Cells as Therapeutic Agents

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# Table of Contents

1. **CAN WE USE CELLS AS THERAPEUTIC AGENTS TO RESTORE THE TISSUE FUNCTION?** ................................................................. 3  
   1.1. **Sources of Cells** .................................................................................................................. 3  

2. **HOW DO WE USE CELLS AS THERAPEUTIC AGENT FOR VARIOUS TISSUE DEFECTS?** .............................................................................................................. 4  
   2.1. **Cells used to restore the mechanical defects** ................................................................. 5  
   2.2. **Cells used to restore the metabolic defects** ................................................................. 7
1. Can we use cells as therapeutic agents to restore the tissue function?

Yes. Cells are the building blocks of tissues, which contribute to the respective functions. Cell based therapies are a distinct class where cells are utilized as therapeutic agents to treat the pathological conditions. However, cell-based therapies are not new because for many decades people are practicing blood transfusion to anemic patients to restore the oxygen supply. Similarly, platelet transfusion for blood clotting defects; bone marrow transplantation for cancer patients is widely practiced now.

Cell based therapies can also be used to repair the cartilage. Hepatocytes and kidney cells are also used extracorporeal support devices to carryout the functions of the liver and kidney respectively. Similarly, beta-islet cells for diabetes, sheets of fibroblasts for ulcers and burns, genetically modified myocytes for muscular dystrophy have also been used clinically with varying degrees of success. We will look in to how cells are used to treat various defects in a short while.

1.1. Sources of Cells

The fundamental question is from where do we get the cell?

There are different cell sources available. They are:

- Autologous: Cell can be taken from the donor and introduced back to donor itself i.e., where donor and recipient are same. Limited supply and the donor site surgery are the major drawbacks.

- Allogenic: Cells can be transferred from donor to recipient of same species. However, difficult to reduce the patients risk against the transplant antigens.
2. How do we use cells as therapeutic agent for various tissue defects?

To answer this question, we should first know what are the different types of tissue defects based on the functions? Tissue defects can be classified as mechanical, metabolic, synthetic, communication and combination defects based on the tissue functions. For example the major organ is affected in mechanical tissue defect is cartilage or bone since the major function of these tissues are providing the mechanical strength to the body. Similarly in case of metabolic defects, liver is the chief organ for metabolism. Hence is there any abnormality in the liver function leads to metabolic defect.
Pancreas is the prime organ for synthesis of hormone like insulin, which is a primary regulator for glucose metabolism. Thus any defect in the insulin production or dysfunction of pancreas will lead to synthetic defects. Nerve is the only organ used to communicate as well as coordinate all body functions. Hence, the dysfunction of nerve due to any injury will promote the communication defects. Skin is largest organ performing multiple functions including immunological barrier; vitamin metabolism; maintain homeostasis, and so on. Thus the defect in skin tissue is coming under combination defects.

Now let us see how cells can be used in the restoration of tissue functions.

2.1. **Cells used to restore the mechanical defects**

Let us take an example of cartilage tissue defect. First of all the major challenge in the functional cartilage restoration relies in the native structure of this tissue. That is, they are avascular (no blood vessels for nourishment), aneural (no innervations), and alymphatic tissue (absence of lymphatic capillaries). This tissue is an unusual biphasic tissue, which is made up of solid matrix called the extra cellular matrix (ECM) and fluid phase (synovial fluid).

The major component of cartilage is ECM where terminally differentiated chondrocytes will be dispersed at low densities. This architecture promotes frictionless surface with pain free motion. In aged population, osteoarthritis is the common problem where there is a deterioration of cartilage including loss of chondrocytes and ECM architecture. This deterioration cannot be repaired due to the lack of blood vessels resulting in acute pain during movement.

Cartilage defects in the knee can be treated by autologous transplantation. Briefly, biopsy is collected outside the affected area from the patients and subjected to enzymatic treatment where the chondrocytes will be harvested. These chondrocytes are sub-cultured for expansion and then injected back to
patient at the lesion. About 200,000 patients are undergoing this type of cell-based therapy every year.

Fig 2: Autologous transplantation of chondrocytes in osteoarthritic patients

Restoring Mechanical Function

Fig 2: Autologous transplantation of chondrocytes in osteoarthritic patients

Note: Can be viewed only on Acrobat Reader 9.0 and above
2.2. **Cells used to restore the metabolic defects**

Let us take liver as an example. Liver plays a major role in metabolism (protein, fats and carbohydrates), detoxification of foreign compounds, production of vital serum proteins (albumin and clotting factors) and production of bile for digestion. Loss of liver function is mainly by hepatitis C, cirrhosis or excessive alcoholism or even cancer. Whole organ transplantation can use to treat liver defect at the end stage. However, this has many disadvantages like immune reactions/rejections, limited supply of donor organs. Hence there are other some temporary approaches can be used mainly non-biological approach (Charcoal resins and dialysis) and biological approach such as blood exchange and animal organ perfusion. Extracorporeal hepatocyte based bioreactors are even used to culture human hepatocytes and can able to maintain the liver function in the form of bioartificial liver (BAL).

Hepatocytes are the chief cells present in the liver, which are highly proliferative cells. But the major problem is associated with the hepatocyte *in vitro* culture is transdifferentiation, that is the capacity of hepatocytes to differentiate into fibroblast. Thus, the phenotype of hepatocytes is lost within a week and then it become functionally inactive. Usually, a bioreactor with hollow fiber cartridge, charged with the immobilized hepatocytes (intraluminally or extraluminally) is used. This device is connected outside the body to blood or plasma circulation of patient. The hepatocytes can also be embedded in a collagen hydrogel to avoid hydrodynamic damage and then injected in the hollow fibers. Due to the hydrogel nature of the collagen, it contracts thus forming a lumen, which helps in the diffusion of medium and plasma. This type of extracorporeal device can improve the detoxification and synthetic and even regulatory function of diseased liver.