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Editorial

RNA therapeutics in hematology

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The 2023 Nobel Prize in Physiology or Medicine is jointly awarded to Katalin Karikó and Drew Weissman.[1] They discovered "nucleoside base modifications in RNAs that enabled the development of messenger RNA (mRNA) vaccines against COVID-19."

RNA therapeutics, an ever-expanding arsenal of genomic-era medications, has offered a growing influence on a variety of benign and malignant hematologic illnesses. RNA-targeted therapeutics offer a platform for drug development with the use of chemically altered oligonucleotides, a variety of cellular RNAs, and a unique target-binding motif called Watson–Crick base pairing. Many RNA therapeutics have been created and have either received approval or are undergoing clinical trials at different stages; to name a few are- (1) Antisense oligonucleotides (ASOs), (2) RNA interference, (3) Small interfering RNAs (siRNAs). The different RNA molecules, such as microRNAs, ASOs, and small interfering RNAs (siRNAs), can directly target mRNAs and noncoding RNAs through Watson–Crick base pairing.[2] Therefore, by choosing the appropriate nucleotide sequence on the target RNA, they potentially target any gene of interest. As the majority of the DNA sequences from the human genome are translated into noncoding transcripts, just 0.05% of the human genome has been affected by the currently approved protein-targeted treatments (small-molecule drugs and antibodies).[3] Target RNA sequences can be directly altered using genome editing with the help of clustered, regularly interspaced short palindromic repeats (CRISPR) to cure particular diseases.[4] RNA aptamers (also known as chemical antibodies due to their synthetic origins) having a similar mode of action to antibodies can also suppress protein activity.[5] Thus, RNA-based therapeutics are considered as most appealing since they broaden the number of druggable targets.

Researchers have developed "*in vivo*" RNA-based gene editing tools for different kinds of blood disorders, such as thalassemia and sickle cell disease that allow modifications of different kinds of blood cells inside the body. These could be translated into clinical applications that may help us to minimize the cost of therapy in terms of no further need to go for costly chemotherapy and stem cell transplantation. To target hematopoietic stem cells (HSCs), the researchers use liquid nanoparticles (LNPs) that are coated with antibodies directed against CD117 (a receptor on the surface of HSCs). This CD117/LNP encapsulating mRNA encodes a Cas9 gene editor that can target the specific mutation (e.g., the mutation in severe combined immunodeficiency).[6,7] With the recent advent of RNA-based therapeutics, the landscape of hemophilia treatment is changing rapidly. The siRNA therapeutics can knock down some clot regulators, e.g., antithrombin and protein S. The CRISPR/Cas9 gene editing technique may, in the near future, enable us to individualize treatment in a person with hemophilia in terms of reduced bleed and no factor use and thus to avoid the untoward effect of inhibitor formation in many cases.[8]

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