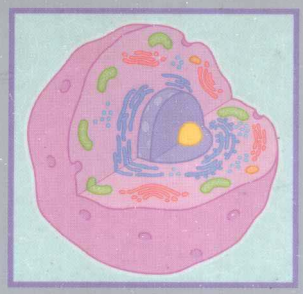
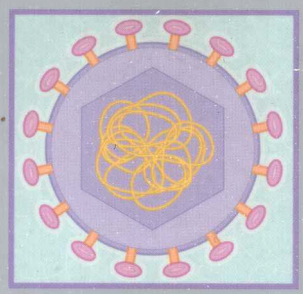
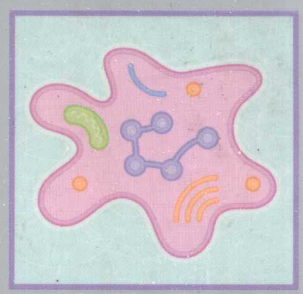

Flesh and Bones of MEDICAL CELL BIOLOGY

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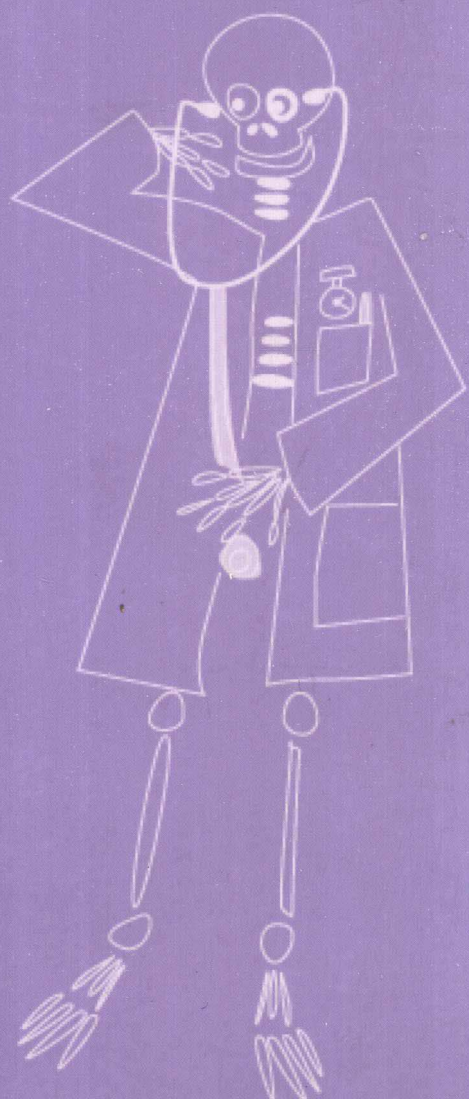

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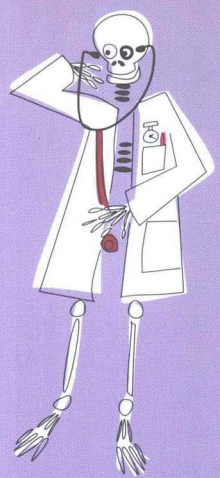

Flesh and Bones of MEDICAL CELL BIOLOGY

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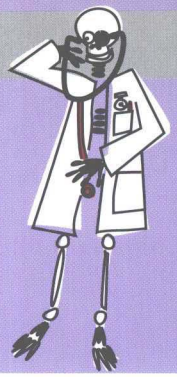

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Contents

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1 The big picture

The key to understanding cell biology is to consider the cell as a large collection of integrated structures and functions, and tissues as a collection of different cell types with different specializations. The biology of all cells is based upon a common set of underlying principles regardless of specialization. It is essential for activities within the cell to be integrated to produce a concerted response to its environment, which will include being responsive to the demands and stimuli of the surrounding tissue.

The occurrence of a common set of underlying principles upon which the biology of all cells is based allows a general picture to be drawn that pertains to any cell of interest. To understand cell biology is to grasp the individual principles and to see them in the context of the integration of structure and function in a whole cell. It is important to remember that cells do not exist in isolation in the human body; rather they are organized into tissues, which often contain a range of different cell types with different specializations. In this context, it is important for a cell not only to integrate its activities within itself to produce a concerted response to its environment but also to be responsive to the demands and stimuli of the tissue in which it is located.

