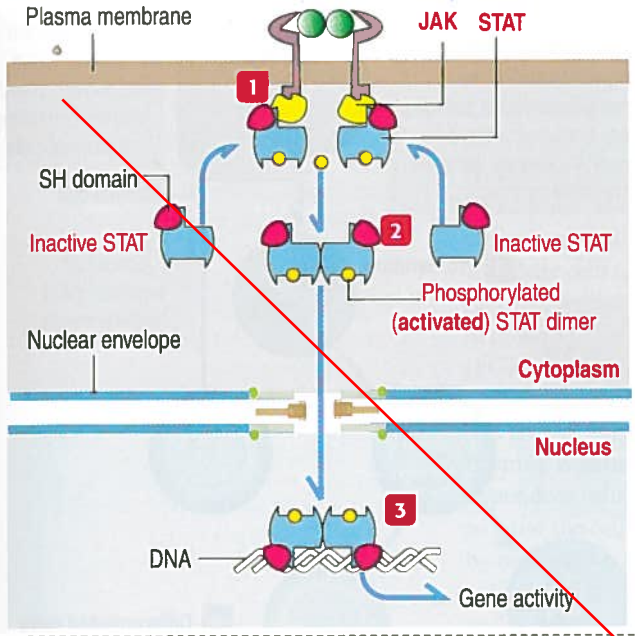
Figure 3-10. JAK-phosphorylated STAT dimer pathway



The JAK-STAT pathway

1. Ligand binding to a cytokine receptor leads to the attachment of the inactive transcription factor STAT to the receptor-associated **JAK protein tyrosine kinase** via their **SH2 domains**.
2. Phosphorylated **STAT dimerizes**.
3. The phosphorylated STAT dimer translocates to the nucleus where it activates transcription of target genes.

Transcription factor genes: *SOX9*

Genes encoding proteins that turn on (activate) or turn off (repress) other genes are called transcription factors. Many transcription factors have common DNA-binding domains and can also activate or repress a single target gene as well as other genes (a cascade effect). Therefore, mutations affecting genes encoding transcription factor have **pleiotropic effects** (Greek *pleion,* more; *trope*, a turning toward).

Examples of transcription factor genes include homeobox-containing genes, high mobility group (HMG)-box–containing genes, and the T-box family.

The HMG domain of Sox proteins can bend DNA, and facilitate the interaction of enhancers with a distantly located promoter region of a target gene. Several *SOX* genes act in different developmental pathways. For example, Sox9 protein is expressed in the gonadal ridges of both genders but is up-regulated in males and down-regulated in females before gonadal differentiation. Sox9 also regulates chondrogenesis and the expression of type II collagen (see Chapter 4, Connective Tissue). Mutations of the *SOX9* gene cause skeletal defects (campomelic dysplasia), and sex reversal (XY females).

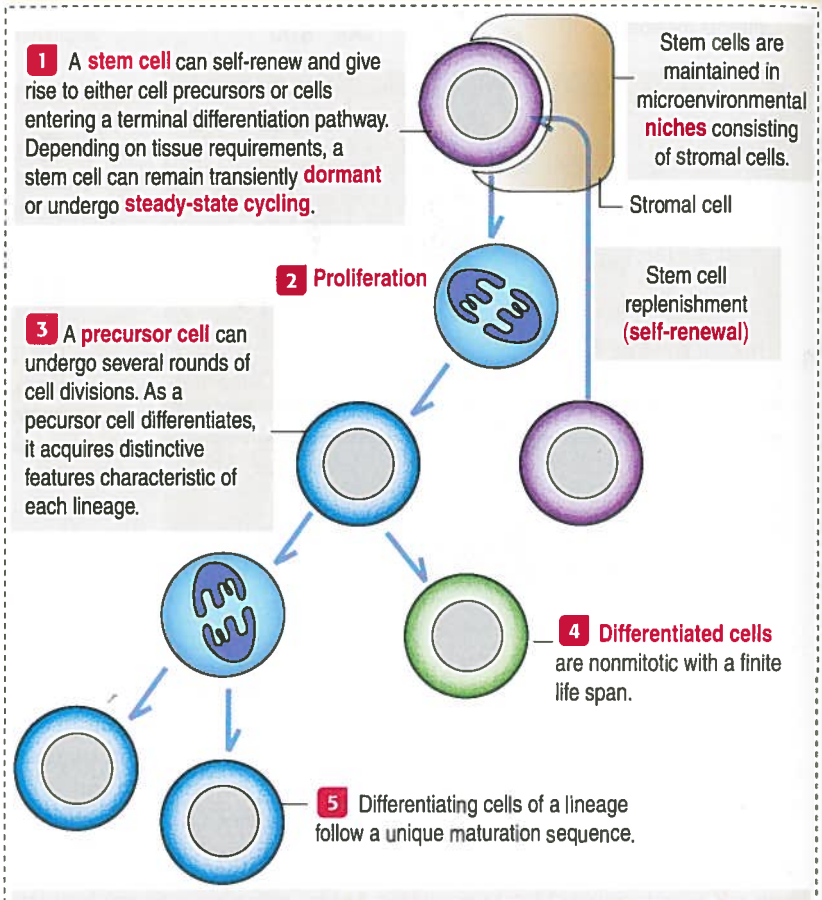
Stem cells: A multipotent cell population

Cells in the body show a remarkable range in ability to divide and grow. Some cells (for example, nerve cells and erythrocytes) reach a mature, differentiated state and usually do not divide. Such cells are referred to as **postmitotic cells**. Other cells, called **stem cells**, show continuous division throughout life (for example, epithelial cells lining the intestine and stem cells that give rise to the various blood cell types). Many other cells are intermediate between these two extremes and remain quiescent most of the time but can be triggered to divide by appropriate signals. Liver cells are an example. If the liver is damaged, cell division can be triggered to compensate for the lost cells.

