Synthetic Biology: paving the way with novel drug delivery

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Synthetic biology is a multidisciplinary field that focuses on the rational design and construction of novel genetic tools for the purpose of engineering cells to behave in controllable and predictable ways. The promise of this modern technology relies on our understanding of basic genetics and gene expression to engineer cells with unique functions. This is accomplished by designing biological parts and assembling them into higher-order gene circuits that control cell operations through tight regulation of gene expression, effectively reprogramming and rewiring the cells. In this article, we review the basic concepts of gene expression, discuss the framework of how synthetic biologists reprogram cells and outline how cells can be engineered to function as new vehicles for delivering therapeutic proteins.

Introduction

Whether we like it or not, we are the genetic product of our biological parents. The phenomenon of heredity is central to the definition of life, and diversity is maintained because parents hand down genetic information that specifies all of the characteristics required for offspring to maintain their individual species identification. Higher organisms, such as mammals, are composed of groups of cells that perform specialized functions that are linked by complex molecular communication systems. Miraculously, we all started as a single cell that was first fertilized, then grew into full-fledged humans over the course of many years. In our bodies, we have at least 200 different cell types and each one has the same DNA in its genome. So, how do we acquire such an assortment of cells in our bodies? How is it that a muscle cell responsible for producing force and motion and a retinal cell responsible for carrying visual information from the eye to the brain can have such different functions, yet have the same exact DNA in its genome? This observation makes it clear that DNA alone does not necessarily dictate cell function. Rather, it is how a cell decodes its genome that ultimately dictates function, a feat accomplished by controlling which genes are expressed. We, as synthetic biologists, build genetic tools to alter this process for the purpose of programming cells with unique functions that will likely change how we approach diagnosing and treating disease.

How does this work?

Regardless of species, all cells process genetic information according to this hierarchy: DNA to RNA (transcription) and messenger RNA (mRNA) to protein (translation) (Figure 1A). This hierarchy is much like a construction site where construction workers (mRNA molecules) interpret the blueprint (DNA) to know which proteins (buildings) to make (Figure 1B). In general, more construction workers (mRNA molecules) means more buildings (proteins) are made. Overall, it is the sum of all mRNA molecules and the level of protein expression in each cell that specifies cell function that ultimately contributes to each tissue and organ function. Ensuring efficient and effective communication between all levels of the construction site is essential for maintaining operational performance—or the health of cells, where a breakdown in communication results in operational errors, or disease.

Cells are sophisticated information processors

Proteins are involved in almost every process in living cells. They coordinate the localization and the spatial organization of cells, perform biochemical reactions, and are essential for replicating and decoding the genomic information for cell specialization and function.
Altogether, cells integrate the use of proteins and RNA to construct interconnected biological networks that ensure proper function of their specialized cell types. Such networks allow the assembly of complex tissues, like the retina, that contain sophisticated neural signals that encode visual information that is relayed to the brain.

Cells naturally direct their behaviour by processing the many signals that surround them. A typical cell in a multicellular organism is exposed to hundreds of different signals in its environment. These signals can be soluble, bound to the surrounding extracellular matrix or bound to the surface of neighbouring cells, and they can act in concert to regulate cell behaviour. At their core, all cells are complex information-processing systems that have the remarkable ability to assess their surrounding environment, process this information, store relevant inputs and execute specialized cellular behaviour based on these inputs (Figure 2A). This information processing, or biocomputing, enables cells to navigate their environment and quickly adapt to changes in their surroundings, which is essential for regulating many cell processes. Disturbances in the ability of cells to regulate information-processing systems can lead to the development of disease (e.g. cancer, diabetes, etc.). This begs the question: is it possible to alter cell behaviour by reprogramming their biocomputers (Figure 2B)?!

**Hijacking cells with synthetic biology**

The field of synthetic biology is a discipline that seeks to control cellular behaviour using genetic tools to reprogram the native function of a cell by rewriting, or editing, a cell's blueprint to change which genes are expressed to execute a desired function. This is achieved using components of individual genes and assembling them into more complex genetic circuits that change a cell's behaviour (Figure 2C). These genetic circuits can be designed with predefined rules that enable processing specific inputs to make decisions about whether to execute an output. Boolean logic gates are at the core of programming cells with this ability: Boolean logic is a form of computing that can be engineered into cells where decisions are made based on input cues from the environment. The processed inputs have a threshold state of '0', and, if the signal is above the threshold, the cells respond by turning on an output. This type of cell programming has the potential to create 'smart cells' that are capable of detecting and treating disease. This is very important for diseases like cancer where successful therapy requires the discrimination between healthy cells and cancer cells. By further engineering cells to deliver a toxic protein when, and only when, they enter the target tissue AND recognize unique identifiers of cancer, we have the potential to reprogram our own cells to selectively kill malignant cancer cells.

Cell reprogramming has also shown promise for improving the stability of insulin and glucose levels in mice with type 2 diabetes, a condition that affects millions of people worldwide. Insulin is a hormone that is essential for regulating blood glucose levels in the body. Patients with type 2 diabetes struggle to control their blood glucose levels because they either do not produce enough insulin or their cells are resistant to it, resulting in dangerously
chemotherapy is to stop or slow the growth of cancer cells, but systemic treatment with chemotherapeutic agents has an exhaustive list of side effects due to uncontrollable off-target activity. Many patients suffer from health problems including nausea, vomiting, neuropathy, organ and tissue damage, and immune deficiencies for prolonged periods of time. Reengineering cells for the targeted delivery of therapeutic molecules has the potential to surpass traditional pharmaceutical approaches because cells can be programmed to sense a hostile environment and become activated to release therapeutic proteins. These therapies that can adapt to different patients and eradicate a wide range of cancer cells while avoiding systemic side effects have the potential to change the way we treat disease.

Conclusion

Our ability to treat disease is built on an understanding of the underlying molecular mechanisms that cause the disease in the first place. By constructing genetic circuits from highly defined genetic parts, we can begin to parse out the complexity of cellular dysregulation. As synthetic biologists, we combine genetic circuits into biological networks to probe cellular interactions, alter cellular behaviour, and, someday, change the way we diagnose and treat disease.

Using cells as novel delivery devices

Cells have an inherent therapeutic potential that is distinct from small molecule pharmaceutics because cells can be engineered to sense and respond to the changing physiological needs of the patient. There are many advantages to using cells as delivery devices for treating a range of illnesses and injuries because of their ability to: (i) interpret a diverse array of biological signals, (ii) circulate extensively throughout the body, (iii) move to specific sites in the body, (iv) self-regulate their response to changes in the environment and (v) function longer than pharmaceutical alternatives due to extended lifespans in the body. The most significant fault of pharmaceutical approaches is that they are systemic and impact the entire body. Current treatments for many diseases generally require systemic therapy. For example, the goal of high blood glucose levels. If left untreated, this increases the risk of heart disease, stroke, loss of sight and nerve damage. To address this, synthetic biologists have reprogrammed cells to control secretion of glucagon-like peptide 1 (GLP-1), a hormone that increases the sensitivity to insulin and boosts its production. When implanted into diabetic mice, these engineered cells have lowered blood glucose levels to within a healthy range.

Figure 2. Cells are sophisticated information processors. A) Cells (purple) are capable of receiving various inputs (blue ball), processing that information (biocomputer) and deciding the best output (pink ball). B) Engineering cells to behave in desired ways by reprogramming their biocomputer to change how inputs are processed by the cell to achieve a desired output (green ball). C) Cells' biocomputers can be engineered by taking individual genes (i) and assembling them into more complex genetic circuits (ii).
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