THE CELL

The cell is the fundamental unit of life. Any cell is a discrete collection of chemical entities that has the ability to self-replicate. To be able to reproduce itself, a cell must be able to convert chemicals and energy from its environment into new constituents to permit growth and cell division. This requires the cell to isolate its chemical environment from that of its surroundings so that it can have independent control, **homeostasis** (Fig. 1.1). To achieve such control, cellular contents are enclosed by a cell membrane that is highly impermeable to water-soluble chemicals, thereby preventing ready exchange of chemicals with the environment. Exceptions to this general rule are nutrients and waste materials. Import and export of these chemicals is facilitated by the insertion of specific transporter proteins, which confer selective permeability to the cell membrane. It is also important for viability that a cell can make appropriate responses and adaptations to changes in the external environment. To this end, cell membranes also contain receptor molecules that can recognize external stimuli and the transducing and effector proteins

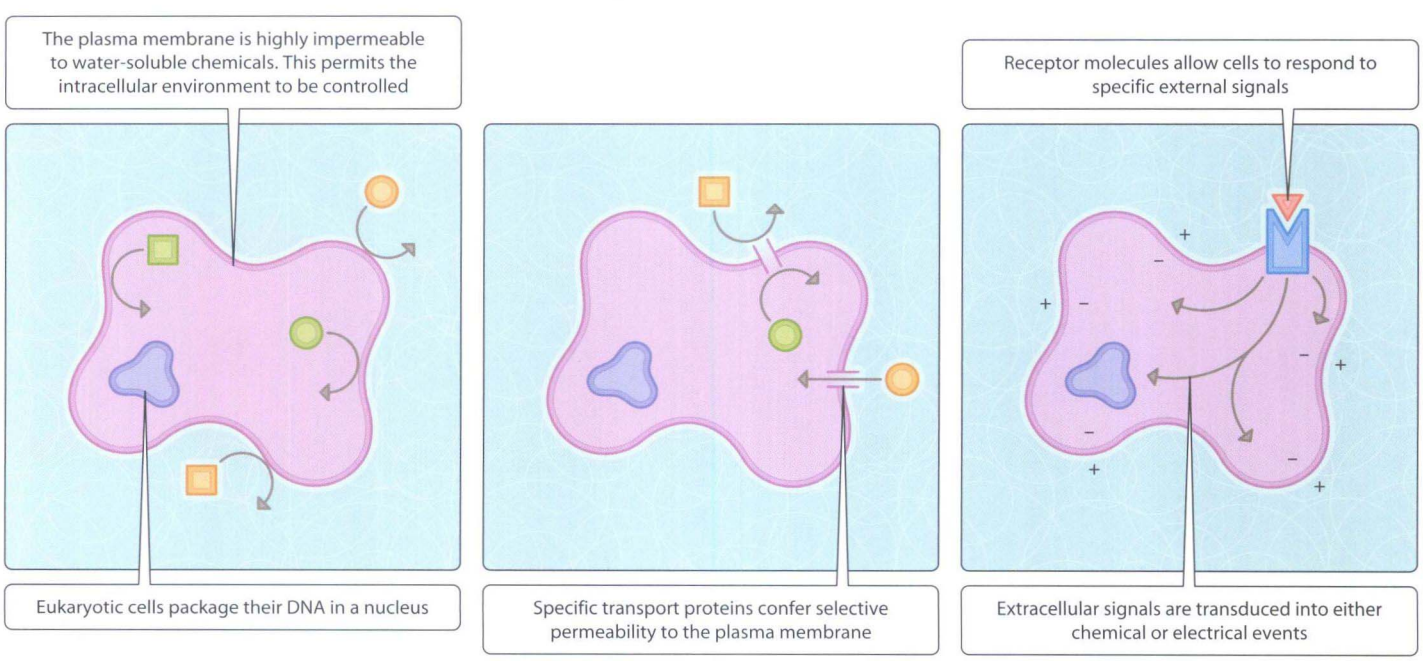

Fig. 1.1 The cell achieves internal homeostasis by controlling passage of molecules through the plasma membrane and by responding to stimuli.

necessary to convert these signals into intracellular events that can modulate the intracellular chemical environment. Responses may be either chemical or electrical.

