Stem Cells as Cellular Therapy and for Endogenous Repair

Learning Outcomes

- Understanding use of Haemopoietic Stem Cells and other Cellular therapies
  - Haematopoiesis : HSCs Haemopoietic Stem Cells
  - Bone marrow Transplantation as a Cellular Therapy for Blood Disorders
  - Complications of Haemopoietic Stem Cell Transplantation
  - Gene editing for Correction of Genetic diseases
  - Gene editing for Chimeric Antigen Receptor Immunotherapy

Genetic Basis Human

Every individual unique biological makeup is encoded within a single cell, specifically in the 46 chromosomes. These chromosomes contain all the developmental and functional programs inherited from the parents, which have been programmed and stored throughout evolution. This genetic information is highly ordered and regulated, governing gene expression patterns at specific stages and in different tissues, thus controlling intrinsic cell behavior. The genetic code acts as a living, mutable record of our evolutionary history, enabling the development from a fertilized blastocyst to a fully formed human being.

Overview of Stem Cells

Stem cells are undifferentiated cells with the capacity to regenerate all functional cells within a tissue. Totipotent stem cells, such as those formed immediately after fertilization, can develop into any cell type. When sperm fertilizes the ovum, under optimal conditions, a human develops, guided by these stem cells. Other tissue-specific stem cells are more restricted in their potential but still possess the ability to self-renew, meaning they can generate more stem cells. These cells are rare, often quiescent (inactive), and resistant to cytotoxic stresses, which is crucial for their survival during therapies.

Identification and Characteristics of Stem Cells

Stem cells can be identified by specific genes or surface protein markers, often used in research to locate and isolate them from tissues. Over recent decades, extensive research has focused on identifying stem cells in various tissues across humans and other species. Despite their rarity, stem cells are vital for tissue maintenance and repair, especially under environmental stresses such as infections, heat, or cytotoxic agents.

Role of Progenitor Cells and Tissue Repair

Not all tissues rely solely on stem cells for homeostasis and repair. Some tissues contain progenitor cells—more differentiated but still capable of proliferation and differentiation—that can develop into mature tissue cells without depleting the stem cell pool. These progenitors are particularly active during stress conditions, providing a rapid response for tissue maintenance. However, they cannot regenerate entire organ systems independently, which underscores the importance of stem cells in extensive tissue regeneration and organism survival.

Regeneration and Tissue Turnover

Humans continuously regenerate tissues through endogenous repair mechanisms. The current state of the body differs from a decade ago because cells are constantly dividing, differentiating, and dying to replace damaged or aged tissues. This process depends on the intrinsic ability of cells to proliferate and differentiate, influenced by environmental cues. For example, the gut epithelium undergoes constant renewal, with stem cells located in the crypts of villi, marked by genes like LGR5. These stem cells give rise to various cell types in the intestinal lining, maintaining gut integrity throughout life.

Examples of Tissue Regeneration

- **Intestinal tissue:** Continuous renewal from crypt stem cells, marked by LGR5 gene expression.
- **Liver:** Contains bipotential progenitor cells capable of becoming hepatocytes or cholangiocytes, with differentiation influenced by signaling pathways like TGF-beta (cholangiocytes) and extracellular matrix signals.
- **Lung:** Contains alveolar epithelial cells, such as those marked by Axin2+, which regenerate alveoli after trauma or infection like influenza.

These examples demonstrate how environmental signals and cellular context influence stem and progenitor cell differentiation, essential for tissue-specific regeneration.

Blood Stem Cells and Hematopoiesis

The concept of blood stem cells originated from experiments by Tiller McCulloch, who proposed that a single cell could regenerate the entire blood system. Bone marrow transplants confirmed that hematopoietic stem cells (HSCs) can reconstitute blood lineages, including red cells, white cells, and platelets. These stem cells are rare, quiescent, and resistant to cytotoxic stress, which allows patients to recover blood counts after chemotherapy or radiation therapy. Not all those stresses will call on those stem cells, and for example for bleeding and certain infections, a progenitor pool may be called upon that can repopulate the system without calling on the stem cells or needing the stem cells to be activated.

