of the autoantibody response in RA [26]. Smoking is the leading known environmental risk factor for RA, as it is evident from epidemiologic studies. The interactions between a significant environmental risk factor (smoking), major susceptibility genes included in the shared epitope (SE) of HLA–DR, and the existence of the most specific autoimmunity known for RA (i.e., antibodies to proteins modified by citrullination) were studied. Also, smoking and HLA-DRB1 alleles synergistically increase one's risk of having anti-citrullinated protein antibodies (ACPA) [27].

McInnes., *et al.* in their study described the environment-gene interactions as illustrated in Figure 2. These interactions promote loss of tolerance to self-proteins that contain a citrulline residue, which is generated by post-translational modification. This anti-citrulline response can be perceived in T-cell and B-cell compartments and is perhaps initiated in secondary lymphoid tissues or bone marrow. Subsequently, localization of the inflammatory reaction occurs in the joint as a result of poorly understood mechanisms that probably include microvascular, neurologic, biomechanical, or other tissue-specific pathways [15].

Nephrotoxic-nephritis (NTN)

The Goodpasture syndrome (GPS) is a rare autoimmune disease in which antibodies attack the basement membrane in the kidneys and lungs, instigating bleeding from these organs, leading to lungs and kidney failure. Also, it's reported that the antibodies attack the alpha-3 subunit of type IV collagen of these organs (Figure 3) [28]. GPS is uncommon, affecting about 0.5–1.8 per million people per year in Europe and Asia. It is also rare among autoimmune diseases

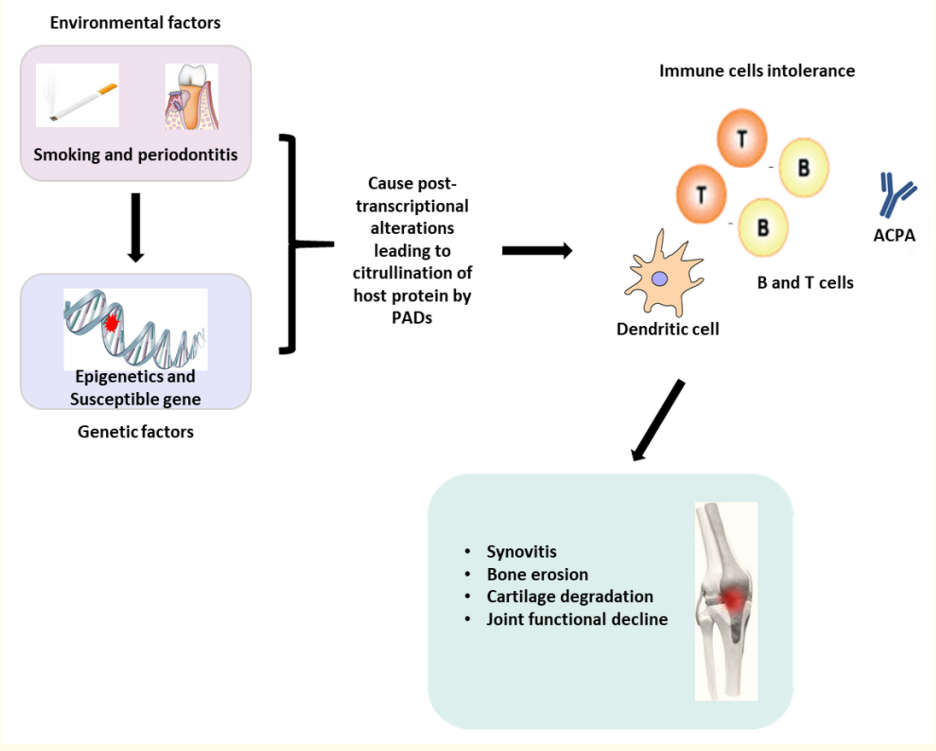


Figure 2: Risk factors to the Development of Rheumatoid Arthritis. The major risk factors, i.e., Environmental factors, and genetic factors (Epigenetic modification,and susceptible genes) leading to the loss of intolerance to host proteins by the immune cells perpetuating RA. ACPA: Anti-citrullinated protein antibody.

in that it is more common in males than in females [29]. Goodpasture syndrome consequently brings about Nephrotoxic-nephritis (NTN) in the kidney, which is characterized by improper filtration at the glomerular basement membrane, resulting in hematuria (blood in urine). Another effect of NTN is the Glomerulosclerosis, the hardening of the glomerulus in the kidney- the scarring of the kidneys' tiny blood vessels, the glomeruli (the functional units in the kidney) that filter urine from the blood. The symptoms of GPS may initially include fatigue, nausea, vomiting, and weakness. Also, the lungs are usually affected before or at the same time as the kidneys, and symptoms can include cough and short breath. The progression from initial signs to the lungs being affected may be very swift. Symptoms that ensue when the kidneys are affected include blood in the urine or foamy urine, high blood pressure and swelling in the legs.

