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The role of gene therapy for primary immunodeficiency

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Abstract. Primary Immunodeficiency disease (PID) is a wide genre of inborn defects that affect the patients immune system. More than 430 distinct phenotypes have been reported and more are being identified. Traditional treatments to PID include clearance or prevention of infections, avoidance of exposure to pathogen and live vaccines, immunoglobulin replacement therapy, and haematopoietic stem cell transplantation (HSCT). Mostly HSCT would be the only feasible radical solution, while others only offer temporary suppression of the condition. On the other hand, with the advancements in technology, gene therapy starts to show promising effects in multiple diseases including PID. In this review, we mainly discussed the effect and resent progresses of gene therapy on two common kinds of PID, SCID and WAS.

Keywords: gene therapy, PID, SCID, WAS.

1. Introduction

PID, abbreviation of Primary Immunodeficiency disease, is a heterogeneous group of disorders which causes abnormal function and development of immune system. There are more than 430 distinct disorders genetically identified so far. It is categorized by disorder of innate immunity and adaptive immunity. Patients often have recurrent infections in multiple systems, susceptibility to autoimmunity and malignancies, etc. Some severe complications might include severe pneumonia, cognitive difficulties and skin abscesses. The approximate prevalence of the disorder in America is 1 in 1200 births [1].

Current treatments on PID are mainly focused on two aspects: clearance or prevention of diseases and reconstruction of immunity. Patients often need to take anti-infection medicines for long periods to combat the possible fatal infections led by defected immunity. In severe cases, they need to be segregated from people and outer environment since daily activities will post a catastrophic risk to them. The avoidance of live vaccine is also a common matter of concern. Immunoglobulin replacement therapy (IRT) is one of the alternative treatments, which can temporarily support the abnormal immunological functions. But it also requires long-period treatment and the IRT administration has to be done every 1-4 week depending on the conditions of patient and the methods of injection. Besides above therapies, patients often have to accept a haematopoietic stem cell transplantation (HSCT) for cure.

HSCT is the major way of radical treatment for PIDs. It involves the administration of healthy bone marrow into the patient′s body, thus replacing the dysfunctional stem cells and reconstruct the defected immune system. Stem cells from a human leukocyte antigens (HLA) matched donor is crucial for this

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therapy, otherwise rejection can be potentially life threatening. Post surgical regiment and immunosuppressive medicine is also important to ensure survival after treatment. The successful rate of HSCT in PID decreases with the age of patients, but suitable donor is so scarce that the optimum time window is likely to be missed [2].

With the development of technology, gene therapy has gradually shown its potential as an alternative to HSCT. The same as HSCT, it offers radical cure for PID patients by replacing the defected stem cells with functional ones. The difference is that gene therapy obtains the healthy cell by genetically editing the original body cell of the patient. Although the therapy is not totally mature at this stage, it has already shown some promising effects to the disease and advantages compared to HSCT. For instance, rejection would not happen because the transplanted cell is genetically identical to the patients. And the therapy could be conducted at any time since there's no need for seeking a donor.

2. Brief review of PID treatment

2.1. Classification of PID

Since 2013, the International Union of Immunological Societies (IUIS) has published an updated phenotypic classification of PID. In the newest version released in 2019, 430 single-gene underlying phenotypes has been reported. The phenotypes are classified into 10 broad categories, including immunodeficiencies affecting cellular and humoral immunity, predominantly antibody deficiencies, and auto-inflammatory disorders, etc. Severe combined immunodeficiency (SCID) is one of the focuses belonging to the large category of immunodeficiencies affecting cellular and humoral immunity. SCID is defined by CD3 T cell lymphopenia and the defect often occurs at stages of T-cell replication or the development, causing different degrees of disorder in adaptive immune system. Since B-cell-mediated antibody generally depends on T-cell function, most of the defects in T-cell causes combined deficiencies. Mutation in a series of genes have been identified to cause SCID and most common ones are: IL2RG, ADA, ARTEMIS, RAG1, RAG2, CD45, JAK3 and IL7R. While another commonly studied PID to be introduced here is Wiskott-Aldrich Syndrome (WAS). It belongs to the category of "CID with associated or syndromic features". WAS is manifested with combined conditions including congenital thrombocytopenia, recurrent infections, eczema, bloody diarrhea, and autoimmune disease [3].

