

Bioengineered Immunotherapy Techniques for the Treatment of Select Secondary Immunodeficiency Disorders

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Abstract

The inner workings of the immune system are quite complex. Each component works diligently in order to protect us from invaders such as pathogens: viruses, microbes, and fungi. Unfortunately, the immune system may become dysfunctional, which can result in secondary immunodeficiency diseases. The treatments available for these disorders and diseases of the immune system do not typically serve to cure, and much too often the side effects associated can exacerbate the conditions. As an alternative, the area of immunotherapy seeks to remedy the limitations of today's medicine. Through this review, insight into the current conventional treatments available for select secondary immunodeficiency diseases will be provided, particularly in Human Immunodeficiency Virus disease and Systemic Lupus Erythematosus. The modern immunotherapy approaches that are underway will then be analyzed in their capacity and potential to treat these defects of the immune system.

Keywords: Immune system; Secondary immunodeficiency disorder; Autoimmune disease; Acquired immune deficiency; Immunotherapy; Human immunodeficiency virus; Systemic lupus erythematosus

Introduction

The very framework of our immune system consists of organs, tissues, and cells that interact systematically to block the passage of foreign bodies and prevent disease. This defense network also can recognize and destroy said molecules, in addition to abnormal cells that originate from an individual's own tissues. In other words, the immune system is designed to differentiate between self (healthy and unhealthy cells) and non-self (invader microbes). Inclusively, anything that initiates such a response is deemed an antigen. In some individuals, however, the immune system may become confused and direct their destruction on healthy tissues or cells that would be considered harmless otherwise. This leads to disorders and diseases of the immune system, such as autoimmune diseases and allergies [1-6]. Depending on the type of disorder and how it was acquired, there are a multitude of treatments available. Yet, most therapies are intended to provide relief from symptoms and prolong the infancy stage of the disease, rather than provide a cure. There has been a recent influx of research in the realm of Immunotherapy. Immunotherapy seeks to enhance or suppress an individual's immune response to weaken or eradicate the disease of concern. This method tends to be entwined with the treatment of cancers [1]. However, the techniques used can also be applied to some disorders and diseases of the immune system. To gain an appreciation of the deficits which may occur, it is pivotal to first understand how a healthy immune system should operate. Once this baseline has been established, a comparison can be made with individuals that suffer from select secondary immunodeficiencies, including subsets from the acquired immune deficiency and autoimmune disease categories. An examination on the modern research in immunotherapy techniques which are being incorporated in the treatment of these secondary immunodeficiencies will then be conducted. Consequently, with respect to the disorders reviewed, the possible enhancements and developments that can be applied to further improve the effectiveness of the treatments will be analyzed.

Patient N

Patient N will serve as a representative of the population that has a healthy and fully operational immune system. Since numerous deficits of the immune system occur at the

cellular and molecular level, the basis of review will be focused on those components.

Innate Immunity

In Patient N, the immune responses and mechanisms of the immune system can be characterized as either innate immunity or adaptive immunity. Through innate immunity, a nonspecific defense mechanism is invoked when foreign particles are initially encountered. The immune system's first line of defense includes

the skin, cornea, and mucosa of the respiratory and digestive tracts. When this physical barrier has been breached, Toll-Like Receptors (TLRs) are able to collectively recognize general danger- or pathogen-associated-patterns of microbes that may enter. This recognition in turn triggers expression of genes and thus the innate responses by the immune cells. The innate cell types involved, and their respective specialized functions are summarized in Figure 1; [2-6].

MACROPHAGE	NEUTROPHIL	BASOPHIL	EOSINOPHIL	INTERFERON (IFN)	DENDRITIC CELL	NATURAL KILLER (NK) CELL	COMPLEMENT PROTEIN
<ul style="list-style-type: none"> • Enlarged phagocytic monocyte. • Capable of engulfing microbes • Antigen-presenting cells (APCs) - present antigens to T-Cells, activate other immune cells. 	<ul style="list-style-type: none"> • First line of defense against infection (inflammatory response). • Constitute 40%-70% of total White Blood Cells. • Type of granulocyte. • Capable of engulfing microbes. 	<ul style="list-style-type: none"> • Type of granulocyte. • Contains histamine and other molecules that promote inflammation. 	<ul style="list-style-type: none"> • Target cells that are too large to ingest. • Type of granulocyte. • Substances released penetrate the target cell's membrane. • More active against parasites. 	<ul style="list-style-type: none"> • Protein. • Cells release in an attempt to prohibit the virus/microbe to cause disease. • Triggered by viral infection. • Some promote the synthesis of additional MHC proteins. • Major histocompatibility complex (MHC) proteins are surface proteins on all normal cells; these are unique to the individual. 	<ul style="list-style-type: none"> • Located in many tissues of the body that are in contact with the external environment. • An antigen-presenting cell. 	<ul style="list-style-type: none"> • Able to recognize abnormal cells by using a killer-activating receptor and killer-inhibiting receptor. • If the killer-inhibiting receptor binds to a Major histocompatibility complex (MHC), killing is stopped. • Produce cytokines, assisting in the regulation of T cell, B cells and macrophages. 	<ul style="list-style-type: none"> • Group of proteins. • Activated by chemical reactions that are triggered by either innate or adaptive mechanisms.