In the past, Goodpasture syndrome was fatal. But currently, the use of immunosuppressing drugs such as cyclophosphamide, prednisone, and rituximab [30], prevent the formation of new anti-glomerular basement membrane (anti-GBM) antibodies from avoiding further damage to the kidneys and lungs, which further help reduce the severity of the disease [31]. Also, plasmapheresis (filtering out the plasma to get rid of the autoantibodies) is carried out, and the clean blood is given back to the patient intravenously [32].

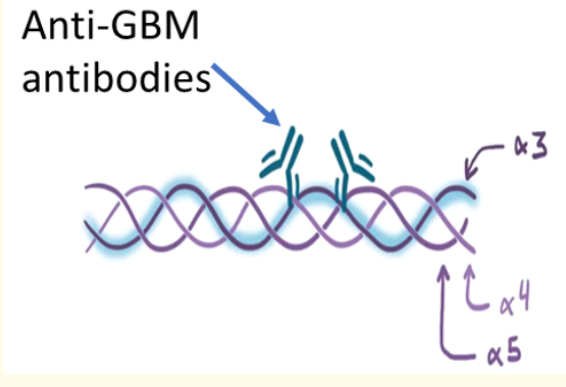


Figure 3: Type IV collagen glomerular and pulmonary basement membrane attacked by anti-GBM.

The plasma, clear liquid part of the blood, comprises the anti-GBM antibodies that attack the affected person's lungs and kidneys are filtered out as previously stated. Plasmapheresis is an expensive treatment therapy, and hence other treatment therapies like gene and immune therapies are also being extensively studied. Pagan., et al. in their study, converted endogenous pathogenic antibodies to anti-inflammatory ones by engineering solubilized glycosyltransferases that attach galactose or sialic acid to the glycan at the Fc portion of the antibodies [33].

The causes of GPS are not fully understood. There is an increased risk for this condition in people who smoke or use hair dyes. Also, the exposure to hydrocarbon fumes, metallic dust, and certain drugs, such as cocaine, may also raise a person's risk of suffering from GPS. On the other hand, genetics may also play a part in causing the disease [34].

Treatment therapy

Various treatment therapies are available for RA, such as the use of biological drugs and radio-isotopes for treating RA. However, 30% of RA patients do not respond to these expensive drugs and can cause severe side-effects. The effective intra-articular treatment with radio-isotopes in RA has significant restrictions related to the use of radioactive material [35,36]. This review focuses on the gene and immune therapy which are less harmful and commonly used.

Gene therapy

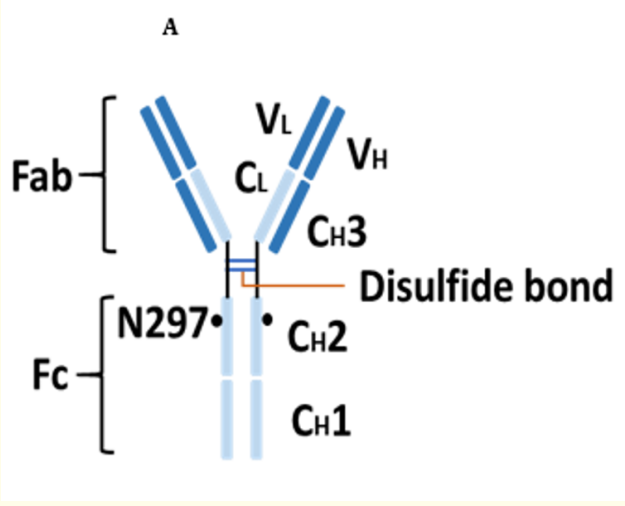
Gene therapy is the introduction of nucleic acids into a host cell for therapeutic purposes [37]. Numerous reviews summarize the pre-clinical and experimental findings concerning arthritis gene therapy broadly. Genes may be transferred to the joints of experimental animals using *ex vivo* or *in vivo* strategies in conjunction with a variety of viral and non-viral vectors [38]. Gene therapy vectors usually contain components of bacteria, viruses, or other microorganisms. Bacteria supply the plasmids used as small vehicles for transgenes. Viruses hold considerable appeal as gene therapy vectors because they are naturally able to incorporate foreign genetic material within the host cell genome [39]. If the host immune response is not activated, intra-articular transgene expression can persist for months, and possibly years, when using viral vectors. Intra-articular transgene expression using non-viral vectors tends to be low and transient [40].

