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The Ethical Concerns of CRISPR Editing in Embryos

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ABSTRACT

CRISPR is a tool in molecular biology with many far-reaching uses in medicine and research. Along with its well-known benefits for diagnostics and treatments, recent research has focused on how CRISPR can be used in gene editing in germline cells. This paper explicitly discusses and comments on the ethics of such genetic modifications and explores future solutions to resolve the ethical concerns of this field of research.

Introduction and The Uses of CRISPR In Medicine

CRISPR, or Clustered Regularly Interspaced Short Palindromic Repeats, is a tool that edits deoxyribonucleic acid (DNA). By editing DNA, CRISPR can be used to modify gene expression and thus has potential applications for the correction of genetic defects and treating diseases.

Of the three leading types, the type II CRISPR-Cas system, which uses the Cas9 protein, is the most widely used system because of its simplicity and efficacy (Liu et al. 2017; Ran et al. 2013). This system is made up of two parts: a Cas9 protein and a single-guide RNA (sgRNA). The Cas9 molecule has been developed from the innate defensive systems of single-cell microorganisms. This enzyme has been adapted to be applied to genomic editing assays in eukaryotes. In its full enzymatically active form, the Cas9 protein makes double-stranded cuts through DNA at specific genomic sites. The sgRNA component of the system contains a 20-nucleotide guide sequence that binds to the Cas9 molecule and directs it to a corresponding 20-base pair DNA target in order for the Cas9 protein to cut at the intended site (Ran et al. 2013).

The entire Cas9 and sgRNA complex facilitates genome editing by creating a double-stranded break (DSB) at the target DNA site. After cleavage by Cas9, the DSB undergoes DNA damage repair in one of two ways: Non-Homologous End Joining (NHEJ) or Homology Directed Repair (HDR), as shown in Figure 1.

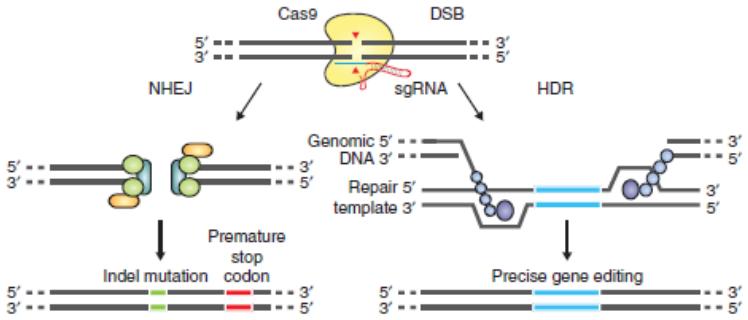

Figure 1: Figure taken from Ran 2013. The Cas9 protein in the CRISPR system works through enzymatic activity to cut a double-stranded break of DNA (DSB) at a specified location in the genome. The two most common modes of DNA repair used to incur genetic editing are NHEJ and HDR, which work by different repair methods.

During NHEJ, in order to repair the DNA, enzymes in the nucleus process and re-ligate the ends of the DSB. However, this process is prone to leaving insertion/deletion mutations. The NHEJ type of DNA repair is useful for attempting to disrupt or mutate a gene, most of the time with the goal of rendering its protein product non-functional. Conversely, during HDR, an externally introduced DNA repair template helps create precise modification at the target locus. For this reason, HDR is the preferred DNA repair pathway when the goal of gene modification by CRISPR is to introduce a specific modification to a gene.

The use of CRISPR in medicine is typically used for the modification of gene expression patterns known to cause disease in order to remove or at least mitigate deleterious effects driven by defective gene patterns. Yet recent studies have shown that CRISPR may also be used to detect diseases. CRISPR is currently undergoing clinical trials for targeted therapies that treat cancer (Hui and Meng 2019). One application of CRISPR technology is in high-throughput screening in which the Cas9 protein is used to detect the efficacy of drugs in cancerous tumors (Hui and Meng 2019). During the pandemic that has ravaged the world over the past year and a half, Arizti-Sanz and others at Harvard University developed a diagnostic tool that detects SARS-CoV-2, the pathogen that causes COVID-19. They combined HUDSON, a technique that releases the intracellular components of patient nasal swabs or combined nasal and saliva samples, and SHERLOCK, a procedure that uses CRISPR technology to amplify and detect the pathogen RNA in the released intracellular components as a way to quickly test for the presence or absence of the virus (Arizti-Sanz et al. 2020). CRISPR is also theoretically able to prevent diseases. For example, by using gene drives and CRISPR technology, scientists can modify the mosquito vector for malaria and suppress the spread of the disease in humans (Barrangou and Doudna 2016).

The two major classes of cell types in which CRISPR therapies work are somatic and germline. Somatic editing occurs when any non-reproductive cell has been edited, such as those found in the lung and kidney. In this case, only the organism being treated will be affected. On the other hand, germline editing occurs when reproductive cells are modified. It is suspected that the edits made in these cells can be passed down to offspring (Brokowski and Adli 2019). Ma et al. have claimed that in zygotes, or fertilized egg cells, CRISPR-Cas9 can be used for recognizing the specific genomic sequences for certain genetic diseases and inducing DSBs to correct them (Ma et al. 2017). Germline editing has many ethical considerations and has been a point of contention within the gene-editing field for years.