2.2. Conservative therapies for PID

Major therapies of PID includes anti-infectious treatment, immunesupression and IRT support. Infections usually can be controlled by long term therapy of antibiotics and antiviral medication, isolation from pathogens since the common lifestyle and intact to people could be fatal for patients with some types of PID and avoidance of live vaccines. A number of medication and biologics can be used in treatment by increase or decrease immune function. Monoclonal antibodies, corticosteroids, small molecule inhibitors and other immunosuppressant. In addition, about 60% of classified PIDs are related with hypogammaglobulinemia demonstrating a reduction in total number of Immunoglobulin G (IgG) and its subclasses. IRT is thus one of the most commonly applied treatment to PID. By replenishing the shortage of IgG, IRT could prevent infections and preserve organ function, thus significantly improving the condition. Nonetheless, immunoglobulin could only last for a relatively short period of time, administration is required for every 1-4 weeks [4]. However, above mentioned therapies could not improve conditions of the immune system. The reconstruction of immunity is therefore essential for significantly improve the living standard of patients. And permanent improvement could only be reached by very few therapies. The most widely considered is HSCT.

2.3. HSCT

HSCT involves the administration of functional stem cells (usually bone marrow) in patients, which aims to replace the cancerous cells or reconstruct normal immune function. Large proportion of PID have their primary genetic effect on haematopoietic stem cell, so the replacement of dysfunctional cells with normal donor stem cell will be the optimum way of curing the source of transplanted cells could

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be obtained from multiple ways including the patients themselves (autologous transplantation), siblings or unrelated donors (allogenic transplantation) and identical twins (syngeneic transplant). Autologous and syngeneic transplantation have shown higher survival rates after transplantation but diseases might not be fundamentally eliminated since the genomes are highly similar to the pathological cells. Allogenic transplantation could often more effectively cure the diseases, but are also accompanied with much more severe complications and higher chance of rejection [5]. In cases of allogenic transplantation, human leukocyte antigens (HLA) matched donor is criterial for avoidance of rejection. But an optimal matched donor is not available for most of patients. Chance of finding a donor with high-resolution-match at HLA-A, HLA-B, HLA-C and HLA-DRBL varies from 75% to 16%, depending on ethnic groups. European descent has the highest likelihood, while South or Central Americans′ own the lowest. Donor missed matched at 1-2 HLA loci could be found by almost all patients under age of 20 and 80% patients older than 20. However, mismatch of only on loci could reduce 5-year survival rate by 8% [6].

3. Gene therapy strategies for PID

Gene therapy is a novel treatment to inborn disease on the base of genetic edition. It is performed by inserting a corresponding segment of gene in normal cell into the pathological cell to replace mutated genes, thus molecules can be produced or abnormal expression pathway can be halted. Though it is at early stage of development, gene therapy holds great potential to multiple complicated diseases including AIDS, cystic fibrosis and diabetes. PID, as conditions caused by inborn errors, naturally becomes one of a main field of application of this therapy. Among the wide variety of PIDs, SCID and WAS are generally most worthy for research and clinical usage of gene therapy [7].

3.1. SCID

SCID is a type of PID defined by CD3 T cell lymphopenia (CD3+T cells <300 μL). Currently, at least 14 molecular defects have been identified including: L2RG, JAK3, RAG1, RAG2, DCLRE1C, PRKDC, IL7R, CD3D, CD3E, CD247, PTPRC, CORO1A, ADA, and AK2. Patients suffer from low number or complete absence of functional T-cells with or without dysfunction of B-cells. As examples, ADA defect would cause both T- and B- cell absence, while IL7R mutation would only lead to dysfunction of T-cell. However, since B-cell′s function is dependent on the T-cell, most mutations effecting the proliferation and survival of T-cell would result in combined Immunodeficiency. The dysfunctional immune system makes patients extremely vulnerable when exposed to a wide range of bacteria, fungi, viruses and protozoa. Symptoms usually start to occur by 2~7 months of age. Urticaria-like eruption could be the only signal in the early stage, though sometimes severe infections might also happen. If treatment is absent, Infection-related death usually occurs between age of 1 to 2 years [8].

3.1.1. Gene therapy for SCID. Gene therapy for SCID involves the abstraction of patient's hematological stem cells, insertion of normal gene inside the cells, and the transplantation of them back to the patient. Retroviruses are the most common vector while lentiviruses and adenoviruses are also being used. They have to be emptied of their original genome and obtain a healthy set of replica of the mutated gene. Then the viruses would infect the isolated hematological stem cells and insert the normal allele to replace defective genes. Finally, the cells with healthy set of genome would be transplanted back into the patient's body, thus, curing the syndrome by eliminating the fundamental cause.

