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EDITORIAL

The promise of gene editing

Iftikhar Qayum

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Author Information
From: Department of Medical Research, Rehman Medical College, Peshawar, Khyber Pakhtunkhwa, Pakistan.

Dr. Iftikhar Qayum,
Director Medical research
Email:
iftikhar.qayum@rmi.edu.pk

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ABSTRACT

The advent of a new age of genetics that was ushered in due to the discovery of gene editing based on CRISPR-CAS9 kinase tools is discussed, and salient features and milestones highlighted. More importantly, current and future applications of the technique for human health are presented along with the ethical implications that are likely to be hot topics of debate for years to come.

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INTRODUCTION

The world of genetics changed in 2012,[1] perhaps the biggest revolution since Gregor Mendel (Principles of Inheritance, published in 1865), and the discovery of the DNA helical structure by Watson & Crick (1953). Scientists had for long yearned for some level of control over genes other than the processes of natural selection and crop modifications by selective grafting. Little did they know that a well-known but previously overlooked biologic process found in lowly bacteria would come to their rescue.[2]

Although a few techniques existed for gene editing, such as Zinc Finger Nucleases (ZFNs), and TALENs (transcription-activator-like effector nucleases), these were technically cumbersome and often not accurate enough to be applied for any large-scale human or biological applications.[3] It soon became evident that the CRISPR system, basically a bacterial defense strategy against invading bacteriophage DNR/RNA, could be easily adapted for editing the genomes of other species, including mammalian cells.[3]

Even more fascinating is how the CRISPR system works as a defense in bacteria and other organisms including mammals.[3] An acronym for Clustered Regularly Interspaced Short Palindromic Repeats, this RNA-mediated defense (immune) system requires an assembly of *Cas* (CRISPR associated) family of endonuclease protein enzymes to function as the demolisher of inserted foreign genomic materials. Of the different Cas endonucleases, Cas9, derived from *Streptococcus pyogenes*,[4] is the most powerful effector molecule that can cleave specific sites in foreign DNA after attaching to it through a complementary RNA strand synthesized by the host cell after reading the foreign DNA sequence. Hence the derivation of the formal nomenclature of CRISPR/Cas9 as the main gene editing tool that has been used to modify DNA selectively. It is obvious that by modifying the complementary RNA strand (called guide RNAs; gRNA), DNA can be cleaved at different sites, hence its utility as a gene editing tool. This has enabled researchers to develop cassettes that can target specific genes of interest for both research and therapeutic genetic interventions.[4,5]

The fact that a hitherto 'sacrosanct' realm, the human genome, could be so easily accessed and modified raised a lot of debate about the pros and cons of gene editing. A poll of US citizens carried out by Pew Research in 2016[6] revealed the staggering amount of reluctance (68% worried) by citizens of the most developed nation towards gene editing applications for human health. Moreover, US adults were almost evenly split (48% and 50%) about wanting gene editing to help prevent diseases in their newborn babies; however, among those more aware about gene editing, 57% agreed to such use of gene editing.

Furthermore, 64% of US citizens with strong religious commitments viewed gene editing as 'meddling with nature' and up to 73% Americans thought that there would be various types of negative consequences for society in future due to gene editing developments. Regarding the moral issues related to gene editing, up to 41% US citizens surveyed were unsure about giving any opinion, while 30% thought it to be morally unacceptable; religious reasons were given for why they considered it morally unacceptable.

Deliberations on these issues were highlighted in a session of the International Summit on Gene Editing,[7] held in Washington D.C. in December 2015. The conclusion was that it would be considered irresponsible if germline editing was pursued further at this time, and that further research work should be done before embarking on clinical applications of gene editing; however, the prospects of somatic gene therapy should be given more focus.

The technological ease with which gene editing could be done and applied to real life situations gave rise to major ethical concerns to ensure that these techniques

do not fall into the wrong hands or are not exploited towards wrong directions. In an insightful review article, Kohn et al.[8] provide the rationale and need for ethical conduct of gene editing, particularly for patient care. Two main areas of concern arose, that of "Germline" and "Somatic" cell gene editing.

Germline editing refers to all changes that could be incurred in the DNA of a person's gametes due to genetic interventions. Conventionally this has been the subject for teratogenic drugs, but now the potential for gene editing at the gamete level has added to the complexity of ethical debate surrounding such interventions. Germline changes have been attributed to "Unintentional" or "Intentional" depending on the method by which these changes can be incurred.[8] Unintentional changes could be derived from any number of somatic therapeutic measures taken for some other diseases or conditions and are considered as incidental risks of approved standard therapies. Intended germline editing, on the other hand, are directed towards alleviation of inherited diseases in the offspring of carriers of genetic traits or diseases and/or the alleviation of familial diseases from the pedigree. Despite arguments for and against gene editing, the general consensus is that germline alterations are unethical due to unknown or unforeseen risks that could be incurred upon the developing fetus and the newborn. However, in a landmark achievement, British scientists were given a green signal to modify human embryos through CRISPR/Cas9 systems, but only for purposes of research.[9]

Somatic gene therapy, on the other hand, does not raise many fundamental ethical issues of concern. Thus, such gene editing has been performed using the ZFNs, TALENs, and CRISPR/Cas9 systems for a limited number of diseases.[8] Nevertheless, these interventions must pass through the regulatory filter specifics of risk/benefit analysis, informed consent, and approval from regulatory authorities.

Some of the currently known major risks associated with gene therapy include genotoxicity due to inadvertent activation of normally suppressed undesirable genes, and off-target editing that could result in introducing errors in a previously normal DNA sequence. Further adding to the complexity is the possibility of increasing the default mutation rates (1-3 mutations per cell division) in dividing cells and that current mutation detection assays may not be sensitive enough to detect all induced mutations.[8]

It should also be considered that gene editing offers a very powerful and accurate tool for beneficial use to enhance the genomic potentials of all biological species. Potentially given enough time, it offers the possibility of eradicating all genome-based diseases in individuals as well as down the family lines, so that the problem of risky marriages could be resolved once and for all. Moreover, individuals and families can be imbued with beneficial genetic traits such as intelligence, beauty, athletic ability, skillfulness, etc., that would ultimately make for a balanced and caring society. Applications in agriculture and livestock could also eradicate the problem of food imbalance and malnutrition on a global scale. For humans, the greatest impact would be on developing the field of Personalized Genomic Medicine as an entirely new paradigm shift in patient care.

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