Genetic information

Although there is an incredible diversity of cell types, the basis of cell structure and function in all cells is surprisingly similar. The information specifying the genetic blueprint for a cell or organism is contained in coded form within the sequence of four different nucleotides within genomic deoxyribonucleic acid (DNA) molecules. The information is divided into units, called genes, each of which encodes a defined protein component (Fig. 1.2). To allow the cell to use the information, single genes are copied or transcribed into smaller related molecules of ribonucleic acid (RNA). The genetic information is then decoded, or translated, from RNA molecules to direct the synthesis of protein molecules. Groups of three nucleotides (triplets) each specify one of 20 different amino acids, such that the nucleotide sequence in the RNA specifies exactly the sequence of amino acids in the translated protein. The amino acid sequences of translated proteins fold into distinct structures prescribed by the amino acids they contain, such that the two-dimensional code of a gene is translated faithfully into a three-dimensional protein structure. The distinct structures adopted by protein molecules define their function. Some proteins are structural components upon which other cellular functions are built. Most often, protein structures define catalytic sites in enzymes that permit cellular biochemical reactions to proceed at appropriate rates under physiological conditions. Yet others form specialized functional molecules, such as ion channels or molecular motors. In this way, the genetic code is translated to provide the full range of specific functionality necessary to define the cell.

Cell types

In the simplest of cells, all constituents, including the DNA, are contained within a single cytoplasmic compartment bounded by the cell membrane. Cells that do not contain a nucleus are termed **prokaryotes** and are generally single-celled organisms. Cells that package their DNA into an organelle enveloped by a double membrane, the nucleus, are termed **eukaryotes**. Some eukaryotic organisms exist as a single-celled organism (e.g. yeast) but most are multicellular assemblies. Once present in an assembly, eukaryotic cells may take on specialized functions to contribute to the benefit of the whole colony. In higher organisms, only the germline cells retain the function of reproduction of the species and the majority of cell types play more specialized supportive roles.

Compartmentalization

In addition to a nucleus, eukaryotic cells also contain a range of other membrane-enclosed structures, or organelles (Fig. 1.3). The subcompartmentalization of eukaryotic cells is the key to the complexity of function that can be achieved by a single cell. By packaging specific activities into discrete membrane-enclosed organelles, cellular processes can be kept separated from each other and can be regulated independently, if necess-