Figure 1: Innate immune cells and their functions- Patient N.

Adaptive Immunity

In addition to the defense mechanisms supplied by the innate system, there is further protection provided through the adaptive system for Patient N. In adaptive immunity, the cells involved are more specialized. Instead of recognizing general patterns, these cells can recognize specific signals. The antigens that were processed by the innate system are presented to the adaptive cells so that appropriate action can be taken. The main types of lymphocytes involved are B cells and T cells. The

genes for the B-cell receptors (BCRs) and T-cell receptors (TCRs) undergo recombination during certain cell maturation states. This randomization results in a diversity of receptors. The functions of the cells involved in the adaptive system are summarized in Figure 1. In addition to the functions specified in Figure 1, B cells and T cells both undergo processes of positive and negative selection. As a result of positive selection, the cell can mature and thus survives, whereas in negative selection, the cell undergoes programmed cell death. The latter typically occurs if the immature cells bind to self-antigens [2-6]; Figure 2.

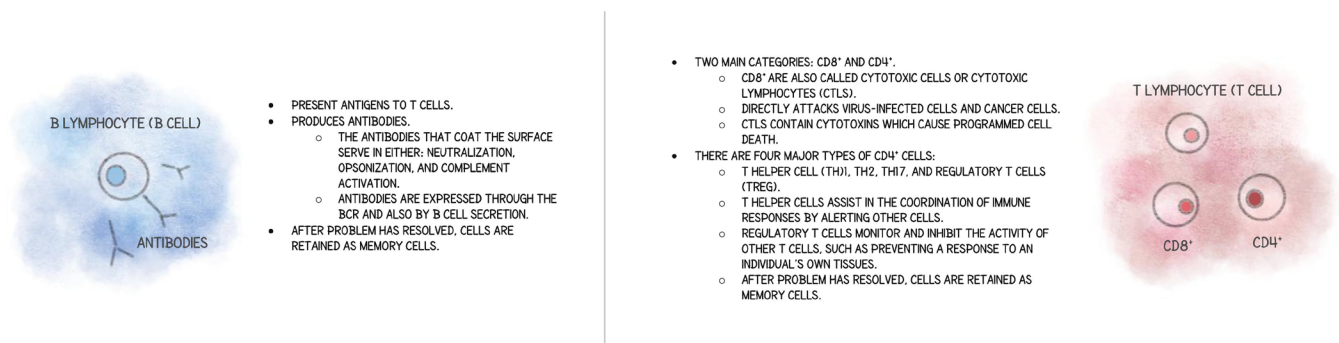


Figure 2: Adaptive immune cells and their functions- Patient N.

Through Patient N, a baseline of the appropriate functioning of the immune system has been developed. With this information, insight into what occurs in select secondary immunodeficiencies can be better appreciated.

Acquired immune deficiency diseases

Acquired Immune Deficiency Diseases are attained and developed as a result of certain external interactions. Under this subset of secondary immunodeficiency disorders are conditions including: Acquired Immunodeficiency Syndrome (AIDS) and Human Immunodeficiency Virus (HIV), in addition to Graft Versus Host Disease. The first will be reviewed in detail [1].

Patient H

Patient H was born with a similar immune system functioning to the same degree as that of Patient N. However, Patient H has contracted HIV. The Human Immunodeficiency Virus (HIV) is transmitted through the exchange of select bodily fluids including breast milk, blood, semen, vaginal, cervical and rectal secretions,

with an HIV-positive individual. HIV ravages the immune system by depleting the number of CD4⁺ T cells, which can debilitate the system and allow for further infections and cancers to prosper. With the development of these opportunistic infections, the individual has reached Stage 3 of the virus: Acquired Immunodeficiency Syndrome (AIDS). There are currently no cures available, however the current treatment involves the use of antiretroviral therapy (ART). When taken as prescribed, ART has the capability to slow down the progression of the virus from proliferating into the deadly last stage [7,16]. Though ART has been a useful treatment of HIV, there have often been cases of remission, and even death. This is due to the virus' proviral DNA remaining latent in CD4⁺ T cells. As a result, a life-long administration of ART would be necessary to prohibit the reactivation of the virus and hinder the development of AIDS. However, with the continued use of ART, the virus continues to proliferate which can open the doorway to additional non-AIDS related cancers and comorbidities; a possible fate for Patient H [8]. As a possible alternative, the current research and studies available in the field of immunotherapy provide a plethora of potential treatments Table 1.

Table 1: Modern immunotherapy techniques reviewed- Patient H.

Immunotherapy Technique	Description	Results		Theorized Improvements (If Applicable)	References
		Advantages	Disadvantages		
Dendritic Cell	<i>Ex vivo</i> injections of HIV antigen-expressing autologous dendritic cells to induce antiviral Cytotoxic T Lymphocytes (CTLs).	Activate latent HIV reservoir.	Virus eventually will rebound after few weeks of halting ART.	Target dendritic cells directly with TRIMIX adjuvant and HTI.	[8,9]
		Decrease viral reservoirs.	One of the components of TRIMIX activates programmed cell death protein 1 (PD-1) and other immune checkpoints.		
		Meta-analysis showed 38% overall success rate.	The TRIMIX/HTI mixture may be prone to degradation.		
		The generated CTL would lead to expression of the chemokine receptor CXCR5. Subsequently, CD8 ⁺ T cells would be signaled to the B cell follicles, where the latent HIV mainly resides.	Through separate study, found that dendritic cell-based therapy would have to be tailored to HIV+ individual (different DC product).		
Bispecific Antibodies	Use of Broadly neutralizing antibodies (bNabs) to target Env (viral gene) and simultaneously engage CD3 (T-cell co-receptor) on CTLs.	Induce CTL-mediated destruction of latent HIV-infected CD4 ⁺ T Cells in vitro and reduce HIV protein expression ex vivo (as determined through studies on ENV-specific Dual-affinity retargeting molecule (DART)).	Limited access of the HIV specific CD8 ⁺ T cells into the B cell follicles and germinal centers (major sites for HIV reservoir establishment).	Engineer bsAbs to also include additional components to combat co-inhibitory receptors that affect the survival of CD8 ⁺ T cells and also can increase the potent cytotoxic capacity to reach the limited access areas.	[10,11]

Chimeric Antigen Receptor (CAR)-Modified Natural Killer (NK) Cell	Use CAR-modified NK to treat chronic HIV infections.	NK cells can directly recognize HIV-infected cells	NK Phenotype and function can be altered by HIV.	Genetically modify the NK cells to enhance innate immunity.	[12-14]
		Can rapidly secrete IFN-gamma to initiate anti-HIV response.			
		Can target T follicular helper cells (critical HIV reservoir)			
Monoclonal antibodies (disruption of programmed cell death (PD-1)/programmed death-ligand 1(PD-L1) axis	In addition to use of ART, target PD-1/PD-L1 pathway. One reason supporting the selection of this pathway is that in nearly 90% of primary CNS lymphoma that was reviewed, there was expression of PD-1 and/or PD-L1 on the tumor cells or within the microenvironment.	Possibly can increase CD4 ⁺ lymphocytes.	Proposes to incorporate ART, which has some negative side effects.	N/A	[15]
		Can have anti-cancer affect.			
		Possible alternative to chemotherapy.			
Transgenic T cell Receptors (TCR)	Use of HIV-specific molecularly cloned TCRs to target HIV infection.	In a study using a humanized mouse model, a lentiviral vector was developed that could recognize the HIV-1 gag epitope SL9, in turn elicits potent antiviral response.	Concern with using cloned TCRs – possibility of exogenous TCR impairment.	Use of stem cell-based gene therapy in conjunction with TCRs.	[14]
		TCR CD8 ⁺ T cells showed no signs of HIV-1 infected peripheral blood mononuclear cells (PBMCs).			
Interferon type 1 (IFN-I) blockade	Blocking the IFN-1 signaling through the use of an anti-interferon alpha receptor 2-blocking antibody.	With the use of a humanized Bone marrow-liver-thymus (BLT) mouse, it was found that there was decreased immune activation, decreased expression of T cell exhaustion markers and reduced plasma viral loads.	IFN-I induces antitumor responses, promotes CD8 ⁺ T cell priming.	Using this therapy in conjunction with ART resulted in rapid viral suppression. Also reduced viral reservoirs.	[14]

Referring to Table 1, it is apparent that there is the need to determine how to eradicate the HIV reservoirs. In addition, there seems to be a debate on whether it is still necessary to use ART for the reviewed immunotherapies. Each technique is promising, but further research will be necessary in order to confirm the validity and applicability.

Autoimmune diseases

Unlike acquired immune deficiency diseases, the culprit behind the dysfunction in autoimmune diseases is not always known. For diseases and disorders of this nature, the immune system can start to attack healthy tissues, rendering certain functions altered and at times so damaged that it can no longer function at all. For the purposes of this review, a deeper look into Systemic Lupus Erythematosus will be analyzed, as represented through Patient L [1, 9-16].

Patient L

Patient L has been diagnosed with Systemic Lupus Erythematosus (SLE), an inflammatory disease. This chronic disease can be mild or severe, in which it causes inflammation in connective tissues. SLE can affect many organs and systems. At its most severe, SLE can lead to inflammation of the kidneys, nervous system, brain and/or arteries, which can be life threatening. It is theorized that the disease is onset by a combination of genetic mutations and environmental factors, however, the exact cause has not been fully uncovered. Currently there is no cure for SLE. However, the disease is typically treated with a combination of immunosuppressants and lifestyle changes. The exact treatment depends on the symptoms experienced by the patient and the organs that are affected. The available therapies seek to control the production of autoantibodies, in addition to the levels of INF-1 and

various chemo-attractants [17,18]. As a promising alternative, the current research and studies available in the field of immunotherapy propose some potential treatments [19-24].

Referring to Table 2, it can be observed that there are

contrasting viewpoints on what is the appropriate molecule/cell to target in order to reduce the responses experienced by individuals with SLE, such as Patient L. Each are still in the preliminary phases and will require additional experimentation.

Table 2: Modern immunotherapy techniques reviewed- Patient L.

Immunotherapy Technique	Theory/Hypothesis	Results		Theorized Improvements (If Applicable)	References
		Advantages	Disadvantages		
Treg Therapy: Low-dose IL-2 Supplement	IL-2 production is impaired in SLE. Also, there are lower levels of CD25 expression, which in turn affects the proper function of Tregs. To correct issue, it is proposed to provide a low dose IL-2 supplement.	Based on a study, low dose injections given on five consecutive day for four cycles with 9-16 days of separation, showed clinical improvement.	Injections are needed more frequently due to short half-life in human serum.	To address the short-life concern, it is proposed to use a modified form of IL-2; polyethylene glycol-modified IL-2.	[19]
		It was observed that the five patients had an increase in Treg numbers. No major side effects were noted.		Rapamycin and CAMK4 inhibitors can be potential medications used to enhance Treg function.	
B Cell Therapy: anti-CD20 monoclonal antibody rituximab	Therapy targets CD20 antigen, which is expressed on majority of B-cell.	Induces B-cell depletion	Retreatment is required. Response is short lasting	CD20-mimotope peptides vaccine	[20,21]
		Can help control severe SLE nephritis, to a certain degree.	Runs risks of hypersensitivity and tachyphylaxis	Through the experiment conducted using a humanized mouse model, the vaccine was able to prolong induction of B-cell depletion	
CD28 Blockade	Selective blockade of CD ₂₈ in order to inhibit the activation of effector T cells.	Prevented development of lupus nephritis.	Effect lasted for a few weeks after the end of treatment.	N/A	[22]
		None of the mice treated with monovalent anti-CD ₂₈ Fab' fragment died.			
		There was a reduction in the production of anti-double stranded DNA autoantibodies.			
		Reduction in inflammatory cytokines			
Soluble MHC class II-driven therapy	Findings imply that soluble class II major histocompatibility complex (sMHCII) influence tolerance maintenance within the immune system.	Decrease specific anti-dsDNA antibody production	Requires monthly injections	N/A	[23]
		Induce suppressive markers (i.e., IL-10)	More so to help alleviate symptoms, rather than provide a cure		

Conclusion

Through the analysis of Patients N, H and L, an intimate look into what occurs in the immune system in a healthy individual versus when the person has a secondary immunodeficiency disease was observed. The slightest disruption to the framework of the immune system can result in damage to healthy tissues leading to cancers, infectious diseases, and autoimmune diseases. The immunotherapy available for HIV seeks to eventually eradicate the virus by targeting the immune cells that are harvesting the deadly latent strands. In addition, many are aiming to reduce or even cease the use of ART as a life-long treatment. For SLE, the immunotherapies being researched are still trying to determine which immune cell is the most appropriate to suppress. Each category of immunotherapy is promising, however additional research is necessary to confirm many of the advantages that have been described in the articles. Though it may seem that there is still a long way to go, it is imperative that research is continued in these fields. Immunotherapy provides hopes of improving the lives of those affected by these and other debilitating secondary immunodeficiency diseases.

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