mRNA reprogramming: A review of methods and obstacles to the bedside

Benjamin Bunnell[1], Dhruv Patel[1], & Zachary I. Merhavy[1]

[1]**Ross University School of Medicine**

Introduction

mRNA programming of various cell types is an emerging area of molecular biology with therapeutic potential in the clinic. By reprogramming cells, scientists and clinicians gain access to novel therapeutic treatments that can help heal medical concerns ranging from cancers to organ repair. One relevant example of a successful breakthrough this technology has facilitated is the vaccine for COVID-19. This field has made progress but has obstacles to the bedside such as a low number of laboratory studies, measuring long-term effects, and a variable efficiency of reprogramming depending on the method of mRNA delivery to the cell.

Obstacles to the Bedside

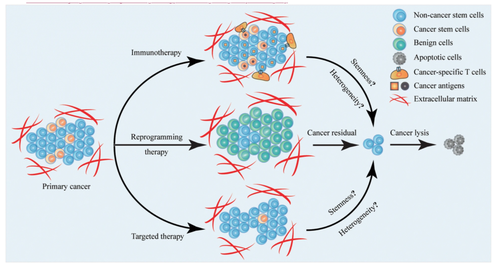
1.) The field needs more data to analyze
- o Accuracy of data
- o Potential unwanted long-term effects

2.) Public perception
- o More effective communication is needed between scientists and the public

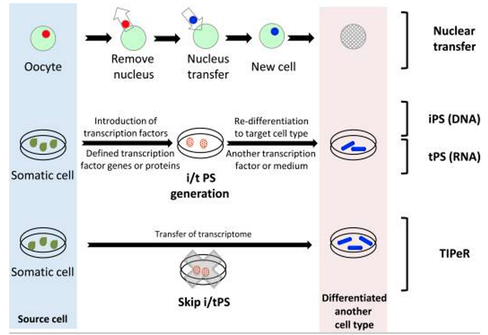
3.) Understanding how to practically apply this technology to patients
- o Accessibility
- o Not applicable in emergency cases

4.)Takes a lot of time to work
- o More time and studies are needed
- o RNA has been notoriously difficult to extract, purify, and use in the laboratory [1]

An Example of Theory and Current Research Methods



The above image is taken from a paper titled, "Cancer cell reprogramming: A promising therapy converting malignancy to benignity" by Gong, et al. [2]. Researchers have explored many avenues to combat cancer. Among these are manipulating the immune system, manufacturing medications to kill the affected cells, or reprogramming cancer cells into benign cells. The latter operates on the theory that cancer stem cells can cause a reemergence of the cancer. With reprogramming, one can convert cells to benign from malignant. To date, there are no clinical trials with this technology, as much more data is needed.



The image above is taken from, "Perspectives on Cell Reprogramming with RNA" by Sul, et al. This image shows a simplified diagram of the different uses of RNA to reprogram cells. The first is a somatic nuclear transfer into an oocyte that is fertilized. In the middle, transcription factors are used to dedifferentiate a somatic cell to an induced pluripotent stem cell (iPSC). At the bottom, there is a schematic showing how TIPeR methodology uses the transfer of transcription factors to transdifferentiate a cell. This is a small example of the various methods one can use for cellular reprogramming [3].

With mRNA reprogramming, somatic cells could be differentiated into any specialized cell. An overview of the method of reprogramming fibroblast cells was conducted by Kehler, et al. is mentioned below. A reprogramming medium was created consisting of human newborn foreskin fibroblasts to increase the efficiency of iPSC generation. Human dermal fibroblasts are reprogrammed into iPSCs using microRNA for priming followed by a daily delivery of mRNAs. The human dermal fibroblasts are then inserted into the reprogramming medium and incubated in a reduced O_2 incubator 2 hours before transfection to reduce triggering of innate immunity. Fibroblasts are transfected initially with mRNA to enhance cell division and make the cells more susceptible to reprogramming with mRNA followed by a daily transfection of Oct4, Sox2, Klf4, c-MYC, and Lin28 mRNAs, creating the mRNA transfection complex. Transfections are stopped once primary iPSC colonies are produced. These colonies then can be isolated and differentiated to the desired specialized cell [4].

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Conclusions

1.) mRNA reprogramming can be utilized to identify cancer cells and are able to reprogram them. Factors like oncogenes that increase the proliferation of cancer cells or tumor suppressor genes that are being suppressed could be identified and manipulated to stop the growth of cancer cells.

2.) Vaccines could be created from identifying the protein on the surface of pathogen or cells. This protein can then be synthesized through hiPSC to create an immune response against it. This method of creating vaccines could be more efficient with causing less adverse effects.

3.) Gene editing could be used with mRNA reprogramming to change the harmful effect of disruptive cells by changing the gene itself. Disease-causing cells could be identified and proliferated through mRNA reprogramming, which then CRISPER can be used to correct the mutations.

4.) Certain diseases result in the loss of functioning cells with no potential for the cells to be revived on its own. With mRNA reprogramming, cells that were damaged could be proliferated from another somatic cell to regenerate the loss of functioning cells.

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