Chapter 1

Introductory Chapter: Concepts of Tissue Regeneration

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Additional information is available at the end of the chapter

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1. Biology of regeneration

Regeneration means the re-growth of part of the affected or lost organs of the remaining tissue. Animals can regenerate some organs, such as the liver. If a part of the liver is lost due to illness or injury, the liver grows back to its original size, but not in its original form.

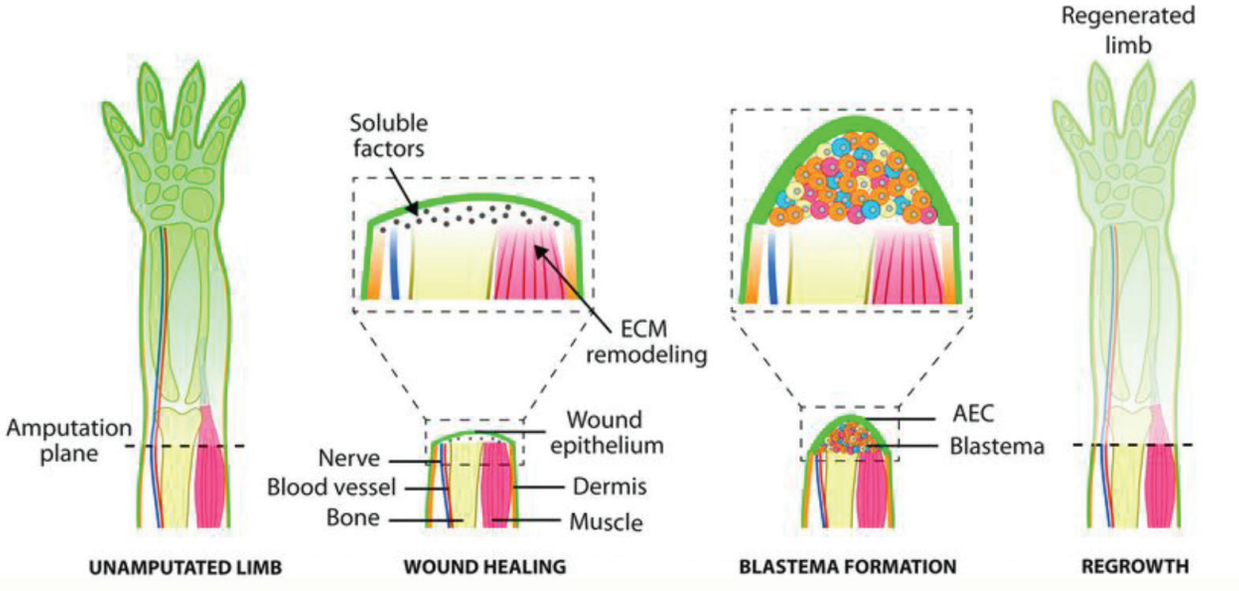

Figure 1. The amphibian renewal preceding amphibian growth may offer hints to humans. After amputation, the wound heals to form the skin layer, and the underlying tissue undergoes a matrix reshaping, and cells in the region secrete soluble factors. The heterogeneous cell mass, blastema, is formed by the proliferation and migration of cells from neighboring tissues. Next, the blastema leads to the appearance of different new tissues that are spatially plastered to reconstruct the structure of the original limb (credit: Lina et al. [1]).

Different species have significant capabilities to regenerate parts of the body or whole organism after injury (**Figure 1**), but a thorough understanding of the molecular basis of regeneration mechanisms will require detailed genomic resources.

2. Building blocks and matrix

2.1. Cells

Cells are building units of tissues and organs and tissues are the basic unit of function in the body. In general, cells secrete their own support materials and structures, which are called an *extracellular matrix*. This matrix, or scaffold, is supporting the cells; it also performs as a relay station for a number signaling molecules [2].

2.2. Messages/signals

Cells acquire messages through multiple sources that grow available from the local environment. Each signal can enhance or initiate a series of responses that decide what will happen to the cell. By understanding how individual cells react to signals, interact with their surrounding environment, and organize them into tissues and organisms, researchers can manipulate these processes to repair damaged tissue or even create new cells.