The Ethics of Use Of CRISPR Technology in Embryos

One of the main concerns about the future of modified organisms is whether the modified genes will affect future generations (germline editing) or if they will only affect the organism being treated (somatic editing). Currently, it is difficult to envision the future of genetically modified organisms because of how little is known about the intricacies of life forms. This uncertainty hampers accurate pro/con analyses which makes moral decision-making difficult. A final concern stems from the lack of understanding of the connection between genotype and phenotype; so, there remains unclear potential for eventual biological consequences. Thus this concern is the basis of one of the major points of contention about CRISPR technology's potential use in engineering human embryos. Particularly, researchers can not agree on whether the status of a human embryo at 14 days has "personhood". This disagreement is implicated by the fact that some think the editing of one's genes should be decided by that individual themselves. Yet, because embryos do not have the awareness to make such a conscious decision, leaving the choice to them is not a plausible solution. Thus the current ban on viable human embryo gene editing could save the embryo from lethal, research-related harm.

When looking at the implications of CRISPR in somatic cells, the risk is much lower and is comparable to regularly practiced biomedical testing. However, it can be argued that similar to germline editing, there is added risk because of future unknown consequences.

Due to limited research on the subject, scientists have no way of assessing CRISPR risk in human participants. Furthermore, the application of CRISPR in germline editing may open into the return of eugenics. Eugenics,

which gained traction in the early twentieth century, is the theory that planned breeding will help improve the genetic "quality" of a population. Because of CRISPR technology's unprecedented power, it may be possible for scientists to enhance human features like height, muscle mass, vision, learning aptitude, or memory (Brokowski and Adli 2019). The ethical question of modification of physical features is difficult to answer because the real question is how society defines what a "norm" is and what a biological phenotype is, such as a disease that needs treatment. "Medical necessity" becomes unclear.

Although the future of genetic editing is certainly an unknown risk, using CRISPR systems to treat diseases in embryos could save many lives. To make truly informed decisions about the ethics of CRISPR, experimentation in the field is needed, but international laws and bans make that currently impossible. Thus, data about CRISPR's risks and benefits are unavailable (Brokowski and Adli 2019). Many support the idea of an independent organization that will decide how to handle the aforementioned ethical questions. In the end, legal systems, principal investigators, and institutional review boards are likely to be in charge of enforcing ethical research laws and guidelines.

Addressing The Arguments of Using CRISPR in Embryos

There are two schools of thought when determining whether it is ethical to edit embryos. CRISPR critics say that editing zygotes could open a *Pandora's box*. This method that is intended to cure diseases can also create genetically enhanced human beings. For example, how CRISPR treats muscular dystrophy can enhance muscles to improve speed and strength. This has many negative societal implications. For example, only the wealthy are able to afford this technology. It would be possible for the privileged to secure their status and authority permanently by improving every aspect of their offspring, like their intelligence and beauty, and deleting any genetic "imperfections". This would eliminate opportunities for people at the bottom of the social ladder, widening the wealth gap.

On the other hand, CRISPR promoters say that we should go ahead with CRISPR testing, even through to the application of CRISPR in human embryos. Many diseases and mutations are genetic, so using CRISPR to treat them not only cures one patient but the rest of the bloodline as well. Scientific research should not be met with fear of the consequences, but rather with hope for its benefits. For example, when in-vitro fertilization (IVF) was emerging, people were frightened, as they are now with CRISPR. Risks associated with the IVF procedure were unknown, but as science went ahead with it, the field saw that IVF has had nothing but a positive outcome, with only minimal medical risks and over 8 million people owing their lives to this technology (Loike 2018). Germline editing supporters say that research should go ahead, just as it did with IVF, and take the necessary risk to see the potential benefits.

Conclusion

CRISPR technology continues to get better. The potential benefits of this tool are infinite, but so are the dangers and ethical concerns. The largest problems are rooted in our lack of information about CRISPR, the use of this tool in humans, as well as the intricacies of biological systems in general. Concerns also focus on social issues, like the status of a human embryo and whether it has the agency to decide on its genetic editing. Among the many worries that CRISPR critics have, a notable concern is how the use of CRISPR as treatment for disease may turn into a situation where the wealth gap widens as a result of the privileged using CRISPR to enhance the physical features of their offspring. CRISPR supporters believe that germline editing has the potential to eradicate many diseases from bloodlines, benefiting not only the current generation but many others as well.

The answers to these ethical queries will likely be up to legal systems, such as an independent organization founded for the purpose of creating and enforcing ethical research laws and guidelines. As technology evolves, researchers and scholars worldwide will continue presenting new information and ideas about how to best integrate CRISPR technology into clinical practice.

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