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Scientific success in embryo editing re-opens reg debate

By Nuala Moran
Staff Writer

LONDON – U.S. scientists are calling for a rethink of current restrictions on using CRISPR/Cas9 gene editing in human embryos after successfully correcting the MYBPC3 hypertrophic cardiomyopathy mutation, the commonest cause of heart failure and sudden death in apparently healthy young people, without causing any off-target effects or mosaicism.

In the research published in *Nature* on Wednesday, 58 donor eggs were simultaneously injected with sperm from a man carrying the MYBPC3 gene and a CRISPR/Cas9 construct designed to correct the mutation.

Forty-two (72.4 percent) of the resulting embryos contained two mutation-free copies of the MYBPC3 gene. Subsequent genetic analysis showed that editing out the mutation at the point of fertilization and before the first cell division, ensured the mutation was corrected in all cells, preventing mosaicism.

In addition, teams in South Korea and China, using two different whole genome sequencing techniques, showed there were no off-target effects or genome instability.

The results show it is time to reconsider the regulatory framework, said Shoukhrat Mitalipov of Oregon Health and Science University (OHSU), who led the research.

Currently, the National Institutes of Health does not fund research into altering the human germline for clinical purposes and the FDA is prohibited from considering any clinical trial relating to germline genetic modification.

In February the Committee on Human Gene Editing report, published by the U.S. National Academies of Sciences and Medicine took a slightly more relaxed view, suggesting genome editing may be appropriate in serious inherited disorders where there is no alternative.

But since it is possible to use preimplantation genetic diagnosis to test if in vitro fertilization embryos are carrying heterozygous mutations, Mitalipov's research would not appear to pass this threshold.

However, Mitalipov claimed that when the committee members were deliberating, they were swayed by concerns about mosaicism and low efficiency in editing, which his technique has overcome. "Now we have shown it is not going to be a big issue, I hope they will reconsider. I hope the committee will move forward."

In the case of a heterozygous gene defect it would be expected that 50 percent of embryos would be mutation-free and Mitalipov confirmed this in a control study in which nine of 19 embryos fertilized in vitro did not inherit a mutant copy of MYBPC3.

Increasing the number of embryos without the defect from 50 percent to 72.4 percent may not seem to be a huge advance, but co-author Paula Amato, associate professor of obstetrics and gynecology in the OHSU School of Medicine said the need for fewer IVF cycles to generate embryos suitable for implantation would be a significant benefit, especially for older women with fewer eggs. One woman she treated recently underwent three cycles of IVF but no embryos suitable for implantation were generated.

"If proven safe, this technique could potentially decrease the number of [IVF] cycles needed for people trying to have children free of genetic disease," said Amato.

The edited embryos developed similarly to the control embryos, with 50 percent reaching the blastocyst stage, indicating gene editing does not block development, according to the researchers.

Mitalipov highlighted also that in addition to showing it is possible to correct mutant genes, the researchers appear to have discovered a DNA repair response that is unique to human embryos. Rather than using the injected synthetic DNA template, the team found that the embryos used the normal maternal gene as the template to make the repair once CRISPR/Cas9 enzymes had cut out the defective gene.

In cell and animal models CRISPR/Cas9 can be used to introduce external DNA, but said Mitalipov, "It doesn't seem like it is going to work with [human] embryos."

When the CRISPR/Cas9 MYBPC3 gene editing construct was tested on induced pluripotent stem cells (iPSCs) generated from adult skin cells from the sperm donor, the success rate in correcting the defect was far lower. "Our expectation was that this was how embryos would respond. We saw a very different response – no template was used – this was very surprising," Mitalipov said.

The finding has wider implications for research, Mitalipov noted. It was thought iPSCs could replace the use of embryos, but the finding that iPSCs do not have the same DNA repair mechanisms means "embryo research is still vital, despite the constraints, both ethical and practical."

Mitalipov now wants to replicate the study with other mutations and other donors, to improve efficiency. "To move to the clinic . . . we need to improve the efficacy. Even though the yield of wild-type [embryos] is higher, there is still room to improve."