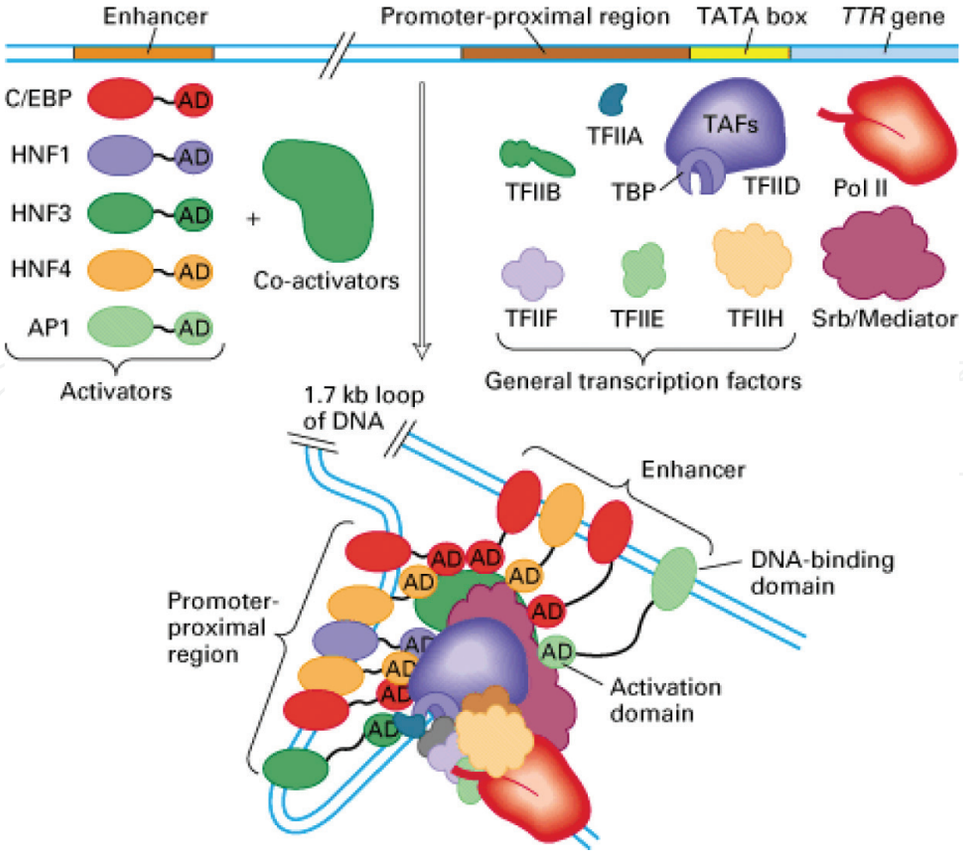

Figure 2. A view of a eukaryotic gene, its control elements in the DNA and the proteins that guide the RNA polymerase to the correct starting point for transcription [3].

In all organisms, a *DNA-dependent RNA polymerase* is performing the production of mRNA for protein synthesis or the various non-coding RNA molecules that are used in the cell. *Transcriptional control* is the main method to control what proteins (and nucleic acids) are produced in the cell, and in what amounts (**Figure 2**).

3. Stem cells and regeneration

Tissues in the human organism are generated, maintained, and repopulated by *stem cells* (**Figure 3**). These are specialized cells capable of cell renewal and can differentiate into different cell types in the human body. Stem cells have several differentiation programs; therefore, they possess information to allow them to become any cell in the body or a restricted cell type with a specialized function. These abilities make stem cells extremely useful for biomedical applications and regenerative medicine and have become the main molecular tool for these purposes. Skeletal muscles have some ability to regenerate and form new muscle tissue, while cardiac muscle cells do not regenerate. However, new research suggests that cardiac stem cells may be coaxed into regenerating cardiac muscles with new medical strategies. Smooth muscle cells have the greatest ability to regenerate.

