Revista de Ciencias Médicas de Pinar del Río

ISSN: 1561-3194 **RNPS:** 1877
Rev Ciencias Médicas. 2024; 28(2024): e6386

LETTER TO THE DIRECTOR

Regarding the article: Update on the genetic bases and therapeutic perspectives in X-linked Agammaglobulinemia or Bruton´s disease

A propósito del artículo: Actualización sobre las bases genéticas y perspectivas terapéuticas en la Agammaglobulinemia ligada al X o enfermedad de Bruton

Noel Taboada-Lugo [1]

[1]Provincial Center of Medical Genetics of Villa Clara, Cuba.

Received: April 24, 2024
Accepted: April 26, 2024
Published: June 22, 2024

Citar como: Taboada-Lugo N. A propósito del artículo: Actualización sobre las bases genéticas y perspectivas terapéuticas en la Agammaglobulinemia ligada al X o enfermedad de Bruton. Rev Ciencias Médicas [Internet]. Año [citado: fecha de acceso]; 28(2024): e6386. Disponible en: http://revcmpinar.sld.cu/index.php/publicaciones/article/view/6386

Dear Editor:

It was with interest that I read the article "Update on the genetic basis and therapeutic perspectives in X-linked agammaglobulinemia or Bruton's disease", authored by junior researchers in the field of immunology. (1)

The profound impact that the development of genetics and molecular biology techniques has had on the field of immunology is well known. In the opinion of some researchers, these tools are essential in the study of inborn errors of immunity.(2)

The authors in their article state that "The advent of the sophisticated gene editing technology known as CRISPR (Clustered Regularly Interspaced Short Palindromic Repeats) provides a promising new approach to treat X-linked agammaglobulinemia and inborn errors of immunity in general, keeping transgene expression under the control of endogenous regulatory elements".(1)

Given the dizzying development of CRISPR/Cas technology in recent years, from its discovery as a microbial immune system to its current evolution as a powerful tool for modifying gene expression, we consider it appropriate to provide some information on its discovery and its therapeutic potential in this primary immunodeficiency and in other genetic diseases of monogenic origin.

CC-BY-NC- 4.0

ISSN: 1561-3194 **RNPS:** 1877
Rev Ciencias Médicas. 2024; 28(2024): e6386

The discovery of these repetitive DNA sequences dates back to 1987, when Ishino and a group of researchers from the University of Osaka, Japan, described the discovery of five repetitions of 29 nucleotides spaced by 32 nucleotides in the genome of the bacterium Escherichia coli. Later, in 1993, Spanish microbiologist Francisco Mojica identified these repetitive sequences in the genome of Archea haloferax mediterranei. Interest in these bacterial sequences, whose function was still unknown, grew and it was in 2002 that the term CRISPR was coined to designate these repeated sequences, which translates into Spanish as clustered and regularly interspaced short palindromic repeats.

In-depth study of these sequences led to a new discovery: they all had highly conserved adjacent sequences, which would later be called Cas genes (CRISPR-associated proteins), including the Cas9 and Cas12 nuclease. Thus, a CRISPR locus consists of short direct repeats separated by sequences called spacers and flanked by several Cas genes, as well as two types of RNA, one programmable (crRNA) and one transactivated (tracrRNA).[2,3]

Since 2012, the CRISPR-Cas system has become the most widely used genome editing tool in molecular biology laboratories, which led to the award of the Nobel Prize in Chemistry in 2020 to Enmmanuelle Charpentier and Jennifer A. Doudna for the development of this technology.

The most widely used Cas protein to date for genome editing is SpCas9, which is a large multidomain, multifunctional endonuclease that produces two cuts in the DNA double strand that generate blunt ends, and is therefore interchangeably referred to as "genetic scissors, genomic scissors or molecular scissors".[3]

The CRISPR-Cas system has the potential to be used to regulate endogenous gene expression, including both transcriptional and epigenetic regulation. One of the most recent uses of this technology is base editing, which allows programmable nucleotide substitutions and thus targeted manipulation of the genome, enabling its use as a new therapeutic option for genetic diseases caused by point mutations such as X-linked agammaglobulinemia in the BTK (Bruton Protein Kinase) gene.[1,3]

