mechanisms of cellular proliferation and regeneration, and then the salient features of regeneration and healing by scar formation, and conclude with a description of cutaneous wound healing and fibrosis (scarring) in parenchymal organs as illustrations of the repair process.

Cell and Tissue Regeneration

The regeneration of injured cells and tissues involves cell proliferation, which is driven by growth factors and is critically dependent on the integrity of the extracellular matrix, and by the development of mature cells from stem cells. Before describing examples of repair by regeneration, the general principles of cell proliferation are discussed.

Cell Proliferation: Signals and Control Mechanisms

Several cell types proliferate during tissue repair. These include the remnants of the injured tissue (which attempt to restore normal structure), vascular endothelial cells (to create new vessels that provide the nutrients needed for the repair process), and fibroblasts (the source of the fibrous tissue that forms the scar to fill defects that cannot be corrected by regeneration).

The ability of tissues to repair themselves is determined, in part, by their intrinsic proliferative capacity. Based on this criterion, the tissues of the body are divided into three groups.

- **Labile (continuously dividing) tissues.** Cells of these tissues are continuously being lost and replaced by maturation from tissue stem cells and by proliferation of mature cells. Labile cells include hematopoietic cells in the bone marrow and the majority of surface epithelia, such as the stratified squamous epithelia of the skin, oral cavity, vagina, and cervix; the cuboidal epithelia of the ducts draining exocrine organs (e.g., salivary glands, pancreas, biliary tract); the columnar epithelium of the gastrointestinal tract, uterus, and fallopian tubes; and the transitional epithelium of the urinary tract. These tissues can readily regenerate after injury as long as the pool of stem cells is preserved.
- **Stable tissues.** Cells of these tissues are quiescent (in the G_0 stage of the cell cycle) and have only minimal proliferative activity in their normal state. However, these cells are capable of dividing in response to injury or loss of tissue mass. Stable cells constitute the parenchyma of most solid tissues, such as liver, kidney, and pancreas. They also include endothelial cells, fibroblasts, and smooth muscle cells; the proliferation of these cells is particularly important in wound healing. With the exception of liver, stable tissues have a limited capacity to regenerate after injury.
- **Permanent tissues.** The cells of these tissues are considered to be terminally differentiated and nonproliferative in postnatal life. The majority of neurons and cardiac muscle cells belong to this category. Thus, injury to the brain or heart is irreversible and results in a scar, because neurons and cardiac myocytes cannot regenerate. Limited stem cell replication and differentiation occur in some areas of the adult brain, and there is some evidence that heart muscle cells may proliferate after myocardial necrosis. Nevertheless, whatever proliferative capacity may exist in these tissues, it is insufficient to produce tissue regeneration after injury. Skeletal muscle is usually classified as a permanent tissue, but satellite cells attached to the endomysial sheath provide some regenerative capacity for muscle. In permanent tissues, repair is typically dominated by scar formation.

Although it is believed that most mature tissues contain variable proportions of continuously dividing cells, quiescent cells that can return to the cell cycle, and nondividing cells, it is actually difficult to quantify the proportions of these cells in any tissue. Also, we now realize that cell proliferation is only one pathway of regeneration and that stem cells contribute to this process in important ways.

Cell proliferation is driven by signals provided by growth factors and from the extracellular matrix. Many different growth factors have been described; some act on multiple cell types and others are cell-selective (Chapter 1, Table 1-1). Growth factors are typically produced by cells near the site of damage. The most important sources of these growth factors are macrophages that are activated by the tissue injury, but epithelial and stromal cells also produce some of these factors. Several growth factors bind to ECM proteins and are displayed at high concentrations. All growth factors activate signaling pathways that ultimately induce the production of proteins that are involved in driving cells through the cell cycle and other proteins that release blocks on the cell cycle (checkpoints) (Chapter 1). In addition to responding to growth factors, cells use integrins to bind to ECM proteins, and signals from the integrins can also stimulate cell proliferation.

In the process of regeneration, proliferation of residual cells is supplemented by development of mature cells from stem cells. In Chapter 1 we introduced the major types of stem cells. In adults, the most important stem cells for regeneration after injury are tissue stem cells. These stem cells live in specialized niches, and it is believed that injury triggers signals in these niches that activate quiescent stem cells to proliferate and differentiate into mature cells that repopulate the injured tissue.

Mechanisms of Tissue Regeneration

The importance of regeneration in the replacement of injured tissues varies in different types of tissues and with the severity of injury.

- In labile tissues, such as the epithelia of the intestinal tract and skin, injured cells are rapidly replaced by proliferation of residual cells and differentiation of tissue stem cells provided the underlying basement membrane is intact. The growth factors involved in these processes are not defined. Loss of blood cells is corrected by proliferation of hematopoietic stem cells in the bone marrow and other tissues, driven by growth factors called colony-stimulating factors (CSFs), which are produced in response to the reduced numbers of blood cells.
- Tissue regeneration can occur in parenchymal organs with stable cell populations, but with the exception of the liver, this is usually a limited process. Pancreas, adrenal, thyroid, and lung have some regenerative capacity. The surgical removal of a kidney elicits in the remaining kidney a compensatory response that