Stem cells have three properties: **self-renewal**, **proliferation**, and **differentiation**. These properties depend on their specific microenvironment, called **stem cell niche**, that supplies the required factors for their development.

Stem cells have the potential to generate a large number of mature cells continuously throughout life. When stem cells divide by mitosis, some of the progeny differentiates into a specific cell type. Other progeny remains as stem

Figure 3-11. Properties of stem cells



Stem cells have three characteristics: **self-renewal**, **proliferation**, and **differentiation** into mature cells. Stem cells are housed in **niches** consisting of stromal cells that provide factors for their maintenance.

Stem cells of the embryo can give rise to cell precursors that generate all the tissues of the body. This property defines stem cells as **multipotent**.

Stem cells are difficult to identify morphologically. Their identification is based on specific **cell surface markers** (cell surface antigens recognized by specific monoclonal antibodies) and on the lineage they generate following **transplantation**.

Three typical examples are the stem cells of **bone marrow**, **intestine**, and **testes**.

cells (Figure 3-11). The intestinal epithelium, the epidermis of the skin, the hematopoietic system, and spermatogenic cells of the seminiferous epithelium share this property. We discuss in detail the significance of stem cells in each of these tissues in the appropriate chapters.

Following stress and injury, other tissues, such as the liver, muscle, and the nervous system, can regenerate mature cells. For example, it has been shown that bone marrow stem cells can produce muscle tissue as well as hematopoietic tissue in an appropriate host system (see Chapter 7, Muscle Tissue). Cultured stem cells of the central nervous system are capable of hematopoiesis in transplanted irradiated mouse recipients.

Recall that embryonic stem cells, forming the **inner cell mass (embryoblast)** of the early embryo (the blastocyst), give rise to all the tissues and organs except the placenta. Embryonic stem cells provide an experimental source of medically useful differentiating tissues such as pancreatic islets for the treatment of diabetes, skin for the treatment of burns and wounds, regenerating cartilage for the treatment of arthritis, and endothelial cells for the repair of blood vessels affected by arteriosclerosis. A potential complication is that embryonic stem cells injected into mature mice develop an embryonic tumor called a **teratoma**.

Pour en savoir plus!

In vitro cell proliferation, senescence, and telomerase

Cell culture techniques have been a powerful tool for examining the factors that regulate cell growth and for comparing the properties of normal and cancer cells.

Many cells grow in tissue culture, but some are much easier to grow than others. Culture medium contains **salts**, **amino acids**, **vitamins**, and a source of energy such as **glucose**. In addition, most cells require a number of **hormones** or **growth factors** for sustained culture and cell division. These factors are usually provided by addition of **serum** to the culture medium.

For some cell types the components supplied by serum have been identified, and these cells can be grown in **serum-free, hormone and growth factor–supplemented medium**. Some of these factors are hormones, such as insulin. A number of growth factors have been identified, for example, EGF, fibroblast growth factor (FGF), and PDGF.

When normal cells are placed in culture in the presence of adequate nutrients and growth factors, they will grow until they cover the bottom of the culture dish, forming a monolayer. Further cell division then ceases. This is called **density-dependent inhibition of growth**. The cells become quiescent but can be triggered to enter the cell cycle and divide again by an additional dose of growth factor or by replating at a lower cell density.

Cells cultured from a tissue can be kept growing and dividing by regularly replating the cells at lower density once they become confluent. After about 50 cell divisions, however, the cells begin to stop dividing and the cultures become **senescent**. The number of divisions at which this occurs depends on the age of the individual from which the initial cells were taken. Cells from an embryo will thus keep growing longer than cells taken from an adult.

In our discussion of mitosis (see Figure 1-53 in Chapter 1, Epithelium), we call attention to the role of **telomerase**, an enzyme that maintains the ends of chromosomes, or **telomeres**.

In normal cells, insufficient telomerase activity limits the number of mitotic divisions and forces the cell into **senescence**, defined as the finite capacity for cell division. **Telomere shortening and the limited life span of a cell are regarded as potent tumor suppressor mechanisms**. Most human tumors express **human telomerase reverse transcriptase** (hTERT). The ectopic expression of hTERT in primary human cells confers endless growth in culture. The use of telomerase inhibitors in cancer patients is currently being pursued.

Occasionally, cells that would normally stop growing become altered and appear to become **immortal**. Such cells are called a **cell line**. Cell lines are very useful experimentally and still show most of the phenotype and growth characteristics of the original cells.

An additional change known as **transformation** is associated with the potential for **malignant growth**. Transformed cells no longer show normal growth control and have many alterations, such as **anchorage-independent growth**. Normal cells can grow when anchored to a solid substrate.

Cells in culture can be transformed by **chemical carcinogens** or by **infection with certain viruses** (tumor viruses). Tumor viruses will also cause tumors in certain host animals, but in different species they may cause ordinary infections. Cancer cells cultured from tumors also show the characteristics of transformation. We will discuss at the end of this chapter the role of retroviruses in carcinogenesis.

Apoptosis, or programmed cell death

Cell death occurs by necrosis or apoptosis. Under normal physiologic conditions, cells deprived of survival factors, damaged, or senescent commit suicide through an orderly regulated cell death program called **apoptosis** (Greek *apo*, off; *ptosis*, fall).

Apoptosis (Figure 3-12) is different from **necrosis**. Necrosis is a nonphysiologic