Abstract

The cell is the smallest structural and functional unit of living organisms, which can exist on its own. Therefore, it is sometimes called the building block of life. Some organisms, such as bacteria or yeast, are unicellular—consisting only of a single cell—while others, for instance, mammalians, are multicellular.
The human body is built from an estimated 100 trillion or $10^{14}$ cells. Such complex living systems have developed several levels of organization depending on each other, for example, organs, tissues, cells, and subcellular structures (Fig. 2.1). For the understanding of these biological systems, small units must be investigated at a time. The logical starting point for the examinations is the cell, since at the cellular level, all life is remarkably similar.

2.1 Introduction

The term cell comes from the Latin word cellula, meaning a small room. This descriptive name for the smallest living biological structure was chosen by Robert Hooke in 1665 when he compared the cork cells he saw through his simple microscope to the small rooms monks lived in.

The cell theory developed in the middle of the nineteenth century by Theodor Schwann, Matthias Jakob Schleiden, and Rudolf Virchow states that all organisms are composed of at least one cell and all cells originate from preexisting ones (Omnis cellula e cellula). Vital functions of an organism take place within cells, and all cells contain the hereditary information necessary for regulating cell functions and for transmitting information to the next generation of cells.

Modern research in cell biology is based on integration of originally distinct research areas. It combines cytology, the initial way to study cells using morphological techniques with biochemistry and genetics/molecular biology to reveal the principal mechanisms of cells.

2.2 Cell Architecture

Generally, two kinds of cells are discerned, eukaryotes and prokaryotes, which developed from a common ancestor (Fig. 2.2). Most prokaryotes are unicellular organisms; they are classified into two large domains, Bacteria and Archaea. Eukaryotic organisms may be single cell or multicellular organisms. The four
kingdoms of eukaryotic organisms are Fungi, Plantae, Protista, and Animalia. To the latter group, all mammalian species belong, including humans.

Schematic depictions of prokaryotic and eukaryotic cells are indicated in Fig. 2.3. One principal distinction is that the genetic material of eukaryotes is contained within a nucleus. Furthermore, the genetic material is less structured in prokaryotes than in eukaryotes, where it is organized in chromosomes. Prokaryotes are usually much smaller than eukaryotic cells. This results in a higher surface-to-volume ratio, which enables a higher metabolic and growth rate and thereby a shorter generation cycle. Eukaryotes, in contrast, have various membrane-bound functional units, termed organelles. These subcellular structures help to compartmentalize the cells and to provide optimal conditions for various metabolic reactions. As a result, many distinct types of reactions can occur simultaneously in eukaryotes, thereby increasing cell efficiency. The majority of organelles are found in all types of eukaryotic cells, however, with cell-specific characteristics. Plant cells are characterized by additional organelles such as chloroplasts (responsible for photosynthesis) and vacuoles (fluid-filled organelles maintaining, e.g., the cell shape, and serving as dynamic waste baskets).

### 2.3 Eukaryotic Cell Differentiation, Structure and Size

Although, the principal structural units of all eukaryotic cells are similar (Fig. 2.3), more than 200 different cell types build up the adult human body. Their cell shapes vary considerably. Usually, the shape is typical for concrete cell types and represents the manifestation of the cell-type-specific function and state of differentiation. For example, the distinctive biconcave shape of red blood cells optimizes
their flow in large blood vessels, their remarkable flexibility helps them to squeeze even through tiny capillaries, and their surface-to-volume ratio is optimized for CO₂/O₂ exchange (Fig. 2.4). Epithelial cells line all inner and outer surfaces and cavities of the body insuring contact with and at the same time forming barriers against the environment. As a consequence, they are densely packed, with only

Fig. 2.3 Principal structures of (a) prokaryotic and (b) eukaryotic cells
narrow space between them. Entirely different, nerve cells, conducting impulses over long distances, exhibit multiple afferent processes (dendrites) and one efferent process (axon, neurite). Axons innervating muscle fibers in the limbs might reach lengths of 1 m in humans. A cell-type-specific shape, however, is not static, but changes depending on the stage of differentiation, the functional state, and signals obtained from the environment.

The multiple cell types in complex organisms such as humans are specialized members of a multicellular community. For the sake of this community, most cells have lost features that allow for their independent survival, but instead became experts for certain activities as a result of cell differentiation. Cell differentiation starts early in embryogenic development. In principle, all cells derived from the zygote have an identical genome (genotype). However, different genes can be activated in daughter cells, which results in the expression of cell-type-specific protein subsets and in cell-specific functions and shapes (phenotypes).

In humans, only the totipotent stem cells at the morula stage (see chapter on reproduction) have the potential to differentiate into any cell type of the organism (Fig. 2.5). Per definition, a stem cell is not finally differentiated and has the capability of unlimited self-renewal (as part of an organism), and upon cleavage, their daughter cells may either remain a stem cell or differentiate (asymmetric cleavage). Even in adults, multipotent stem cells exist (adult or somatic stem cells) and contribute to tissue homeostasis and repair. Major populations are the hematopoietic stem cells, which form all types of blood cells in the body; the mesenchymal stem cells, which, e.g., produce bone, cartilage, fat, and fibrous connective tissue; or the neural stem cells, generating the main phenotypes of the nervous system. The maintenance of the stem cell features relies, however, on their interaction with specific microenvironments called “stem cell niches.” These niches regulate the division of the stem cells, ensuring on one hand their survival and protecting on the other hand the organism from exaggerated stem cell proliferation. Among the regulating niche factors are cell-cell interactions, cell-matrix interaction, oxygen tension, and absence or presence of certain metabolites.

The specialized, differentiated adult body cells were thought for long to represent the end point of the differentiation pathway. Research aimed to replace lost or damaged tissue by differentiation of embryonic or adult stem cells. Recent year’s research now suggests that “reprogramming” of certain differentiated cell types into others could also be possible by a well-controlled process of genetic modification. This strategy may offer an additional possibility for tissue replacement.
Sizes and diameters of most eukaryotic cell types range from 5 to 20 μm (e.g., erythrocytes 7.5 μm, granulocytes 10–15 μm) up to 150–300 μm, which is the size of the oocytes in the female ovaries. Hepatocytes, an example of medium-sized cells, have a diameter of 20–40 μm. The relation of eukaryotic cells to other living organisms, structures, and smaller molecules is indicated in Fig. 2.6. Due to their small size, cells and their subcellular structures are invisible to the naked eye; their visual analysis requires the use of different types of microscopical techniques.

**2.4 Important Molecules of Life**

Besides all differences in function and form, all cells are built according to a common concept using similar molecules and metabolic processes. Usually, water, ions, and small organic molecules make up 75–80 % of the cell mass. More complex polymers (Fig. 2.7) serve for specific purposes. **Deoxyribonucleic acid** (DNA) a polymer of four nucleotides (deoxyadenosine monophosphate, deoxyguanosine monophosphate, deoxycytidine monophosphate, and deoxythymidine monophosphate) is used to
Fig. 2.6 Comparison of the sizes of eukaryotic cells (green) with subcellular elements, prokaryotic cells, and multicellular organisms.

Fig. 2.7 Some major ubiquitously used cellular molecules. DNA deoxyribonucleic acid, RNA ribonucleic acid, ATP adenosine triphosphate, ade purine base adenine, rib pentose sugar ribose, $P$ phosphate group.
encode and store the genetic information in the nucleus and to pass the information to the next cell generation following replication and mitotic division (see chapter on reproduction). Various forms of ribonucleic acids (RNA) are used for the process of gene expression and regulation of gene expression. Messenger RNA (mRNA), for example, is a single-strand copy from a DNA made during transcription. After export from the nucleus, it serves as a template for protein synthesis from amino acids during translation. Proteins execute the myriad of cellular functions required to ensure living. Lipid bilayers separate cell compartments. Various types of polysaccharides (e.g., glycogen) are used to store energy, and molecules like adenosine triphosphate (ATP) are common tools to capture and transfer energy via high-energy bonds.

2.5 Cell Organelles in Animal Cells

Eukaryotic cells are divided into nucleus and cytoplasm, surrounded by the plasma membrane; the cytoplasm is further subdivided into the cytosol, the intracellular fluid, and organelles (see Fig. 2.3b). Analogous to organs, which are discrete functional units within an organism, organelles are compartments with specialized tasks within a eukaryotic cell. Most organelles are delimited by enclosing membranes, the nucleus being a prominent example. However, when organelles are defined by their tasks and specific functions, structures without the delimiting membrane, such as the ribosomes, the centrosome, or the cytoskeleton, may also be defined as organelles. The uniqueness of organelles is, at least partially, defined by their specific protein composition. Most cellular proteins are found only in one or a few compartments. The signals for this specific localization are defined by the amino acid sequence of the protein.

2.5.1 The Nucleus

The nucleus is the most obvious organelle in eukaryotic cells. It is enclosed by a double membrane (nuclear envelope) and communicates with the cytosol via numerous nuclear pore complexes. Within the nucleus the information to build all cellular components is stored. The memory medium is DNA (Fig. 2.7), which in humans has a total length of 2.3 m. The DNA consists of two complementary strains, which are known as the double helix. While for information storage only the coding strain is required, this helix structure increases stability. Within the DNA molecule, triplets of four bases (adenine, guanine, cytosine, thymine) code for each single amino acid. Twenty different amino acids are used to build up proteins.

The separation of the DNA from other subcellular structures became necessary when eukaryotes reached a higher level of differentiation and therefore increased their DNA content by up to 100-fold over prokaryotic cells. To prevent a tangle of
the long DNA molecules, the DNA was not only separated within the nucleus but also split into smaller units (chromosomes) and highly compacted using, e.g., specific proteins such as histones.

The major processes which take place in the nucleus are replication of DNA, transcription of DNA sequences into mRNA molecules, and the processing of mRNA molecules, which are exported to the cytoplasm (see Fig. 2.7). Translation of mRNA into proteins is done outside the nucleus on specific organelles (ribosomes), which are preformed at distinct regions in the nucleus, the nucleoli. Ribosomal subunits are exported through nuclear pore complexes into the cytoplasm.

Following translation, proteins are imported into the various cell organelles by three main mechanisms: (1) Proteins moving from the cytosol into the nucleus are transported through nuclear pores. Pores function as selective gates, which actively transport macromolecules but also allow free diffusion of smaller molecules. (2) Proteins moving from the cytosol into the endoplasmic reticulum (ER), mitochondria, or peroxisomes are transported across organelle membranes by protein translocators (chaperones). Finally, (3) proteins moving from one compartment to the next along the biosynthetic or endocytic pathway are transported via membrane-enclosed transport vesicles.

### 2.5.2 Membranes

All cells are surrounded by the plasma membrane, which on one hand serves as a boundary separating and protecting cells and on the other hand provides communication and exchange with the environment. The framework of the membranes is made up of phospholipids, amphipathic molecules that exhibit a hydrophilic head and a hydrophobic tail region, in which proteins/glycoproteins are distributed (Fig. 2.8). Based on the physicochemical properties of the membranes, the fluid mosaic model has been defined, emphasizing stability and high mobility at once; lipids and to a less extent proteins are highly mobile within the plane of the membrane, a basal feature for many cell functions.

The plasma membrane encloses the cell body. Endomembranes in the interior divide specific metabolic compartments (organelles) surrounded by the cytosol, a complex mixture of molecules in water. Membranes are composed of lipids (phospholipids, cholesterol, glycolipids) and proteins in a rough proportion of 2:1. However, there are great variations with extremes exemplified by mitochondrial cristae membranes (high protein content due to the enzymes of the respiratory chain) or nerve myelin sheets (high lipid content). The fluidity of membranes is defined by the length of the fatty acid chains, the amount of unsaturated bindings, and the amount of cholesterol molecules. Cholesterol stabilizes the membranes and reduces the fluidity.

Embedded proteins act as channels, protein pumps that move different molecules in and out of cells, enzymes, or linker proteins. The membrane is said to be semipermeable, in that it can either let a substance (molecules or ions) pass
through freely, pass through to a limited extent, or not pass through at all. Cell surface membranes also contain receptor proteins that allow cells to detect external signaling molecules such as hormones as well as nutrients (ligands).

Glycolipids mark the outer leaflet of the plasma membrane (directed to the extracellular space) and their oligosaccharide chains protrude from the cell surface. Together with the sugar chains of the glycoproteins, they form the surface coat (glycocalyx) covering the surface of all cells. These sugar chains hold a variety of functions, which range from receptor activity to cell recognition; they are major determinants of the blood group systems and responsible for surface protection of the intestinal or urinary tract.

2.5.3 Endocytosis and Endosomes

Endocytosis is the general term for the uptake of external materials into cells via formation of membrane pits and vesicles at the plasma membrane.

Uptake of particular substances (microorganisms, cells, cell fragments) is termed phagocytosis (cell eating) and is done by specific types of cells (macrophages, granulocytes). Phagocytosis plays a major role in the immune system, tissue remodeling, and cell renovation.

In contrast, all cells form endocytic vesicles with 50–150 nm in diameter (cell drinking). They either contain fluid with dissolved molecules, resulting in fluid-phase endocytosis or specific molecules, which are bound and taken up via receptors. The latter process is termed receptor-mediated endocytosis. In the first case molecules are taken up nonspecifically, according to their concentration in the extracellular fluid. On the contrary, receptor-mediated endocytosis is highly specific and regulated and enables the enrichment of molecules. In the course of vesicle formation, protein complexes are formed on the cytosolic face of the plasma membrane (coat formed by proteins such as clathrin, coatomer proteins, or caveolin), which enable the structural changes of the membrane during
invagination, pinching off, and formation of vesicles. Adaptor protein complexes selectively link receptors and coat proteins. Many surface receptors have specific amino acid sequences in their cytoplasmic parts, which guide them into coated pits and allow efficient uptake of receptors and ligands. Resulting coated vesicles then rapidly shed their coat and fuse with early endosomes. Molecules taken up by receptor-mediated endocytosis are for instance nutrients such as low-density lipoproteins or iron-containing transferrin as well as aged molecules such as asialoglycoproteins.

Material taken up via endocytosis is further metabolized via early endosomes, multivesicular bodies, and late endosomes. The main function of endosomes is the sorting of molecules to different destinations within the cell (lysosome, cell surface). Hereby, the downregulation of pH via proton pumps (acidification) within the endosomes plays an important role. A gradual acidification of the endosomal lumen induces the release of receptors and bound ligands. While most of the receptors recycle back to the plasma membrane for reuse, most ligands end up in lysosomes for degradation and/or utilization in anabolic processes.

### 2.5.4 Cellular Degradation, Proteasomes and Lysosomes

Two major proteolytic systems contribute to the continuous removal of intracellular components.

The **ubiquitin/proteasome system** plays a major role in the maintenance of cellular homeostasis and protein quality control and in the regulation of essential cellular processes. The proteasome is a large cytosolic protein complex with proteolytic activity for degrading of unneeded or damaged proteins that have been marked for degradation by ubiquitination.

**Lysosomes** are membrane-bound organelles specialized for intracellular digestion of macromolecules. They contain ~40 different acid hydrolases that operate best at a low pH (pH 4.5–5.0) and carry out controlled digestion of cellular and extracellular materials. Their unique membrane proteins are unusually highly glycosylated; thus their sugar residues facing the lumen prevent the enzymes inside from destroying the cell. The lysosome’s membrane stabilizes the low pH by pumping in protons (H+) from the cytosol via ATP-driven proton pumps. The digestive enzymes and lysosomal membrane proteins are synthesized in the **endo-plasmic reticulum (ER)** and transported through the **Golgi apparatus** and the **trans-Golgi network (TGN)**. Along this route, lysosomal proteins, after being tagged with a specific phosphorylated sugar group (mannose-6-phosphate—Man-6-P) are recognized by an appropriate receptor. They are sorted out from the biosynthetic secretory pathway and packaged into transport vesicles, which deliver their content via late endosomes to lysosomes.
2.5.5 The Biosynthetic Pathway and Associated Organelles: Endoplasmic Reticulum and Golgi Apparatus

The biosynthetic pathway defines the route of molecules from the site of protein synthesis to the site of their final destination. Starting point is the transcription of one strand of DNA into a complementary mRNA which in a next step is decoded to produce a polypeptide chain specified by the genetic code (translation, see Fig. 2.7). Translation is done at the ribosomes in the cytoplasm; these ribonucleoprotein aggregates are composed of a large and a small subunit, which are assembled in the nucleolus and exported into the cytoplasm. The subunits form the ribosome upon arrival of mRNA strands in the cytoplasm and start translation. Ribosomes either remain in the cytosol (free ribosomes) for translation of cytosolic, nuclear, peroxisomal, and mitochondrial proteins or attach to the endoplasmic reticulum and become membrane-bound ribosomes, thereby forming the rough or granular endoplasmic reticulum (rER). Here, membrane, lysosomal, and secretory proteins are synthesized.

Usually, protein biosynthesis starts on free ribosomes in the cytosol. The exceptions are a few mitochondrial proteins that are synthesized on ribosomes within the mitochondria. The subsequent fate of proteins depends on their amino acid sequences, which may contain sorting signals that direct the proteins to the organelle in which they are required. Proteins that lack this signal remain permanently in the cytosol.

2.5.5.1 Endoplasmic Reticulum

The endoplasmic reticulum is a membrane system participating in synthesizing, packaging, and processing of various molecules. It is an anastomosing network (reticulum) of cisterns, vesicles, and tubules. Transfer vesicles bud from specialized regions and deliver their contents to the Golgi apparatus for further processing and packaging. In mature cells the ER occurs in two forms: the rough ER and the smooth ER, respectively.

The rough endoplasmic reticulum synthesizes proteins for sequestration from the cytosol, including secretory proteins such as enzymes (e.g., digestive enzymes in pancreas acinar cells) or extracellular matrix molecules, proteins for insertion into the plasma membrane, and lysosomal enzymes. All these molecules have the signal sequence in common that binds to a cytoplasmic signal recognition particle (SRP). The SRP-polyribosome complex again is recognized by an ER-docking protein. Via attaching of the ribosome to the ER membrane, the nascent polypeptide chains are translocated into the rER lumen. Signal peptides are then cleaved and nascent proteins undergo folding with the aid of ER-located molecular chaperones. The latter also assist in quality control in that they retain misfolded or unassembled protein complexes. If modifications are unsuccessful, proteins are degraded. Another important posttranslational modification in the ER is core (initial) glycosylation of the growing polypeptide chain.

The smooth endoplasmic reticulum (sER) lacks ribosomes and thus appears smooth in the electron microscope. The tubular-vesicular membrane system
contains enzymes important in lipid metabolism, steroid hormone synthesis, gluconeogenesis, and detoxification. It further plays a key role in regulating cytosolic calcium concentration by sequestering excess calcium. It is abundant in liver cells (hepatocytes), where it participates in glucose metabolism and drug detoxification. Specialized sER is found in striated muscle cells and regulates muscle contraction via sequestering and release of calcium ions.

### 2.5.5.2 Golgi Apparatus

The **Golgi apparatus** (GA) is the center of membrane flow and vesicle trafficking among organelles and has a key role in the final steps of secretion. The organelle is composed of stacks of flattened cisterns, vesicles, and vacuoles indicating the dynamic properties of the organelle. The *cis* face is usually close to the ER and is the entry of newly synthesized molecules. At the opposite side, the *trans* face, the TGN is the sorting, concentration, and packaging station for the completed molecules. Central functions of the GA are polysaccharide synthesis (terminal glycosylation), modification (e.g., sulfation of glycosaminoglycans, phosphorylation of lysosomal enzymes), and sorting of secretory products.

### 2.5.6 Peroxisomes

Peroxisomes are small membrane-bound organelles that use molecular oxygen to oxidize organic molecules and produce hydrogen peroxide (H₂O₂). With the aid of H₂O₂ and specific enzymes (e.g., catalase), peroxisomes oxidize and thereby detoxify various toxic substances such as alcohol. Oxidation reactions are also used to break down fatty acids in a process known as β-oxidation. The end products are then used in anabolic reactions. About 20 metabolic disorders caused by genetic anomalies result in defects in peroxisome function; range and severity of symptoms vary greatly, including biogenesis disorders and multi- or single-enzyme disorders. Among the different cell types, peroxisomes exhibit a high diversity with respect to their enzyme content and, additionally, they can adapt their function to altered environmental conditions.

### 2.5.7 Mitochondria

Mitochondria are membrane-bound organelles that carry out oxidative phosphorylation and produce most of the ATP (Fig. 2.7) of eukaryotic cells. The energy is generated by phosphorylation of pyruvate (derived from carbohydrates) and fatty acids (derived from lipids) in a multistep process. Mitochondria are found ubiquitously in almost all cell types, before all in cells and regions with elevated energy demand (hepatocytes, cardiac muscle cells, and proximal tubule cells of kidneys). Structural components are the outer mitochondrial membrane, the inner mitochondrial membrane (mostly infoldings in the form of cristae), the matrix, and the intermembrane space. The matrix, besides water and solutes, contains a variety of
enzymes engaged in citric acid cycle and lipid oxidation, matrix granules (Calcium regulation), and mitochondrial ribosomes. Intercalated in the inner membrane are the components of the electron transport chain (respiratory chain). Mitochondria have an own circular DNA. This autonomous DNA comprises 37 genes: 13 for encoding proteins, 22 for transfer RNAs, and 2 for ribosomal RNAs. With the exception of chloroplasts, mitochondria are the only organelles in eukaryotic cells apart from the nucleus, which contain DNA. An explanation for the origin of the DNA is given by the endosymbiosis theory, which states that mitochondria as well as chloroplasts evolved from endosymbiotic bacteria.

2.5.8 Cytoskeleton

The cytoskeleton is a mesh of protein filaments in the cytoplasm of eukaryotic cells responsible for cell shape, stability, and the capacity for intracellular transport and cell movement. There are three major filament classes, microtubules, microfilaments (actin filaments), and intermediate filaments, which have a large subset of associated proteins. These proteins are responsible for the regulation of processes that initiate the nucleation of new filaments, their assembly and disassembly, cross-linking, stabilization, attaching to the plasma membrane, or severing into fragments.

**Microtubules** (MTs) are composed of protein subunits (α/β-tubulin heterodimers) and are polarized structures with a rapidly growing end and a decay end. They extend from microtubule-organizing centers (MTOC) close to the nucleus into the cell periphery and undergo rapid changes in length through changes in the balance between assembly and disassembly of the subunits into MTs (dynamic instability). Intracellular vesicular transport is mediated along MTs via the *motor proteins* kinesin and dynein, which in an energy-dependent process walk along MTs carrying their cargo (vesicles and content) from one organelle to another. The mitotic spindle apparatus is also built from MTs, which separate the sister chromatids during cell division (see mitosis, chapter on reproduction). MTs also provide a meshwork for organelle deployment and for cell polarity in, e.g., epithelial cells. Finally, MTs are major components of cell structures such as centrioles, cilia, or flagella, which move cells or move liquid over the surface of cells.

**Actin filaments** (AFs) are the thinnest and most flexible cytoskeletal element (6 nm). The filaments (F-actin/filamentous actin) are formed by polymerization of G (globular)-actin monomers. In some cell types they form rather stable arrays (e.g., muscle cells in association with myosin), while in most cell types, actin filaments are dynamic and repeatedly dissociate and reassemble. In addition to regulation of assembly and disassembly of G- ⇔ F-actin and vice versa, actin-binding proteins arrange microfilaments into networks and bundles (stress fibers), cross-link and attach them to the plasma membrane, and thus help to determine the shape and adhesive properties of cells. AFs are contractile, via interaction with myosin, the only actin-associated motor protein family. In muscle cells, myosin forms thick filaments
(A band of sarcomere). In non-muscle cells, myosin exists in a soluble form which binds to actin by its globular head; the free tail regions attaches to the plasma membrane and other cellular components to move these structures.

Various special formations of AFs in non-muscle cells exist. These are accumulations under the plasma membrane, called terminal web, parallel strands in the core of microvilli, ribbons in the cytoplasm of the leading edge of pseudopods, as well as a belt around the equator of dividing cells.

**Intermediate filaments (IFs)** are the most heterogeneous family with many tissue-specific forms found in the cytoplasm of animal cells. Their common function is to provide mechanical strength and to maintain cell shape. IFs may belong to the families of *nuclear lamins* (nuclear scaffold), *cytokeratins* (epithelial cells), *desmins* (muscle cells), *vimentin* (mesenchyme-derived cells), *glial fibrillary acidic proteins* (glial cells), and *neurofilaments* (neurons). This cell-type specificity, together with the stability and longevity of the single proteins, makes them particularly useful in the immunohistochemical determination of neoplastic cells. In most cell types, IFs form a network around the nucleus and extend throughout the cytoplasm attaching at specific regions of the plasma membranes (mechanical cell junctions: desmosome, hemidesmosome). They are specifically abundant in cells exposed to mechanical stress like muscle cells or keratinocytes of the skin.

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**Further Readings**

Comparative Medicine
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