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Editorial

Potential Genetic Approach to Specific Primary Immunodeficiencies: Which Perspectives?

Giuseppe Murdaca[1,2,*], Francesca Paladin[3], Sebastiano Gangemi[4]

[1]Department of Internal Medicine, University of Genova, Viale Benedetto XV, 16132 Genova, Italy
[2]Allergology and Clinical Immunology Unit, San Bartolomeo Hospital, 19038 Sarzana, Italy
[3]Elderly and Disabeld Department, San Paolo Hospital, 17100 Savona, Italy
[4]Department of Clinical and Experimental Medicine, School and Operative Unit of Allergy and Clinical Immunology, University of Messina, 98125 Messina, Italy
*Correspondence: giuseppe.murdaca@unige.it (Giuseppe Murdaca)
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Primary immunodeficiency diseases (PIDs) represent a disparate group of genetic diseases that impair the progress, control, and activity of the immune system and whose treatment conventionally relies on allogeneic hematopoietic stem cell transplantation (HSCT) and autologous gene therapy [1]. However, since both of these approaches still need to be perfected, gene editing has emerged as a potentially viable solution for treating genetic diseases, including PID [2].

As gene therapy research has advanced, gene editing methods have been developed that can interrupt and then turn off a problem gene, repair a gene mutation, or insert a new copy of it directly into the defective gene itself to control expression of the inserted gene. The most recent progress in gene editing has favored the introduction of several new programmable chimeric molecules that allow site-specific action, thus increasing the specificity of genetic correction and extending the application of gene therapy to more complex PIDs. To date, three main site-specific endonucleases have been developed and applied: homing endonucleases, zinc finger nucleases (ZFNs), transcription activator-like effector nucleases (TALENs), and most importantly, clustered regularly interspaced short palindromic repeats-associated protein 9 (CRISPR/Cas9) [3]. Each of these systems can be engineered to recognize and introduce a DNA break at a site throughout the genome.

In both severe combined immunodeficiency with recombination activating gene defect 1 (RAG1-SCID) and familial hemophagocytic lymphohistiocytosis types 2 and 3 (FHL2 and FHL3), gene therapy techniques with lentiviral vector have been tested; however, a major concern associated with this technique is the potential for insertional mutagenesis [4]. In addition, in FHL3, gene therapy approaches can significantly improve cytotoxic defects by transplanting hematopoietic stem cells (HSCs) that have been corrected to express perforin 1, thereby restoring the cytotoxic capabilities of CD8+ T cells [5]. The development of this technique has made it possible to initiate study protocols for the development of gene editing practices. One such technique is homology-directed repair-mediated knock-in of a corrective sequence exploiting the CRISPR/Cas9-adeno-associated virus type 6 (AAV6) platform to integrate the c.o.RAG1 transgene into the endogenous RAG locus of RAG1-deficient autologous hematopoietic stem and progenitor cells [6,7]. The use of CRISPR-Cas9 nucleases, in FHL3 forms, has been shown to restore the function of CD8+ T cells derived from Unc-13 homolog D-modified HSCs [8]. Also in human leukocyte adhesion deficiency type 1, CRISPR-Cas9-mediated transgenic knock-in techniques, known as homology-independent targeted integration, have been tested at the level of the first non-coding exon of the integrin subunit beta 2 gene. This induces the potential phenotypic correction of the disease [9].

In X-linked lymphoproliferative disease, transfer of the SLAM-associated protein (SAP) gene into SAP-/- HSCs corrects the main cellular and humoral defects in SAP-mouse models [10], providing promising prospects in the field of gene editing therapy. As a genome editing tool, ZFN has found application in adenosine deaminase (ADA)-deficient SCID (ADA SCID), the first disease for which a gammaretroviral vector (Strimvelis®; GlaxoSmithKline) was marketed, approved by the European Medicines Agency in May 2016 [11,12]. Subsequently, gene therapy studies were also conducted on subvariants of ADA SCID, such as those caused by mutations in the ADA gene like c deficiency. In which self-inactivating retrovirus vectors were used with promising results in terms of regenerating competent subpopulations of immune cells [13].

Given these premises, the efficiency and safety of gene therapy could surpass HSCT in the future, also thanks to the reduction in the rate of transplant-related complications, progressively expanding to more patients and indications. Finally, artificial intelligence provides an opportunity to significantly expand our knowledge of the genetic

mechanisms underlying primitive immunodeficiencies and the appropriate targeted therapies [14,15].

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GM, FP, SG: conceptualization, writing and editing; GM, SG: supervision, writing and editing. All authors read and approved the final manuscript. All authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

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