In the study by Hong., et al. there was an innovative strategy for efficient human adenovirus type 5 (HAdV5) gene transfer to FLS coupled to a potent apoptosis-inducing gene for the treatment of chronic synovitis [41]. HAdV5 is a common viral vector for gene therapy. However, the efficiency of the gene delivery of HAdV5 to the FLS is low, and hence there have been several works to enhance the efficacy gene delivery by genetic modification of vector [42]. There was a significant reduction in the FLS in the arthritic joint after implementing this complexed viral vectors form of gene therapy [41]. However, the effect of these viral vehicles in the host remains uncertain even though it was reported not to be accumulated in other vital parts of the arthritogenic mice aside the arthritic joint of injection in the study.

Immune therapy

The immune therapy, on the other hand, is also an effective treatment therapy which directly targets the immune complexes involved in the perpetuation of autoimmune disorders by pathogenic autoantibodies and complement fixation complexes. Immunoglobulin G (IgG) is a central intermediary of host defense owing to its capacity to recognize and eliminate pathogens [43]. With the involvement of autoantibodies generated against native proteins (citrullinated proteins), there is a clinically available treatment therapy, the use of Intravenous Immunoglobin G (IVIG) to suppress inflammation. Because IVIG and the autoantibodies responsible for chronic inflammation and tissue destruction can bind to the same effector cells and molecules, one attractive possibility of IVIG activity is merely to compete for the same effector pathways as the pathogenic autoantibodies. In particular, the anti-inflammatory activity of intravenous IgG is ascribed to a small population of IgGs in which the Asn297-linked complex N-glycans attached to each Fc CH2 domain include terminal α2,6-linked sialic acids [43] (Figure 4). The small amount of the sialylated immunoglobin G (IgG) among the diverse types in IVIG therapy reduces the efficacy of treatment. To achieve high efficiency of IVIG therapy, high doses (1–3 g/kg) of the IVIG are administered making this an expensive treatment methods [44]. *In vivo* studies show that Fc sialylation is the critical factor in IVIG anti-inflammatory activity [45,46]. Sialylated IgG Fc bind type II FcγRs, human dendritic cell-specific ICAM3-grabbing non-integrin (DC-SIGN), or murine SIGN-R1, instead of binding the activating type I FcγRs (Activating FcγR), leading to increased surface expression of the inhibitory FcγRIIB(inhibitory FcγR) on inflammatory effector cells [47]. According Pagan., *et al*. an engineered human IgG fused with glycosyltransferases to convert endogenous IgGs to anti-inflammatory IgGs successfully attenuated autoantibody-mediated inflammation in both NTN induced mice and arthritogenic mice compare with the IVIG treatment [33]. Although the exact mechanism for this treatement is yet to be extensively studied, its been shown that the contribution of IgG gly-

cosylation to infectious diseases and vaccines is increasingly appreciated [48,49].



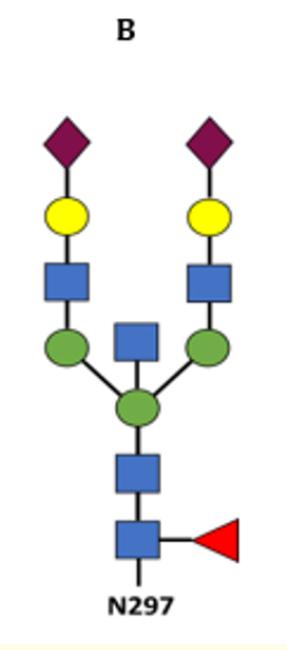


Figure 4: IgG, and Fc glycan structures. (A) Schematic structure of IgG Fab and Fc with a single, N-linked glycosylation site at N297. (B) Fc glycan consisting of GlcNAc (blue squares); mannose (green circles) the core which could be modified with fucose (red triangle), bisecting GlcNAc, galactose (yellow circles), or sialic acid (purple diamonds). C: constant domain; V: variable domain; L and H: Light and heavy chains.

Conclusion

Rheumatoid arthritis' lower prevalence rate has made its awareness minimal. Several studies have been done previously to ascertain the clinical significance of the disease and ways to combat it. Gene therapy and Immune therapy have been of great essence for the treatment of RA and other neurological disorders. But more studies are needed to be carried out to elaborate on the safety administration of this therapy in a clinical setting. i.e., biodistribution and pharmacokinetics. Immune therapy is also promising for the treatment of autoimmune disorders through the engineering of antibodies to block autoantibodies in perpetuating the disease. Recent studies have shown a way of directly targeting specific immune or native joints cells involved in the persistence of autoimmune disorders. For the future prospect, these headways could lead to the merge of these two therapies in a way to significantly reduce the effects of autoimmune disorders by gene therapy and immune therapy restricting native tumor-like cells and blocking pathogenic antibodies respectively. The gene and immune therapies hold great promise for the treatment of severe autoimmune disorders. Further work has to be carried out before these therapies will be present in daily practice similar to the routine use of nonsteroidal anti-inflammatory drugs (NSAIDs) and also cut down the cost of these treatment therapies currently in use.

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