Questions about how and why tissue regeneration attracts the attention of countless biologists, medical engineers, and doctors. Renewable capacity varies widely across organs and organisms and a range of model systems with different technical features and innovation strategies are studied. Several key issues common to natural regeneration are receiving new attention from improved models and approaches, including identification of innovative

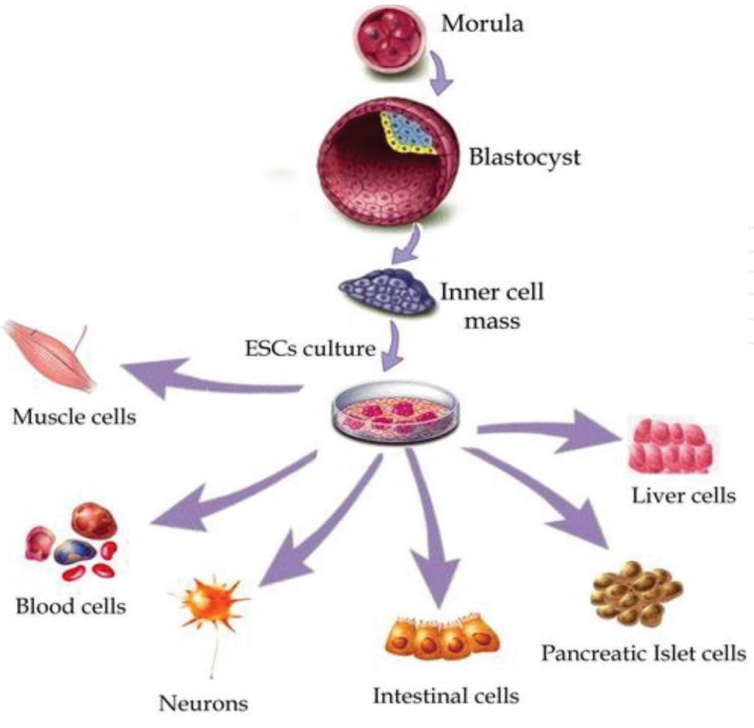

Figure 3. Induced pluripotent stem cells (iPSCs) were first created from human cells in 2007. These are adult cells that have been genetically converted to an embryonic stem cell-like state [3].

capacity; importance of stem cells, differentiation and differentiation; how regeneration signals begin and target; and mechanisms that control proliferation and renewed regeneration.

4. Regenerative medicine

Regenerative medicine is a new branch of medicine that tries to change the course of chronic diseases, and in many cases, regenerates organ systems that fail due to age, disease, damage, or genetic defects. The area has quickly become one of the promising treatment options for patients with tissue failure. It also includes tissue engineering, but also involves the search for self-healing—the body uses its own systems, sometimes with the help of foreign biological materials to reconstitute cells and rebuild tissues and organs. The terms "*tissue engineering*" and "*regenerative medicine*" have become highly interchangeable, with the field hoping to focus on treatments rather than complex and often chronic disease treatments.

Tissue engineering is an emerging biomedical field aimed at helping to restore physical tissue defects to the point of self-repair as well as replacing the biological functions of damaged and injured members using cells with reproductive and differential abilities. In addition to basic research on these cells, there is no doubt that successful tissue engineering is indispensable for creating an artificial environment that enables cells to stimulate tissue regeneration. Such an environment can be achieved using scaffolds for cell proliferation, differentiation, and growth factors, as well as combining them. Growth factors are often required to promote tissue regeneration, as they can stimulate the formation of blood vessels, which supply oxygen and nutrients to the transplanted cells to replace the organ to maintain its biological functions.

It requires functional platforms or scaffolds with specific properties concerning the morphology, chemistry of the surface, and interconnectivity to promote cell adhesion and proliferation. These requisites are not only important for cellular migration but also to supply nutrients and expulsion of waste molecules. Cell type must be considered when designing of using a specific cellular grown system as scaffold; for instance, if they are autologous, allogeneic, or xenogeneic. The challenge in tissue engineering is to develop an organized three-dimensional architecture with functional characteristics that mimic the extracellular matrix. In this regard, with the advent of nanotechnology, scaffolds are now being developed that meet most of the requisites.

