Editorial

Gynecology & Reproductive Health

Would Human Preimplantation Gene Therapy Based on CRISPR-Cas9 Genome Editing Increase Cancer Risk in the Offspring?

Jan Tesarik[1,2*], Raquel Mendoza-Tesarik[1,2,3] and Carmen Mendoza[2]

[1]*MARGen Clinic, Camino de Ronda 2, Granada, Spain.*

[2]*MARGen Mendoza-Tesarik Foundation, Camino de Ronda 2, Granada, Spain.*

[3]*Department of Biochemistry and Molecular Biology, University of Granada, Granada, Spain.*

***Correspondence:**
Jan Tesarik MD, PhD, MARGen Clinic, Camino de Ronda 2, 18006 Granada, Spain, E-mail: jtesarik@clinicamargen.com.

Received: 02 September 2018; **Accepted:** 26 September 2018

Citation: Jan Tesarik, Raquel Mendoza-Tesarik, Carmen Mendoza. Would Human Preimplantation Gene Therapy Based on CRISPR-Cas9 Genome Editing Increase Cancer Risk in the Offspring?. Gynecol Reprod Health. 2018; 2(5): 1-2.

ABSTRACT

Systems using clustered regularly interspaced short palindromic repeats (CRISPR) and CRISPR-associated protein 9 (Cas9), widely used as precision genome editing tools in somatic cells, have also been shown to be able to correct pathogenic gene mutations in human preimplantation embryos. Recent findings, suggesting that CRISPR-Cas9 genome editing in somatic cells may inadvertently increase the risk of cancer if the edited cells are transplanted into a patient, have raised some doubts about a similar risk associated with CRISPR-Cas9 action in human zygotes and preimplantation embryos. Here we resume the current knowledge about the differences in the expression of basic genes involved in the anticancer defense between somatic cells and preimplantation embryos. These data strongly suggest that CRISPR-Cas9 based gene therapy, performed in preimplantation embryos, is highly unlikely to increase cancer risk in the offspring.

Keywords
Preimplantation gene therapy, Germline gene therapy, CRISPR-Cas9, Genome editing, Cancer risk, TP53 gene, p53 protein, Apoptosis, DNA repair pathways.

Systems based on clustered regularly interspaced short palindromic repeats (CRISPR) and CRISPR-associated protein 9 (Cas9) are increasingly used as precision genome editing tools in various types of somatic cells. Recently, Haapaniemi and colleagues [1] published a study suggesting that CRISP-Cas9 genome editing techniques may promote cancer through a selection against cells with a functional p53-mediated DNA damage response, one of the major anti-cancer safeguards. This important finding will have to be taken into consideration in the development of gene-editing strategies to be applied to p53-expressing somatic cells. Here we wish to add some remarks on whether, and how, this discovery is expected to modify our efforts aimed at developing efficient and safe gene therapy techniques to be used in human zygotes and preimplantation embryos.

The probability of the p53-mediated DNA damage response to CRISPR-Cas9, and thus the degree of the selective pressure against the p53-triggered signalling pathway in the successfully edited cells, will depend on the current expression of p53 and the downstream elements of the pathway in the cells treated. Embryonic gene transcription, in general, does not occur until the four-cell stage of human preimplantation development [2], and the first signs of embryonic gene expression have only been detected between the four- and eight-cell stages [3, 4]. In earlier postfertilization stages, the key developmental events, such as the regulation of the cell cycle or establishing of cell polarity, are entirely dependent on the use of stored maternal mRNAs and/or proteins, whereas the regulatory mechanisms of both maternal and embryonic origin co-exist in embryonic cells during some time after embryonic genome activation [5].

As to the TP53 (the gene coding for p53 protein), human oocytes display considerably fewer transcripts as compared to other simultaneously assessed cell-cycle and apoptosis regulating genes, and a further 2 – 3-fold reduction in TP53 transcript number occurs after fertilization, between the two-cell and four-cell stages [6]. Moreover, an ongoing drop in the average TP53 transcript number was observed after the general activation of embryonic gene expression, during progression to the morula stage, followed by a mild increase during blastocyst formation [6].

These observations suggest that the p53-apoptotic pathway is silenced in human embryos even beyond the general activation

of embryonic gene expression, at least until the beginning of blastulation. In addition to TP53, several other genes involved in the regulation of apoptosis and DNA repair pathways, such as BRCA1, BRCA2, ATM, RB1, MAD2 and APC, were also shown to be underexpressed in human preimplantation embryos [6]. The lack of a robust DNA damage response mechanisms may explain the relatively high efficiency of CRISPR-Cas9 genome editing techniques, described in human zygotes and metaphase II oocytes [7, 8].

In conclusion, the above data strongly suggest that CRISPR-Cas9 gene editing can be used for gene therapy of human mature oocytes, zygotes and preimplantation embryos at least up to the late morula/early blastocyst stage without causing apoptosis-related DNA damage reactions or a selection against natural defense mechanisms, which could expose the offspring born from the edited embryos to an increased risk of cancer. This is encouraging for future development of CRISPR-Cas9 based preimplantation gene therapies, although further research is obviously needed to cope with the persisting doubts about other possible, apoptosis-unrelated, side-effects of this technique and to meet the highest demands of efficiency and safety required for its application in clinical practice.

References

1. Haapaniemi E, Botla S, Persson J, et al. CRISPR-Cas9 genome editing induces a p53-mediated DNA damage response. Nat Med. 2018; 24: 927-930.
2. Tesarik J, Kopecny V, Plachot M, et al. Activation of nucleolar and extranucleolar RNA synthesis and changes in the ribosomal content of human embryos developing in vitro. J Reprod Fertil. 1986; 78: 463-470.
3. Braude P, Bolton V, Moore S. Human gene expression first occurs between the four- and eight-cell stages of preimplantation development. Nature. 1988; 332: 459-461.
4. Tesarik J, Kopecny V, Plachot M, et al. Early morphological signs of embryonic genome expression in human preimplantation development as revealed by quantitative electron microscopy. Dev Biol. 1988; 128: 15-20.
5. Tesarik J. Involvement of oocyte-coded message in cell differentiation control of early human embryos. Development. 1989; 105: 317-322.
6. Wells D, Bermudez MG, Steuerwald N, et al. Expression of genes regulating chromosome segregation, the cell cycle and apoptosis during human preimplantation development. Hum Reprod. 2005; 20: 1339-1348.
7. Tang L, Zeng Y, Du H, et al. CRISPR/Cas9-mediated gene editing in human zygotes using Cas9 protein. Mol Genet Genomics. 2017; 292: 525-533.
8. Ma H, Nuria Marti-Gutierrez, Shoukhrat Mitalipov, et al. Correction of a pathogenic gene mutation in human embryos. Nature. 2017; 548: 413-419.