There are tools currently available that could improve efficiency, and Mitalipov said the technique would have to work 90 percent to 100 percent of the time before it would be appropriate to think about moving to clinical trials.

The technique could be relevant to a huge number of couples in thousands of inherited diseases caused by heterozygous mutations, where one partner has a normal allele. Mitalipov thinks it would work if the mutant gene is maternal, but the problem of getting enough donor oocytes will make this difficult to verify.

Mitalipov said he would consider taking the research forward in other countries if governments wanted to offer support for regulated clinical trials. "There is a long road ahead [to the clinic]. It is unclear at this point when we would be allowed to move along."

Although arguing the research should prompt a reassessment of whether it would be appropriate to use germline gene editing to treat serious inherited diseases, the researchers stress in no sense should this be viewed as promoting the concept of 'designer babies.'

"It's a correction: We have not modified anything," Mitalipov said. "The technique was used to make a correction using existing wild-type maternal genes."

Expert reactions

Robin Lovell-Badge, group leader at the Francis Crick Institute in London, said the fact that the embryos did not use the external DNA means new methods must be developed to permit efficient DNA template-directed repair. "The mechanism revealed in this paper would similarly not permit more sophisticated genetic alterations. The possibility of producing designer babies, which is unjustified in any case, is now even further away," Lovell-Badge said.

Although impressed by the advance made by Mitalipov and colleagues, experts feel the technique is far from being ready for clinical use and that preimplantation genetic diagnosis is still the best approach to preventing the transmission of serious genetically inherited diseases.

The work overcomes some of the technical difficulties in editing the genome of the early human embryo, paving the way for future work, but, said Jim Smith, director of science at the medical research charity Wellcome Trust, "We are still a very long way from contemplating the use of this technology in the clinic."

The two major concerns of using CRISPR to edit an embryo, of mosaicism and unwanted edits, are addressed by the research, said Helen O'Neill, director of the women's health, embryology, IVF and

reproductive genetics group at University College London. "The results reflect much-needed progress in utilizing human eggs and sperm in research for the prevention of diseases which have no current cure or treatment." However, O'Neill said, the technology is still in its infancy in terms of true clinical application.

Similarly, Anna Middleton, vice chair of the U.K. association of genetic nurses and counselors, said while the science is "really elegant" it must be replicated extensively before any firm conclusions can be drawn about the accuracy and safety of the approach. "It is far too early to extrapolate this into any clinical application," Middleton said.

James Adjaye, chair of stem cell research and regenerative medicine, Heinrich Heine University, Dusseldorf, Germany, said it is "a major and unexpected observation" that the DNA repair mechanism in early embryos seems to be different from that in human iPSC cells and maybe even somatic cells.

"This is an important finding for basic research and also a necessary pre-requisite for correcting mutations at the oocyte or preimplantation embryo level," Adjaye said.

Daniel Brison, professor of clinical embryology and stem cell biology at Manchester University, agreed that the study appears to be a major advance in human embryo gene editing, which brings the technology a step closer to clinical application in correcting inherited disease. "Using gene editing during fertilization in this way is a clever idea, especially as we know that human sperm naturally contain a high level of damaged DNA due to environmental and other exposures, which must be repaired by the oocyte as part of fertilization during natural conception," Brison said.

For Peter Braude, emeritus professor of obstetrics and gynaecology, King's College London, the "remarkable paper" demonstrates just how rapidly the field of genome editing has progressed since 2015. "Whilst there are still some important potential hazards such as mosaicism and off-target effects, substantial progress has been made here on understanding how they might happen and be ameliorated."

Preimplantation genetic diagnosis with embryo selection is still the only practical option for couples to prevent transmission of genetic disorders to their offspring, but Braude said the paper presents a possible future alternative especially in dominant disorders, like Marfan syndrome, Huntington disease or hypertrophic cardiomyopathy, as the editing correction seems more reliable when there is one normal gene present.

"With this paper the possibility of germline genome editing has moved from future fantasy to the world of possibility, and the debate about its use, outside of fears about the safety of the technology, needs to run to catch up," Braude said.

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