The technology of tissue engineering has evolved from the development of biological materials (biomaterials) and refers to the practice of combining scaffolds, cells, and biologically active molecules of functional tissues. The aim of tissue engineering is to gather functional structures that restore, maintain, or improve damaged tissues or full organs. Artificial engineered skin and cartilage tissues are examples that have been recently authorized by the FDA [2].

The operation is usually initiated by building a scaffold from a wide range of potential sources, from proteins to plastics. When scaffolds are created, cells with or without a "mix" of growth factors can be introduced. Assuming that the environment is appropriate, the tissue grows. Sometimes, cells, scaffolds, and growth factors are mixed together simultaneously, giving the tissue the opportunity to "self-assemble" [2].

Different ways to create a new fabric or tissue is using the present scaffold. The donor tissue or organ cells are stripped and the maintained collagen scaffold is used to form a new tissue. A new tissue has been created in the biological engineering of the heart, liver, lungs, and kidney tissues in rat. This approach holds great promise for the use of scaffolds from human tissues that are discarded during surgery and integrated with the patient's own cells for the work of dedicated members that cannot be rejected by the immune system.

The tissue needs a good "draining and plumbing system" (veins or arteries), a way to feed nutrients into cells and carry waste. Without blood supply or any similar mechanism, cells die quickly. Ideally, scientists would like to be able to create engineered tissue using a plumbing system that has already been built (lattices). New hope for the bum knee: cartilage has been very difficult, if it is not impossible to repair since cartilage lacks a blood supply to promote regeneration. The gel/adhesive combo was successful in regenerating cartilage tissue following surgery in a recent clinical trial of patients.

5. The main goal of tissue regeneration

The main goal of tissue regeneration studies is to acquire knowledge that will enhance the new wide range of regenerative medicine. This information may include evidence to stimulate stem cell activity, structural engineering of better scaffolds or direct initiation of biologic regeneration programs. Scientists already understand some forms of regeneration enough to manipulate and modify major events for therapeutic reasons. For example, the common practice of bone marrow transplantation is to properly guide hematopoietic cells to regenerated blood cells. However, for most examples of innovation, research has begun to acquire knowledge and techniques to try to ban or enhance selective steps selectively during renewal.

5.1. Musculoskeletal tissues

Musculoskeletal injuries impact millions of people globally and affect their health and well-being as well as of their companion and athletic animals. Soft-tissue injuries represent almost half of these and are associated with unorganized scar tissue formation and long time-depending healing processes. Cell based therapeutic strategies have been developed in the past decades aiming at the treatment and reversion of such disorders. Stem cells are appealing in the field, being a responsive undifferentiated population, with ability to self-renew and differentiate into different lineages. Mesenchymal stem cells can be obtained from several adult tissues, including the synovial membrane. Synovia-derived mesenchymal stem cells can be found in individuals of any age and are associated to intrinsic regenerative processes, through both paracrine and cell-to-cell interactions, thus, contributing to host healing capacity. Studies have demonstrated the potential benefit of synovia-derived mesenchymal stem cells in these regenerative processes in both human and veterinary medicine.

5.2. Bone regeneration

Bone regeneration is a surgical technique (**Figure 4**) that uses barrier membranes to direct, or guide, the growth of new bone at the site of the defect. The principle is that the barrier

