Primary immunodeficiency disorders: Genetic causes and therapeutic advances.

Sonya Peebles*

Department of Pathology, University of Utah School of Medicine, USA

Introduction

Primary Immunodeficiency Disorders (PIDs) are a group of rare, genetically inherited conditions that impair the immune system's ability to defend the body against infections. These disorders result from defects in the development, function, or regulation of immune cells, leading to increased susceptibility to infections, autoimmune diseases, and, in some cases, malignancies. Understanding the genetic basis of PIDs has been critical for developing targeted therapies and improving patient outcomes [1].

PIDs are caused by mutations in genes responsible for the normal functioning of the immune system. These mutations can be inherited in various patterns, including autosomal dominant, autosomal recessive, and X-linked inheritance. For example, Severe Combined Immunodeficiency (SCID) often results from mutations in the *IL2RG* gene, affecting the gamma chain of several interleukin receptors, leading to defective T and B cell function. Similarly, mutations in the *BTK* gene cause X-linked agammaglobulinemia, impairing B cell development [2].

Over 450 distinct PIDs have been identified, classified into categories based on the affected components of the immune system. These categories include combined immunodeficiencies, predominantly antibody deficiencies, immune dysregulation disorders, phagocyte defects, and complement deficiencies. This classification helps in understanding the clinical manifestations and guiding specific diagnostic and therapeutic strategies [3].

Patients with PIDs often present with recurrent, severe, or unusual infections that are difficult to treat. Depending on the specific disorder, symptoms may include chronic respiratory infections, gastrointestinal infections, skin abscesses, and failure to thrive in infants. Some PIDs also predispose patients to autoimmune diseases, where the immune system mistakenly attacks healthy tissues, and certain types of cancer due to impaired immune surveillance [4].

Genetic testing has revolutionized the diagnosis of PIDs. Techniques such as next-generation sequencing (NGS) allow for comprehensive analysis of multiple genes simultaneously, enabling the identification of causative mutations. Early genetic diagnosis is crucial for initiating appropriate treatments and providing genetic counseling for affected families. Whole-exome and whole-genome sequencing have further expanded the understanding of rare and novel genetic mutations involved in PIDs [5].

Traditionally, management of PIDs has focused on preventing and controlling infections. This includes prophylactic antibiotics, antifungals, and immunoglobulin replacement therapy to boost immune defense. For conditions like Chronic Granulomatous Disease (CGD), interferon-gamma therapy has been used to enhance immune function. However, these treatments primarily manage symptoms and do not correct the underlying immune defect [6].

HSCT has been a cornerstone curative treatment for severe forms of PIDs, such as SCID. By transplanting healthy donor stem cells, the patient's immune system can be reconstituted. Advances in donor matching, conditioning regimens, and graft-versus-host disease (GVHD) prevention have significantly improved transplantation outcomes. Early diagnosis and timely transplantation are crucial for the best results [7].

Gene therapy has emerged as a promising curative approach for certain PIDs. This therapy involves inserting a functional copy of the defective gene into the patient's hematopoietic stem cells. Successful gene therapy has been demonstrated in conditions like ADA-SCID and X-linked SCID. Lentiviral vectors are now widely used due to their improved safety profile compared to earlier retroviral vectors, reducing the risk of insertional mutagenesis [8].

Recent developments in gene editing technologies, particularly CRISPR-Cas9, offer precise correction of genetic mutations responsible for PIDs. This technology allows targeted modifications of defective genes, potentially providing long-lasting cures. Although still in experimental stages for most PIDs, CRISPR-based therapies hold significant promise for personalized medicine and safer gene correction strategies [9].

Beyond gene therapies, immunomodulatory drugs are being explored to manage immune dysregulation in PIDs. Janus kinase (JAK) inhibitors, for example, have shown potential in treating certain immune disorders linked to hyperactive immune pathways. These targeted therapies can help control inflammation and autoimmunity in patients with immune dysregulation syndromes [10].

Conclusion

Primary Immunodeficiency Disorders, though rare, represent a significant health challenge due to their complex genetic

***Correspondence to:** Sonya Peebles, Department of Pathology, University of Utah School of Medicine, USA, E-mail: sonya.peebles@umcg.nl

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basis and diverse clinical manifestations. Advances in genetic diagnostics and the development of innovative therapies, including HSCT and gene therapy, have transformed the management of these conditions. Continued research into gene editing and immunomodulatory treatments holds promise for more effective and accessible cures, offering hope for improved quality of life and survival for patients with PIDs.

References

1. Bendandi M. Idiotype vaccines for lymphoma: proof-of-principles and clinical trial failures. Nature Rev Cancer. 2009;9:675–81.
2. Muraro E, Martorelli D, Dolcetti R. Successes, failures and new perspectives of idiotypic vaccination for B-cell non-Hodgkin lymphomas. Human Vaccines Immunotherapeu. 2013;9:1078–83.
3. Choudhury BA, J C Liang, E K Thomas, et al. Dendritic cells derived in vitro from acute myelogenous leukemia cells stimulate autologous, antileukemic T-cell responses. Blood. 1999;93:780–6.
4. Cignetti A, E Bryant, B Allione, et al. CD34(+) acute myeloid and lymphoid leukemic blasts can be induced to differentiate into dendritic cells. Blood. 1999;94:2048–55.
5. Li L, Krzysztof Giannopoulos, Peter Reinhardt et al. Immunotherapy for patients with acute myeloid leukemia using autologous dendritic cells generated from leukemic blasts. Int J Oncol. 2006;28:855–61.
6. Boultwood J, Fidler C, Strickson AJ, et al. Narrowing and genomic annotation of the commonly deleted region of the 5q-syndrome. Blood. 2002;99:4638–641.
7. miRNA clusters with down-regulated expression in human colorectal cancer and their regulation. Int J Mol Sci. 2020;21:4633.
8. Takagi T, Iio A, Nakagawa Y, et al. Decreased expression of microRNA-143 and -145 in human gastric cancers. Oncol. 2009;77:12–21.
9. Starczynowski DT, Kuchenbauer F, Argiropoulos B, et al. Identification of miR-145 and miR-146a as mediators of the 5q-syndrome phenotype. Nat Med. 2010;16:49–58.
10. Votavova H, Grmanova M, Dostalova Merkerova M, et al.Differential expression of microRNAs in CD34+ cells of 5q-syndrome. J Hematol Oncol. 2011;4:1.

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