The first gene therapy was conducted in 1990 to treat ADA-SCID, it it also the first trial ever that uses gene therapy to treat human disease. The application of gene therapy on ADA-SCID manifests great success in all trial to date. In SCID caused by other defects, the condition is, however, different. In 1999, the first trial of gene therapy on IL2RG-SCID was conducted. 18 of 20 have their immunity reconstituted, but 5 developed leukemia caused by insertion of Al mutagenesis on LMO2 oncogene of the retroviral vector. Before all trials were halted for this incident, researchers found that the therapy is not suitable for older patients with IL2RG, thus, indicating an optimal time window in this treatment. The gene therapy on IL2RG was suspended for 11 years until researchers restart the program in 2010 using a new self-inactivating-retro-virus vector. 8 out of 9 patients survived, and no insertional

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mutagenesis occurred in following years was observed. Survivors have all obtained normal gene marking in T-cells and immune reconstitution [9].

3.1.2. Future strategies for SCID. Generally, Gene therapy exhibits a bright future for the radical treatment of SCID. In 2016, the first market approval to a stem cell gene therapy is made by the European Commission to a medicine named Strimvelis™, a hematopoietic stem cell gene therapy of adenosine deaminase (ADA)-deficient SCID. This approval is firmly granted by the success of 18 ADA-SCID patients with 100% survival rate for 7 years, long term immunity reconstitution and proved gene correction. It is reasonable to believe that Strimvelis™ is only a starting point of gene therapy's application. Currently, trials of gene therapy to other strains of SCID are also being conducted [10]. For example, groups of investigators are developing lentiviral vectors with self-inactivating capability, and clinical trials are to be conducted soon. With unceasing development of technologies that increase safety and effectiveness of gene therapy, it is reasonable to anticipate more approval therapeutic products on not only ADA-SCID, but also SCID caused by other molecular defects.

3.2. Gene therapy for WAS

WAS is a X-linked recessive disease caused by pathogenic mutations on WAS gene located on chromosome X (xp11.2-11.23), leading to abnormal or absent expression of its encoded WAS protein (WASP). WASP is present in all blood cells and involved in signaling from the surface of white blood cell to actin cytoskeleton. The prevalence of this disease in male infants is 1/250000 regardless of race [11]. Clinically, it is manifested with abnormal immunological functions including immune deficiencies, eczema, autoimmunity and reduced ability to form thrombus. Among them, microthrombocytopenia is the clinical hallmark of WAS and platelet abnormalities are generally inborn and can lead to easy bruising, bloody diarrhea or epistaxis or prolonged bleeding after minor trauma. Microplatelet cytopenia may also lead to small areas of bleeding beneath the skin surface, producing purple spots (purpura), or a rash of varying sizes composed of tiny red spots. Changes in leukocytes can cause decreased immune capacity WAS patients including higher susceptibility to bacterial, viral and fungal infections, and more susceptible to diseases like rheumatoid arthritis, vasculitis, or hemolytic anemia. Besides, WAS patients also develop malignancy like lymphoma, causing severe complication and increasing death rate. And all above reflect the important value of a radical treatment like HSCT in the treatment of WAS.

3.2.1. HSCT for WAS. The estimated incidence of WAS is reported to be between 1 and 10 cases per million males worldwide. The long-term survival probability of children after HSCT is 80%, the overall success probability of transplantation is over 95%, and the 3-year survival rate of graft-versus-host disease is 85% [12]. Before HSCT, the most common skin manifestations in patients with WAS included eczema similar to AD (71%), followed by ecchymosis and/or ecchymosis (58%) and skin infection (17%). Older age and HSCT from alternative donors were identified as risk factors for predicting poor outcomes. Among 197 patients who underwent transplantation in the European blood and bone marrow transplantation association center between 2006 and 2017, 176 patients survived for 44.9 months after HSCT, and the 3-year overall survival rate was 88. 7% and 81.7% of patients without chronic graft-versus-host disease (GVHD) survival, the overall survival of patients with HSCT age <5 years was significantly improved, the incidence of graft failure and mixed donor chimerism was higher in patients receiving endosulfan based conditioning, and the second HSCT was received more frequently. In conclusion, HSCT treatment of WAS can bring excellent survival and low GVHD incidence regardless of donor or stem cell source. However, age ≥ 5 years was still a risk factor for overall survival [13].

