How safe is CRISPR?

The clustered, regularly interspaced, short palindromic repeats, or CRISPR/CRISPR-associated protein 9 (Cas9) (CRISPR-Cas9) system has revolutionised genetic manipulations and made gene editing simpler, faster and easily accessible to most laboratories. The technique has gained considerable traction recently to repair defective genes for potential therapeutic applications. Based on this promise, multiple clinical trials have been initiated in the U.S. and China (using the CRISPR-Cas9 system) to produce gene-edited cells for cancer and HIV-1 therapy.

However, is CRISPR ready for prime time and safe for clinical use?

What studies show

Last year, a study by Stanford University, U.S., found that the CRISPR-Cas9 system introduces unexpected off-target (outside of the intended editing sites) effects in mice. Although the manuscript describing the study results has since been retracted (due to the lack of proper controls ascribing a causal role of the CRISPR-Cas9 system in introducing off-target effects), the fear that the CRISPR system is being prematurely rushed for clinical use lingers. Three recent reports have exacerbated this fear even further.

Two studies, one from the Karolinska Institute, Sweden, and the other from the biopharmaceutical company Novartis, have highlighted that CRISPR-Cas9-edited cells might trigger cancer. The results from both studies were published last month in the scientific journal, *Nature Medicine*.

In the Karolinska study, the authors showed that the CRISPR-Cas9 system induced activation of a protein called P53. This P53 protein acts like a gatekeeper or guardian in the cells to keep them healthy and prevents them (the cells) from turning cancerous. In many cancers, cells lose their ability to repair deleterious genetic changes due to an impaired P53 function. Researchers in the study claim that a functional P53 protein swings into action in the target cell and repairs the edited site rendering the Cas9-mediated editing process ineffective. In cells where editing is adequate, the cell's P53 protein may be dysfunctional. Therefore, a functional pP53 protein is good for the cells to be healthy but makes the Cas9-mediated editing process less effective. On the contrary, a defective P53 protein is ideal for Cas9-mediated editing but makes the cells cancer-prone by introducing genetic changes elsewhere in the genome (outside of the editing sites).

Like in the earlier study, the Novartis study found that a high efficiency of the CRISPR-Cas9 system in human pluripotent stem cells (cells that can self-renew indefinitely in cell culture) is linked to the presence of a dysfunctional P53 protein. Pluripotent stem cells usually have very low editing efficiency due to high Cas9 toxicity in those cells. A possible workaround to decrease Cas9 toxicity and, therefore, enhance the editing efficiency by inhibiting P53 function may increase the risk of mutations elsewhere in the genome in those cells.

A third study, published this month in the scientific journal, Nature Biotechnology, and from the Wellcome Sanger Institute, U.K., provided further evidence for the unintended consequences of the CRISPR-Cas9 system.

The study found that both the mouse and the human gene edited cells suffered from large DNA deletions far from the intended editing sites. The scientists have argued that the commonly used techniques to screen for off-target effects may not be sufficient to identify the adverse-effects sites and comprehensive genomic analyses of the edited cells, using long-read DNA sequencing technology, may be required to pinpoint those.

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The studies, which have showed the dark side of the CRISPR-Cas9 editing system, have, however, not deterred those who think that the system is ready for the clinic. The proponents argue that mice with genome-edited cells developing cancer have not been reported and the cells with adverse studies are not the ones currently in clinical trials. The cautious ones, however, say that it's only a matter of time that a comprehensive whole-genome sequencing of the edited cells will show the adverse consequences of the CRISPR-Cas9 system. No matter which side wins, it will take years before the CRISPR system is ready for prime time and clinical use. It is no surprise, therefore, that George Church of Harvard University, a CRISPR pioneer himself, chose an older gene editing system TALEN over the CRISPR system to create virus-resistant human cells as the TALENs, although with less cleavage efficiency, have more editing precision.

View from India

What are the implications of such findings in India? Although there are no clinical trials or studies to use CRISPR-Cas9 edited cells in the clinic currently undergoing in India, blood-related disorders such as haemophilia, sickle cell anaemia, and Beta-Thalassemia, and other disorders such as Duchenne Muscular Dystrophy are promising candidates for gene editing. In fact, for many of these diseases, results from the proof-of-concept studies have been published from elsewhere. There are many Indian researchers actively working in this area, and for them, the recent studies provide a cautionary tale to conduct a comprehensive genomic analysis before moving to use the CRISPR-Cas9 edited cells in the clinic.

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