Therapeutic revolution: correcting genetic errors using molecular scissors

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The recent approval of a gene therapy to correct the faulty gene that causes sickle cell anemia represents a major breakthrough for modern science.

Bacteria defend themselves against viruses (phages) which attack them by a refined biochemical defense mechanism, called CRISPR-Cas9: this system cuts the virus's DNA into small pieces and carefully preserves these fragments in their genome to keep in memory the passage of the virus.

When another similar virus infects the bacteria, it is immediately greeted by complementary versions of these fragments, which will attach to the DNA of the virus and cause the activation of the Cas9 enzyme that cuts the viral DNA and prevents the infection.

The scientific genius of Drs Emmanuelle Charpentier and Jennifer Doudna (Nobel Prize in Chemistry in 2020) was to consider manipulating this system to our advantage in order to guide the enzyme towards a very specific region of human DNA, to correct genetic diseases. By using fragments that will attach specifically to these regions, we can then eliminate or correct a genetic error responsible for a given pathology.

SICKLE CELL ANEMIA

The enormous therapeutic potential of this approach has just been confirmed by the recent FDA approval of the CRISPR-Cas9 platform for the treatment of sickle cell disease (sickle cell anemia).

In this hereditary disease, a mutation in the gene for hemoglobin (the protein that carries oxygen in red blood cells) causes the red blood cells to become distorted and very sticky, causing clumps of cells that block the blood vessels.

These blockages reduce the supply of oxygen to tissues and cause periods of intense, incapacitating pain.

The newly approved gene therapy (called Casgevy) aims to correct this defect by reactivating fetal hemoglobin (HbF) genes that are normally turned off in adults (1).

The approach used involves isolating hematopoietic stem cells from sickle cell disease patients and using CRISPR-Cas9 to inactivate another gene called BCL11A that prevents the expression of this HbF.

The cells that have been genetically modified in this way are subsequently re-implanted into the patients' bone marrow and, in the months that follow, generate red blood cells containing HbF.

Since the HbF gene does not contain the mutation, its expression in the modified red blood cells supplants the defective hemoglobin and thereby reduces the number of non-functional red blood cells.

In clinical trials, this approach completely eliminated episodes of severe pain in 28 of 29 patients followed for at least a year, representing a truly remarkable success.

A FIRST STEP

This new therapy is excessively complex from a clinical point of view, because it involves several manipulations of stem cells and therefore requires cutting-edge scientific infrastructure, especially found in developed Western countries.

Even though sickle cell disease is the most common genetic disease in the world, with approximately 300,000 people born carrying the mutation responsible for this disease, each year, 80% of cases are found in sub-Saharan Africa and the astronomical costs of treatment (approximately 2 million US dollars per patient) make access to this therapy difficult, at least in the short term, for these countries.

However, as is so often the case with new scientific revolutions, the high prices of early prototypes become more and more accessible over time and a similar trend will likely be observed for these therapies.

We must therefore see this therapy as the first step in a new generation of treatments, which will make it possible to cure serious illnesses hitherto considered incurable, proof of validation of this new scientific concept.

This major breakthrough initially came from scientists who were interested in the response of bacteria to viruses, which shows to what extent fundamental research, which apparently has no immediate concrete applications, is crucial for the discovery of new treatments against the diseases that afflict humanity.

A concrete example of human genius and its incredible ability to understand the world around it to improve the human condition.

(1) Esrick EB et al. Post-transcriptional genetic silencing of BCL11A to treat sickle cell disease. N. Engl. J. Med. 2021; 384: 205-215.

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