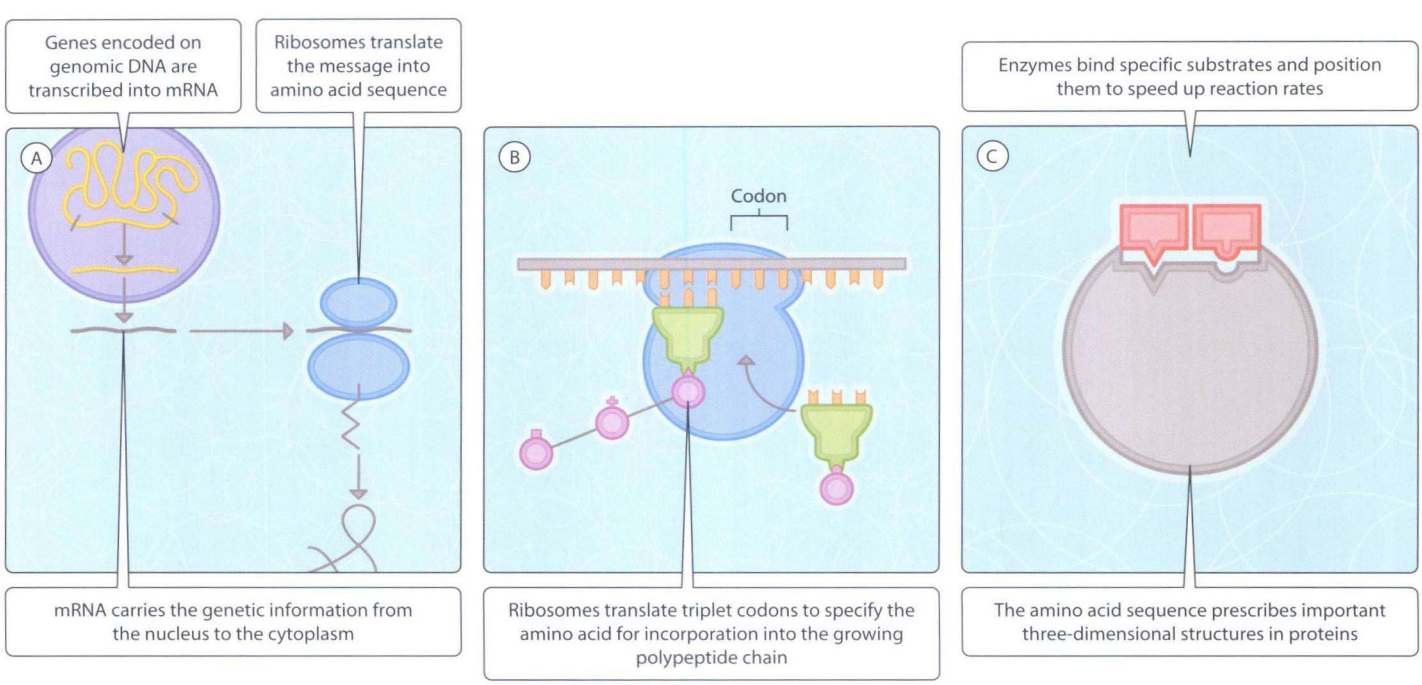

Fig. 1.2 Gene expression (first two panels). Enzyme regulation (C).

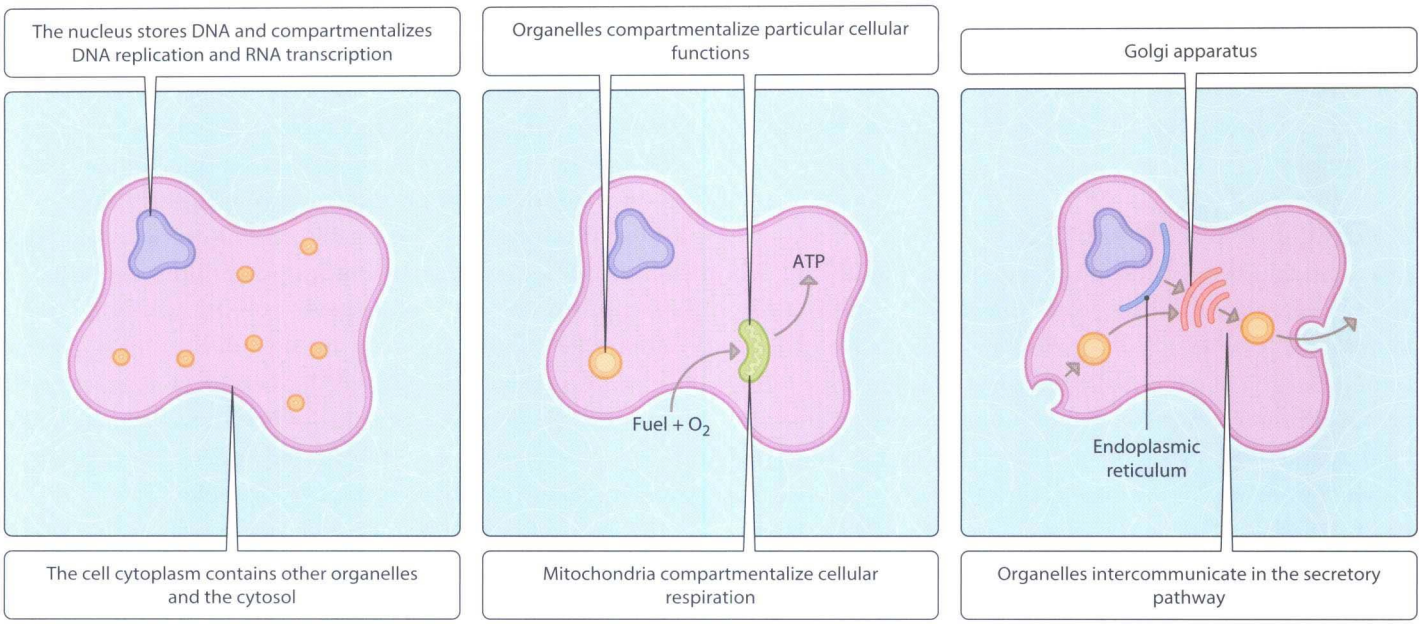

Fig. 1.3 Compartmentalization in eukaryotic cells.

ary. Paradoxically, if the cell is to function as a unit of biology, there must also be extensive communication between different compartments and processes to ensure that a unified and appropriate cellular response is made to the external environment and changing conditions. For this reason, when considering the activity of different components in cell biology, it is always important to remember that they form part of an integrated whole.

Organelles

In somatic cells, in addition to storing two highly condensed copies of the genomic DNA, the nucleus compartmentalizes the reactions of DNA replication and RNA transcription. Ribosome assembly is further compartmentalized to a suborganelle of the nucleus, the **nucleolus**. The nucleus is by far the largest organelle in eukaryotic cells but a range of other organelles also occur within the cell cytoplasm. A second organelle with a double membrane is the **mitochondrion**. This organelle contains its own short DNA molecule encoding 13 proteins and reproduces by division into two. Mitochondria are thought to derive from a symbiotic relationship between a prokaryote and an ancestor eukaryote. The function of mitochondria is to compartmentalize oxidative metabolism and to transfer energy from cell fuels to the production of adenosine 5′-triphosphate (ATP), the energy currency of the cell. Electrons and hydrogen ions removed from fuel molecules are oxidized by molecular oxygen via the electron transport chain in the inner mitochondrial membrane. The energy released is used to drive oxidative phosphorylation of adenosine 5′-diphosphate (ADP) to ATP.

Contiguous with the outer nuclear membrane is the **endoplasmic reticulum** (ER), which forms a series of irregular and interconnected flattened sacs. The ER is a major site of synthesis of cellular components and also those destined for export. It also acts as a centre for detoxification and as an important sink for Ca^{2+}, which when released is important in cellular signalling processes. The **Golgi apparatus** is an organelle consisting of a series of more regularly stacked flattened membrane sacs. This compartment further processes newly synthesized molecules received from the ER. When modifications are complete, the Golgi packages molecules for delivery to other targeted destinations in the cell. One such destination is the **lysosomes**. Lysosomes compartmentalize hydrolytic enzymes, thereby protecting other cellular constituents from inappropriate damage. They are responsible for the digestion of cellular components and those entering the cell by phagocytosis or endocytosis. Other reactions involving molecular oxygen and the production of damaging hydrogen peroxide (H_2O_2) are compartmentalized within **peroxisomes**. Although different organelles carry out different functions, there is considerable transport between organelles, particularly between the ER, Golgi, lysosomes and cell membrane. This is achieved by the budding off of targeted membrane vesicles, which fuse with their targeted organelle and discharge their contents on arrival.

The largest compartment in the cell is the gel-like aqueous environment that remains when all of the organelles are removed, known as the **cytosol**. The cytosol is the site of a large number of cellular chemical reactions. For example, early steps in catabolic

(breakdown) pathways are contained in the cytosol (e.g. the breakdown of glucose to pyruvate by the glycolytic pathway). The cytosol also contains ribosomes, the structures on which protein synthesis against the RNA template strand is accomplished.

CELLULAR SIGNALLING

In a multicellular organism, it is important that individual cells act in a concerted fashion to the benefit of the whole. Communication between adjacent cells may be mediated by direct communication of cell cytoplasm through gap junctions, which permit diffusion of small solutes, or by the release of short-lived, local (**paracrine**) signalling molecules to elicit a concerted response from cells in the same tissue (Fig. 1.4). In the nervous system, specialized junctions between neurons, called **synapses**, localize the release of signalling transmitter and the recognition of the signal in the postsynaptic cell. Signalling between cells that are more disparately distributed in the organism may be achieved using hormones. In this case, specialized cells in endocrine glands release hormone into the circulation, where it is transported to the target tissue to bring about a response. Responses to activating and inhibitory stimuli are integrated by the cell so that an appropriate overall response is made.

For a cell to be able to respond to a chemical signal it must display receptor proteins that specifically recognize the signalling molecule and are activated to bring about a change within the cell. A range of strategies is employed to transduce extracellular signals into intracellular events. Most often, receptor stimulation at the cell membrane results in the activation of a transducing protein, which, in turn, stimulates an effector enzyme or ion channel within the cell. Effector enzyme activation results in conversion of an inert substrate into an active second messenger, which diffuses through the cytoplasm to activate downstream enzymes or intracellular receptors to bring about a cellular response. In some cases, receptors may be linked directly to ion channels, allowing the external signal to be transduced into an electrical event on the cell membrane. Where signalling is mediated by hydrophobic hormones, such as thyroid hormone, the hormone can enter the cell directly and activate receptors located in the cytoplasm or nucleus; these go on to bind nuclear DNA and regulate gene expression.

In electrically excitable cells, such as nerve fibres and muscle cells, extracellular stimulation can result in a change in potential across the plasma membrane. The membrane potential of resting cells is maintained in a polarized state, negative inside relative to outside, by the equilibration of ions across the plasma membrane. A change in permeability for an ion through channels in the plasma membrane can disturb the resting membrane potential. For example, opening of Na^+ channels results in the influx of Na^+ down the electrochemical gradient. This has the effect of depolarizing the membrane potential and is the basis of the action potential of nerve cells. Propagation of action potentials along a nerve fibre membrane allows nerve impulses to be carried along a nerve axon.

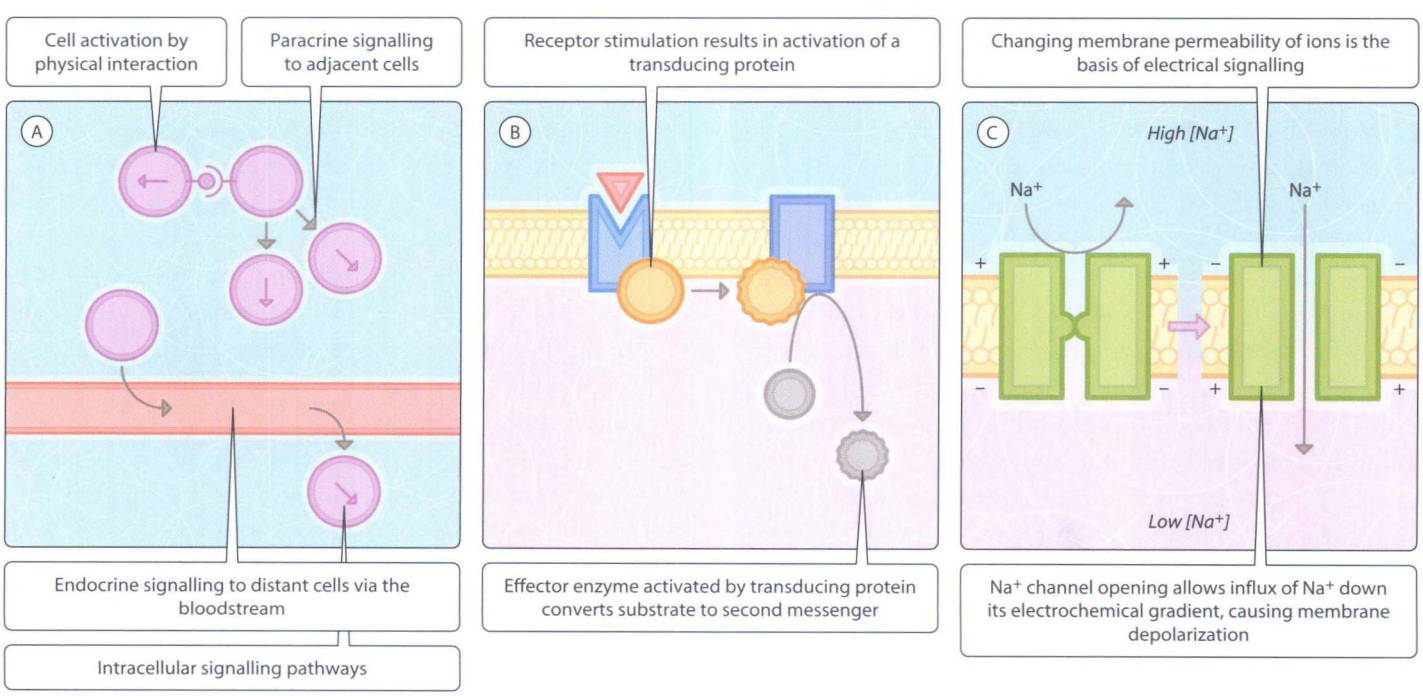

Fig. 1.4 Communication between cells (A). Signal transduction (B,C).

SPATIAL ORGANIZATION WITHIN CELLS

Rather than existing simply as a membrane-enclosed bag of organelles and cytosol, the cell has a much more defined structure. This is determined by a series of protein filaments that combine to form a three-dimensional mesh-like structure, known as the **cytoskeleton** (Fig. 1.5). Cytoskeletal proteins may form attachments with the cell membrane at specific attachment sites or may radiate from near the nucleus. Three main types of filament are employed: thin, intermediate or large diameter. Thin filaments comprise largely the protein actin and are involved in structures in which the generation of contractile forces is involved. Although present in all eukaryotic cells, actin filaments are particularly abundant in muscle cells, where they are further organized into bundles with other contractile proteins. The large-diameter filaments form tube-like structures and so are known as **microtubules**. These structures are particularly important in forming tracks within cells along which membrane vesicles can be directionally targeted to cellular destinations. They are also important in dividing cells as they form the mitotic spindle along which the separation of chromosomes is driven. Microtubules are also found in the specialized structures in cilia and flagella. Here, the relative movement of adjacent microtubules forms the basis of the stroke of cilia or flagella. The intermediate filaments, with diameters between those of the actin microfilaments and microtubules, are a family of proteins that form coiled coils. This group of proteins forms the basis of the tensile strength of the cytoskeleton and provides mechanical stability to the cell overall.

CELL ADHESION AND THE FORMATION OF TISSUES

In higher organisms, the aggregation of cells into tissues allows them to specialize in support of the whole individual. To maintain structural integrity in tissues and to allow a tissue to respond in a concerted manner, the interactions between cells become important. A number of specialized junctional structures form between cells themselves and between cells and the extracellular matrix to anchor them in position within the tissue. Many of these connections also permit communication, for example solute exchange between cells through gap junctions, and the intracellular signal pathway activation by interaction of adhesion proteins. The binding of adhesion proteins within cell–cell and cell–matrix interactions is not static. The strength of adhesion in many interactions may be modulated by the activation of intracellular signalling pathways. These may be activated by chemoattractants or cytokines or may equally be activated by the interaction of adhesion proteins themselves. Thus, cell contacts may make and break in a coordinated fashion, allowing individual cells to migrate within tissues. This is important, for example, in the infiltration of leukocytes and macrophages during inflammatory responses in tissues.

CELL REPLICATION

For a cell to self-replicate it must duplicate its cellular contents, in particular its genetic complement, and must divide into two identical daughter (diploid) cells in a coordinated manner. The process of cell division is cyclical and passes unidirectionally through a series of phases (Fig. 1.6).

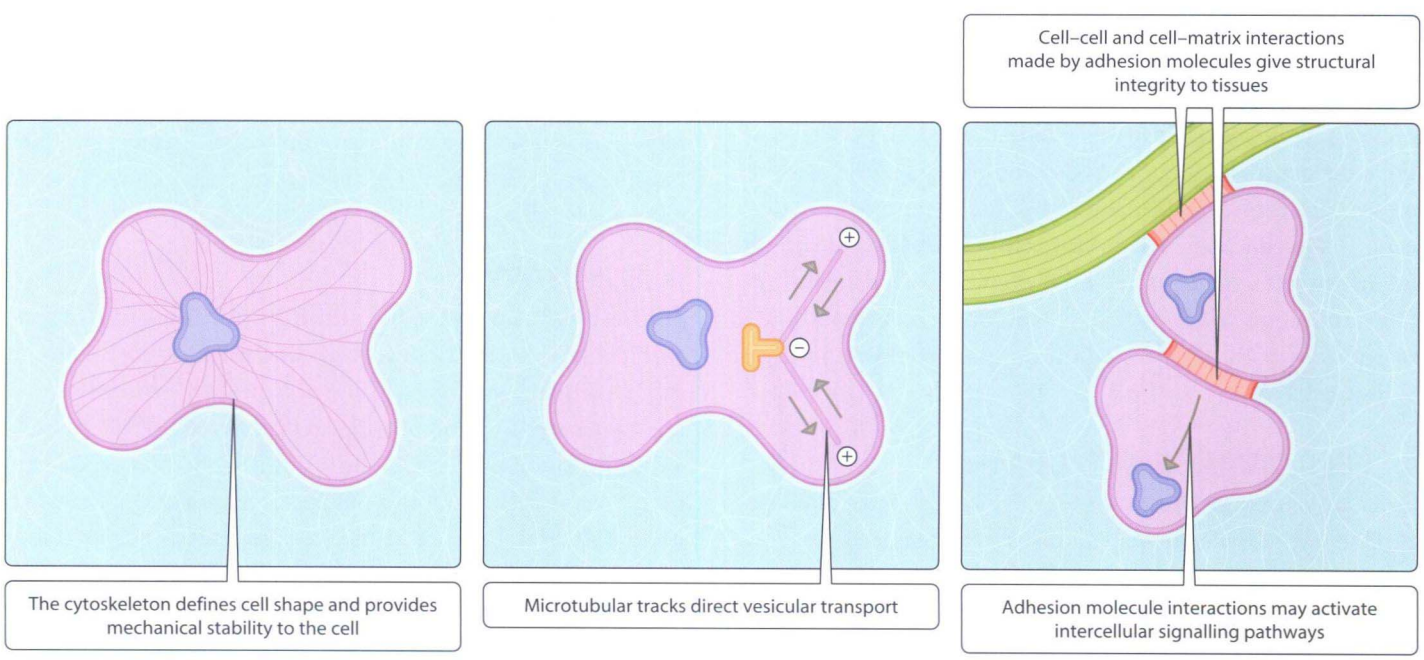

Fig. 1.5 Spatial organization within cells and tissues.

