GEN
Genetic Engineering & Biotechnology News

BioPerspectives

Oct 10, 2013

Cell Therapy: Pushing Cells Around

Harnessing the power of cells as a therapy could transform medicine as we know it.

Eytan Abraham, Ph.D., Lena Pinzur

With the first stem **cell therapy** product approved recently in Canada and New Zealand, and with dozens of ongoing clinical trials, the concept of cell therapy is gaining ground. Cells are the basic functional unit of our body; they have the capacity to proliferate, regenerate, and induce healing processes. Understanding how to harness the power of cells as a therapy could potentially transform medicine as we know it.

One of the major differences between cells and current therapeutic agents is that cells are functional entities that can dramatically change. **Stem cells** can differentiate into various cell types; cells can change the composition of their membrane or secreted proteins thus altering the interactions with their surroundings, etc. To

By exposing the cells to conditions that cause them to respond in a certain way—for instance growing them in hypoxic conditions to "turn on" their proangiogenic properties prior to injection—scientists can optimize the cell biology prior to delivery and possibly significantly increase the cell potency and efficacy vis-à-vis ischemic indications.

function properly in vivo, cells must be capable of responding to a variety of stimuli, whether they're immune cells responding to inflammatory cytokines by becoming activated, endothelial cells responding to a change in blood flow by modulating the endothelial layer, or neurons excited in response to a neurotransmitter. The capacity of cells to sense and react is a basic and required trait and can be a huge advantage for cell therapy if harnessed correctly.

A testament to the plasticity of cells is the recent noble prize in medicine awarded to Sir John B. Gurdon and Shinya Yamanaka "for the discovery that mature cells can be reprogrammed to become pluripotent". This is potentially a significant advance in the field of cell therapy—no need for the ethically problematic use of embryos. Simply take almost any differentiated cell, induce pluripotency, and you have a stem cell. However, this therapeutic concept has many obstacles to overcome and most likely will not be routinely available in the immediate future.

Induced pluripotency is an extreme case of altering cell characteristics. Cells will also change in response to much more subtle alterations in their surrounding physical or biochemical conditions. Mesenchymal stem cells will differentiate into osteoblasts (bone cells) or adipocytes (fat cells), either by addition of certain factors to the media or merely by altering the stiffness of the substrate on which they are cultured. Cells that are cultured in low oxygen conditions dramatically change their gene expression and protein secretion. Cells cultured in three-dimensional (3D) environments differ biologically from cells that are cultured on two-dimensional (2D) surfaces. Many more examples exist, but the bottom line is that cells are responsive and sensitive to changes in their environment, and can be altered by employing fairly simple means.

Some may see this as an obstacle; how do we produce an efficacious and consistent cell product when the components of the drug are so sensitive to change? This is a valid question and indeed a challenge. We are beginning to understand that by employing consistent and robust manufacturing techniques, such as bioreactors and closed automated

systems, and by conducting rigorous in-process and release quality control tests, we can indeed manufacture stable, consistent, and efficacious cell therapies.

However, there is also a huge advantage in the fact that cells can respond to their environment and possess biological plasticity. The advantage is that we can manipulate cells to perform certain functions as needed. This means the ability to produce many products for many diseases using low-cost, abundant, and nonethically controversial cell sources. This approach is usually employed when the therapy mechanism of action (MoA) is cell differentiation and integration; in these cases cells are usually differentiated ex vivo by use of various factors and then introduced into the patient. However, ex vivo modulation of cell properties is also a promising technique for other cell therapy modalities.

MSC and Cell Therapy

An example that is more relevant for the short term is the use and potential manipulation of mesenchymal stromal cells (MSC). MSC are a promising cell type for cell therapy; these cells can be found in many tissues (bone marrow, adipose tissue, placenta, etc.). MSC have a limited differentiation capacity (as opposed to embryonic stem cells), are immune-quiescent, and it is becoming increasingly evident that in many cases MSC exert their therapeutic function by secretion of cytokines, chemokines, growth factors, etc. The secretome of MSC includes angiogenic factors, anti-inflammatory factors, immune-modulatory factors, antifibrotic factors, and more. But what determines exactly what proteins MSC secrete, and at what quantities? As with most cells, this depends on the environmental conditions in which the cell is present. MSC sense their environment and respond by altering gene expression, protein production, and the protein secretion profile. For example, an MSC placed under hypoxic conditions will in most cases increase the secretion of VEGF, a central angiogenic factor.

Currently, the common practice is for MSC to be harvested from a donor or from the patient, expanded by culturing under conditions deemed to be optimal for cell proliferation (glucose, pH, dissolved oxygen, etc.), collected, and injected to the patient. Once in vivo, it seems that MSC can sense the environment and alter their secretion profile accordingly to aid in healing.

Moreover, the cells are continuously adjusting to environmental signals; their secretory profile is dependent on the signals that the cells receive, thus cells will not “oversecrete”. However, this is a battle against time, since in most cases the majority of MSC disappear within several days of delivery; thus, the window for the cells to transform and act in response to the in vivo disease conditions is relatively short.

An alternative concept would be to alter the cells while still in vitro by changing the MSC culture conditions in a way that would “prime” them prior to delivery. By exposing the cells to conditions that cause them to respond in a certain way, for instance growing them in hypoxic conditions to “turn on” their proangiogenic properties prior to injection, we can optimize the cell biology prior to delivery and possibly significantly increase the cell potency and efficacy vis-à-vis ischemic indications. Moreover, by altering cell culture conditions prior to delivery, we may be able to coax cells, by inducing epigenetic changes, to perform functions and to secrete factors which they normally would not perform/secrete.

This example is true for many cell types and therapeutic modalities; by “pushing the cells around” during the in vitro cell culture process cells can be directed down a certain differentiation path, or altered to be less susceptible to immune rejection, or optimized to secrete required factors, and even primed to target a certain organ, all by modulating various aspects of their in vitro culture process. In other words, in cell therapy in many respects “the process is the product”.

The options are almost endless; we may be able to rely on one cell type, form an abundant and ethically acceptable source that could potentially be produced in-mass and at low-cost, to treat multiple diseases. This would be a significant step forward for the fledgling cell therapy industry.

Eytan Abraham, Ph.D., leads the Product Innovation group and Lena Pinzur leads the Basic Research and Preclinical group at Pluristem Therapeutics.