Properties of Hematopoietic Stem Cells

- **Pluripotency:** Ability to regenerate all blood components.
- **Self-renewal:** Capable of dividing to produce more stem cells.
- **Quiescence:** Usually inactive, residing in niches within the bone marrow.
- **Resistance:** Survive cytotoxic treatments, enabling recovery post-therapy.

Stem Cell Transplantation and Therapeutic Uses

Stem cell transplantation, especially allogeneic (from a donor), is used to treat blood disorders and cancers–overcome HLA barriers. Donor stem cells can reconstitute the recipient's blood system, especially after lethal treatments like chemotherapy. However, immune compatibility is critical; mismatched transplants risk rejection or graft-versus-host disease (GVHD), where donor immune cells attack the recipient's tissues. To mitigate this, immunosuppressive drugs are administered during transplantation.

Graft-versus-Leukemia Effect and Cancer Therapy

In cases of blood cancers such as leukemia, allogeneic transplants can be particularly effective because the donor immune system can recognize and attack residual cancer cells—a phenomenon known as the graft-versus-leukemia effect. This immune response significantly improves long-term remission rates, making bone marrow transplantation a pioneering form of immune therapy against cancer.

Introduction to Stem Cell Therapy for Blood Diseases

Stem cells are utilized to replace or repair damaged hematopoietic (blood-forming) systems. This approach is crucial in treating various blood disorders where blood cell production is impaired or abnormal. The primary goal is to restore normal blood cell function by replacing defective or diseased stem cells with healthy ones.

Replace of Repair Damaged or Disease Haemopoetic System

Stem cell therapy is used in several blood-related conditions, including:

- **Sickle cell anemia**: a genetic disorder causing abnormal red blood cells.
- **Thalassemia**: a hereditary anemia affecting hemoglobin production.
- **Bone marrow failure syndromes**: such as aplastic anemia and Fanconi anemia, where the marrow cannot produce sufficient blood cells.
- **Immunodeficiency syndromes**: genetic defects impairing immune function, which can be corrected by replacing the immune system with healthy blood stem cells from donors.
- **Blood cancers**: including acute leukemia and myelodysplastic syndromes, where stem cell transplantation can be curative.

Stem Cells and High-Dose Chemotherapy/Radiation Therapy

Stem cells enable the use of high-dose chemotherapy and radiation therapy, which are otherwise lethal due to their suppression of blood cell production. These treatments destroy cancer cells but also damage the bone marrow, leading to blood count decline. Stem cells are resistant to these therapies and facilitate rapid recovery of the blood system, making aggressive treatments feasible.

Amenable to Genetic Manipulation

- Genetic modification of stem cells to “correct” diseased haematopoietic system
- Haemoglobinopathies (Thalassaemia, Sickle Cell Anaemia: single gene disease)
- Genetic modification of other immune cells to “target” specific blood diseases (CarT cells)

Autologous Stem Cell Transplantation

In autologous transplantation, stem cells are collected from the patient before intensive therapy, then re-infused afterward. This accelerates blood count recovery, reduces infection risk, and minimizes bleeding complications. Although it lacks the graft-versus-leukemia effect, it allows for higher doses of chemotherapy, potentially leading to cures that would otherwise be impossible.

Allogeneic Stem Cell Transplantation

This involves transplanting stem cells from a healthy donor, either related or unrelated. The process includes:

1. Conditioning with chemotherapy and radiation to reduce tumor burden and create space in the marrow.
2. Immune suppression to prevent graft rejection and graft-versus-host disease (GVHD).
3. Engraftment of donor stem cells, which reconstitute the blood and immune systems.

The donor immune cells can also attack residual cancer cells, providing a graft-versus-leukemia effect, which is beneficial in treating certain cancers.

Historical Perspective and Donor Registry

The concept of bone marrow transplantation dates back to the 1950s, initially driven by radiation accident cases. Understanding the HLA (human leukocyte antigen) system was critical in reducing transplant complications like GVHD. Matching donor and recipient HLA types minimizes rejection and GVHD risks.

Donor registries worldwide facilitate finding suitable voluntary donors. Collection methods include: