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Short Communication

Genome Editing CRISPR-Cas 9 Technology: Therapeutic Potential Over Ethical Challenges

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The Genome editing CRISPR-Cas9 originated from type II CRISPR-Cas systems, which helps bacterium to defend itself by mounting an adaptive immunity against invading viruses and plasmids. As invading viruses or plasmids make entry into a bacterial cell, CRISPR system helps to integrate short viral DNA molecules into the CRISPR locus. The biogenesis of CRISPR RNA involves the transcription of CRISPR sequence into RNA, the freshly transcribed RNA subsequently used with proteins encoded by Cas genes to form interference complexes that are used in the formation of RNA molecules to base pair with matching sequences of viral DNA. The CRISPR sequence CRISPRs, "clustered regularly interspaced short palindromic repeats", contain short DNA repeats of viral origin found in the bacterial genome. Cas (CRISPR-associated) is an endonuclease that recognizes and cut the DNA CRISPR-Cas complex of the invading virus and guides the Cas protein to cleave the virus. CRISPR-Cas9 is used to target a particular deleterious and disease causing genes in certain genetic disorders. The targeted genes are modified, and results are the changes in the germline intended to be bequeathed to the next generation so that the disease causing genes can be completely demolished. Manipulating somatic cells with genome editing is at it various clinical stages, is a promising area of therapeutic development.

Genome editing became a therapeutic possibility when a research in 2013 engineered a novel version of CRISPR-Cas9 to edit human genomes through genome editing. Quick speed and high efficiency of CRISPR-Cas9 is a remarkable feature which can enable it to increase the identification of genes that are associated with human diseases and facilitate the development of therapies to correct the mutated gene. Due to its high genetic specificity, scientists are using CRISPR-Cas9 genomic editing technology to facilitate discoveries in cancer biology. Cancer models have been developed using CRISPR-Cas9. The models better reflect the disease in humans. Later same researcher successfully engineered a mice model using CRISPR-Cas9 to model the deleterious effects of mutations in cancer. The ability of their system to introduce loss of function mutations in tumor suppressor genes and gain of function in proto-oncogenes facilitate screening of causal genetic mutations.

This genome editing technology CRISPR-Cas9 is used to target a particular deleterious and disease causing genes in certain genetic disorders. The targeted genes are modified, which brings about the changes in the germline intended to be bequeathed to the next generation so that the disease causing genes can be completely eradicated. Genome editing of somatic cells, which is progressing at various clinical stages, is a promising area of therapeutic development.

Recently, a group of Chinese researchers - a gene function researcher at Sun Yat-sen University in Guangzhou, applied this complex enzyme-editing tool CRISPR-Cas9 as a therapeutic tool to eradicate the human β-globulin (HBB) gene from the germ line of the human embryo. The mutations in HBB gene cause β-thalassemia (a deadly blood disorder). This research was, however, not completely successful. These genome editing technologies currently in various clinical developmental stages are limited to modification of genetic material of somatic cells. Since the techniques of genome editing raise a possibility of unpredictable outcomes, some scientists have argued that cure by genetic engineering techniques should be limited to genome editing of somatic cells.

While some members of the scientific community have argued that moratorium should be called on human genome editing, others have argued that it is unethical to withhold a technology that would fix devastating genetic diseases, such as cystic fibrosis.

One consequence of this technology will be off-target mutations in the genome. Off-target mutations are unintended mutations in the genome. They occur when CRISPR-Cas9 cleaves other DNA sequences within the genome that are homologous to the target DNA sequences. These mutations can be deleterious. Off-target mutations can cause cell death or transformation. Due to some of the limitation of the research, a researcher said that the research should be stopped to allow a broad based discussion about the direction of where we are going. Nevertheless, off-target mutations can be lessened or avoided by using the most recently developed CRISPR-Cas9 as they increased the CRISPR-Cas9 efficiency in site-specific gene targeting using Cas9-modified hiPSC clones.

The cost of germline editing technology is very high to the extent that families coming from rich developed countries could afford it. The developing countries will not have assets to afford the cost of this technology. This may confer an advantage to children born in developed countries.

Genome editing in human embryos using CRISPR-Cas9 could have unpredictable effects to the future generations. CRISPR-Cas9 technology could be used for non-therapeutic modifications. This procedure will open the door to the loss of human diversity and eugenics and will generate custom genetically chosen human race. Last year, a researcher, successfully changed the coat color of the rat suggesting the possibility of inducing a pigmentation change in humans through embryonic editing. So, the genetic enhancement of a specific appearance could cause substantial physical and mental health issues to the children since their appearance is imposed on them through means other than blood relationship.

Genome editing of the human embryo could hinder the ongoing research that involve gene editing of somatic cells that hold promise for therapeutic development. Researcher pointed out, the public outcry about the ethical breach of human embryo genome editing could hinder the promising area of therapeutic development that are involved in making genetic changes in somatic cells. And there should be an open discussion around the appropriate action should a compelling case arise for therapeutic benefit of germline modification. The nuclease may not be as efficient. The nuclease may not necessarily cleave both copies of the target gene or the cells may start dividing before the corrections are completed, resulting in genetic mosaic. Mosaicism is the presence of the populations of somatic cells that are genetically distinct in an organism. Mosaicism is frequently masked. However, mosaicism can cause major phenotypic changes and reveal the expression of lethal genetic mutations. Some of the genetic disorders that result from mosaicism include: Down syndrome, Klinefelter syndrome and Turner syndrome.

CRISPR-Cas9 genome editing technology to an embryo is a very risky affair. Researchers may not be in a position to determine, with precision, the effect of such procedures before birth. The quality control can be performed only on a subset of cells. This limitation shows that it may be impossible to know the effect of genetic modification of an embryo with precision until after birth. Even then, potential problems may take years to develop and show-up to late to correct.

Another question that may arise regarding the embryo genome editing using CRISPR-Cas9 editing technology is the fate of the child produced by such technologies? While it is clear that people's informed consent is secured before genetically engineered somatic cells are used in clinical research, it is not clear what information would be needed from the prospective parents to adequately inform them about the risks involved in germline modification.

The scientific community needs to engage in a discussion to establish rules & guidelines of research involving genetic modification of human germ cells. The discussions should involve stakeholders in different fields: the general public, scientists, bioethicists, public policy and legal experts. Such a discussion should make a clear distinction between genome editing in germ cells and in somatic cells. The significant progress being made in clinical development of approaches to cure deleterious diseases should not be impeded by concerns regarding the ethical implications of germline editing. A voluntary moratorium should be called on genetic modification of human germ cells. The US National Institute of Health has taken the lead in calling moratorium on genome editing of human embryos and earlier this year, the director of US National Institutes of Health, issued a statement that banned NIH-funded research into genomic editing of human

embryos which need to be followed by other countries. As debate begins, among the members of the scientific community, a moratorium is needed to take advantage of outcome of debate on this issue.

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