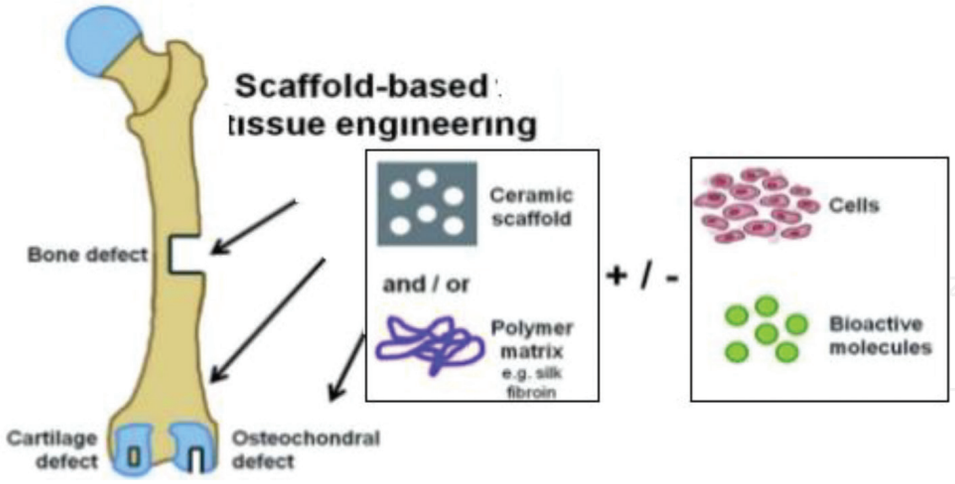

Figure 4. Bone scaffold: the bone capacity or the osteogenic potential of a bone graft is given by cells involved in bone formation, such as mesenchymal stem cells, osteoblasts, and osteocytes. The term osteoconductive refers to the scaffold or matrix which stimulates bone cells to grow on its surface [4].

membranes create and maintain a space above the bone defect; this allows the slower mesenchymal cells with osteogenic potential to populate the defect and regenerate without interference from the more quickly proliferating overlying soft tissues. Protection of the clot in the defect, exclusion of gingival connective tissue cells, and preparation of an enclosed space in which osteogenic cells can migrate from the bone are three essential elements of a successful outcome. Many types of grafts have been used as space maintainers between the membrane and the bone defect. Autografts, allografts, and xenografts have all been used successfully, either alone or in combination, for bone regeneration using particulate materials.

5.3. Applications

Tissue engineering currently plays a relatively small role in treating patients. Additional bladder, small arteries, skin grafts, cartilage, and even the entire trachea have been implanted in patients but the operation is still experimental and of high cost. While the more complex organ tissues such as heart, lung, and hepatic tissue have been successfully reconstituted in the laboratory, they are far from being entirely cloned and ready for transplantation in a patient. These tissues, however, can be very useful in research, especially in drug research [2].

Researchers have developed multi-capacity (pluripotent) stem cells that can be transformed into any type of cell in different types of specific areas and found that they controlled by very specific gene networks that determine the fate of cells. Most other medical research has focused on multivariate stem cells to modify the range of growth solutions in which cells are placed. Bone marrow stem cells in mature cells have been able to take stem cells along the way from multiple-capacity to bone maturation that can be implanted in a patient.

The ability to regenerate a new kidney from a patient's own cells would provide major relief for the hundreds of thousands of patients suffering from kidney disease. The resulting organ tissue was able to remove metabolites, re-absorb nutrients, and produce urine both in vitro and in vivo in rats. This process has been used previously in the heart, liver, and lung tissue.

The development of implantable tissue to replace renal function permanently is a promising hope in overcoming donor deficiency problems and morbidity associated with immunosuppression in transplantation.

One of the main challenges researchers face when trying to cultivate tissue engineering organs is to produce a scaffold, in which new cells can be implanted. While some scientists have followed three-dimensional printed scaffolds, many others focused on decellularization of local tissues to produce non-cellular scaffolds. The decellularization process typically consists of a series of perfused detergents through the organ, stripping the cells and nuclear material behind, and leaving the extracellular matrix. When developing decellularization protocols, researchers must balance the need for cellular material elimination with the need to maintain the properties of an extracellular matrix important.

Humans have limited regeneration ability, all the organ tissues can regrow, but it is very limited except the liver. Studies can find new methods to deal with regeneration. Recently, scientists are investigating the genes and factors which are active during regeneration. Scientists already understand some forms of regeneration sufficiently to manipulate and modify key events for therapeutic causes. So, in future, people will not need to use prosthesis, it will be more comfortable than using prosthesis because limbs will not lose their function and the regeneration of disabled people.

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