Gene editing is a promising therapeutic approach for the treatment of monogenic hematological diseases as well as inborn errors of immunity. Numerous studies now combine this method of genome editing with induced pluripotent stem cells, the discovery of which has been enormously enriching for clinical research.[3,4]

Gray et al.,[5] used the CRISPR/Cas platform to achieve precise integration of a complementary DNA (cDNA) of the BTK gene optimized with corrective codons. The cDNA was modified to include the terminal intron of the BTK gene, leading to a significant increase in BTK expression to potentially therapeutic levels in in vitro cell lines, human hematopoietic stem and progenitor cells.

Donors containing truncated variants of the terminal intron also produced elevated protein expression, although to a lesser degree than the full intron. The addition of the Woodchuck hepatitis virus post-transcriptional regulatory element resulted in a significant increase in expression of the BTK transgene gene. The combination of these modifications resulted in near-physiological levels of BTK gene expression in the cell lines, leading to potentially therapeutic levels in vitro.[5]

CC-BY-NC 4.0

ISSN: 1561-3194 **RNPS:** 1877
Rev Ciencias Médicas. 2024; 28(2024): e6386

These findings support the conclusion of the authors of the article, who state that... "Gene editing is a promising approach to treat X-linked agammaglobulinemia and inborn errors of immunity in general".[1] Suffice it to say that, to date, it has been used to correct mutations that cause various genetic diseases such as cystic fibrosis, beta-thalassemia, Alpha1-antitrypsin deficiency, severe combined immunodeficiency, among others.[3]

The revolutionary CRISPR gene editing is already part of the therapeutic arsenal for the treatment of sickle cell anemia and transfusion-dependent beta-thalassemia, having been approved by the regulatory agencies in the United Kingdom and the United States.[6]

BIBLIOGRAPHIC REFERENCES

1. Hernández-Pacheco JI, Lorenzo-Rodriguez MA. Actualización sobre las bases genéticas y perspectivas terapéuticas en la Agammaglobulinemia ligada al X. Rev Ciencias Médicas [Internet]. 2024 [citado: 20/03/2024]; 28(1): e6271. Disponible en: http://revcmpinar.sld.cu/index.php/publicaciones/article/view/6271

2. El diagnóstico molecular, esencial en el estudio de los errores de la inmunidad innata [Internet]. NIH; 2023 [citado 20/03/2024]. Disponible en: https://healthincode.com/diagnostico-molecular-errores-inmunidad-innata/

3. Sánchez-Artigas R, Díaz-Armas MT, Rodríguez-Duque R, Miguel-Soca PE. Principios y aplicaciones médicas de la edición de genes mediante CRISPR/Cas. Medisur [Internet]. 2021 [citado: 20/03/2024]; 19(6): 1005-14. Disponible en: http://scielo.sld.cu/scielo.php?script=sci_arttex&pid=S1727-897X2021000601005

4. Liu X, Li G, Liu Y, Zhou F, Huang X, Li K. Avances en la terapia génica CRISPR/Cas para errores congénitos de la inmunidad. Inmunol Front [Internet]. 2023 [citado 20/03/2024]; 14: 1111777 Disponible en: https://europepmc.org/article/med/37051232

5. Gray DH, Villegas I, Long J, Santos J, Keir A, Abele A, et al. Optimizing integration and expression of transgenic Bruton's Tyrosine Kinase for CRISPR-Cas9-Mediated Gene Editing of X-Linked Agammaglobulinemia. CRISPR J [Internet]. 2021 [citado 20/03/2024]; 4(2): 191-206. Disponible en: https://www.liebertpub.com/doi/full/10.1089/crispr.2020.0080

6. GOV. UK. MHRA authorises world-first gene therapy that aims to cure sickle-cell disease and transfusion-dependent beta-thalassemia [Internet]. GOV. UK; 2023 [citado 20/03/2024] Disponible en: https://www.gov.uk/government/news/mhra-authorises-world-first-gene-therapy-that-aims-to-cure-sickle-cell-disease-and-transfusion-dependent-thalassemia

CC-BY-NC 4.0