3.2.2. Gene therapy for WAS. As discussed above, HSCT has been proved effective for WAS patients and can eventually rescue the immunological disorder with an acceptable survival rate. But, when a matched donor is often not available, thus infusion of autologous HSPCs modified in vitro by gene therapy is becoming urgent solution. Alternatively, HSPC of WAS patients can be genetically corrected using lentiviral vectors encoding functional WASP and re-injected into the cells at reduced intensity.

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The proportion of lymphocytes expressing WASP increased from a median of 3.9% before gene therapy to 66.7% 12 months after gene therapy. Platelets expressing WASP also increased from 19.1% to 76.6%. In a follow-up more than 1 year of 7 patients, normalized T cell function in vitro, stopped IRT supplementation and antigen-specific response to vaccination were observed [14]. Therefore, it suggests gene therapy indeed a valuable therapeutic option for WAS patients, especially for those without suitable HSPC donors.

Clinical trial conducted at three European centers showed most survivors (31/34, 91%) were continuously multiline implanted with genetically modified cells. After that, lymphoid cells with positive gene markers and protein expression, improved immune function and reduce rate of severe infection were observed. Improved humoral immunity allows for discontinuation of IRT in some patients. And all subjects showed different degree of improvement or absolute resolution of eczema. Platelet counts were increased but remained below the normal range in most patients [15].

3.2.3. Future strategies for WAS. Regardless of all the successes, easier method to get genes into the body and better vectors that can be injected directly and precisely into the patient are still under research., At the same time, the below need to be further developed: the method of delivering genes to the exact location of the patient's genetic material at all times (eliminating the risk of disease caused by gene transfer), and the ability to ensure that the transplanted genes are controlled by the body's normal physiological signals. In this case, insulin is an example: a protein produced in the right amount at the right time will be optimally beneficial to the patient rather than harmful.

3.3. Other potential applications of gene therapies in PID

There are some PIDs that have been successfully treated by gene therapy other than SICD and WAS. Such as leukocyte adaptation deficiency I (LADI) is an autosomal recessive primary immunodeficiency caused by the gene encoding ITGB2β-2 genetic variation of integrin subunits, and is clinically characterized by bacterial infection, pus formation damage and wound healing [16]. Other than LAD1, gene therapy can also be applied in chronic granulomatous disease (CGD) and use lentiviral vector encoding the human gp91phox gene in vitro transduced hematopoietic stem and progenitor cells for X-linkage, such as using the CRISPR/Cas9 nuclease [17]. And the same as previous two examples, gene therapy in hemophagocytic lymphohistiocytosis (HLH) alters the X-linked lymphoproliferative disease genes (SH2D1A and XIAP) [18].

4. Further outlook and Limitations

Initially, gene therapy was thought to be limited in the use of treating genetic disorders such as bladder fibrosis or hemophilia. But now, scientists in America's National Institutes of Health and elsewhere are investigating the possibility of permanent cures not only for some apparently genetic diseases, but also for a host of others as well (heart disease, AIDS and cancer, for example). It holds the potential to prevent or cure diseases that currently kill or disable millions of people.

Besides, gene therapy also remains further development due to several existing issues. First, since viruses infect multiple types of cells. Besides the targeted cells, viral vectors carrying genes can also alter irrelevant cells. Second, when adding genes to the DNA, some new genes can be added to unwanted position by mistake, leading to cancer or other damage. In addition, when DNA is injected directly into the tumor, or when liposome delivery systems are used, there is also the possibility of foreign genes entering germ cells (sperm or eggs) without authorization and causing genetic variation. Another possibility is that genetic interference improves people's abilities, such as memory and intelligence [19]. Therefore, it is hoped that in the future, novel technology can be developed to redirect genetic material, eliminate bad genetic mutations that may occur, preserve good types, and improve genetic quality.

5. Conclusion

Gene therapy is a significant technology for current medical treatment, which can cure many diseases including PID like SCID and WAS. HSCT is so far the most commonly used radical treatment for them,

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but the success rate is generally low, does not cure the genetic changes, and has certain limitations such as an increased risk of other diseases (cardiovascular disease, pulmonary complications, etc.). Thus, using gene therapy technology to introduce foreign genes into target cells, correct or compensate for the purpose of defective genes has become more and more important. This method has a acceptable success rate, can cure genetic mutations and have a certain probability to change the gene shape variation to a better one. But gene therapy also has certain limitations such as the need to use a microscope to operate, more time-consuming and unexpectedly forming unwanted genotypes.

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