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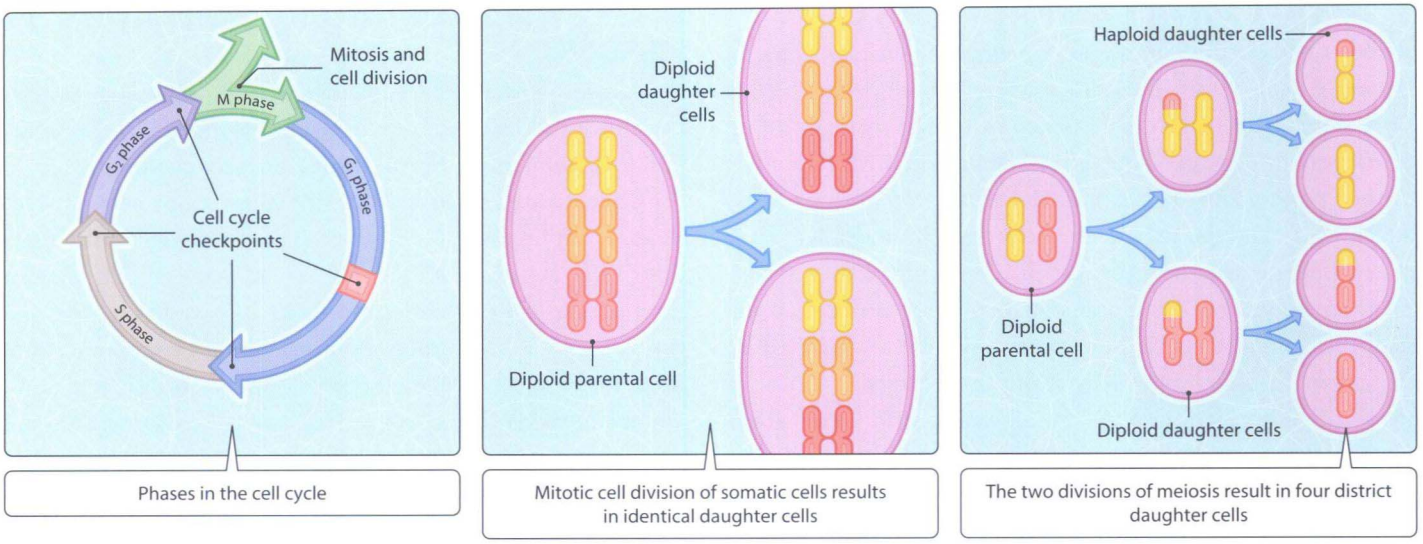

Fig. 1.6 Cell cycle and cell division.

After a period of rapid biosynthesis and growth, the genomic DNA is duplicated and condensed, ready for the separation of paired chromosomes. In **mitosis**, the paired chromosomes are separated to opposite ends of the cell on a mitotic spindle before the cell divides to form two new daughter cells. The cell cycle is controlled at several checkpoints. This allows the cycle of cell division to be arrested if, for example, the nutritional status of the cell is low or if the cell has suffered DNA damage, to prevent replication of damaged DNA.

Gametogenesis and reproduction

In the production of oocytes and spermatozoa, the resulting haploid cells contain only half of the normal chromosome complement of diploid progenitor cells. This is achieved by two cycles of reductive cell division: **meiosis**. In the first cycle, crossing over occurs between paired chromosomes to increase the genetic diversity of the daughter cells. In the second cycle, there is no DNA replication and so sister chromatids separate, resulting in a single copy of each chromosome in each daughter cell. On fertilization of an oocyte, a copy of each chromosome is provided by both gametes and the normal diploid complement is restored.

CELL DAMAGE AND DEATH

Cells are always at risk of damage. This may occur following production of damaging chemicals during chemical reactions. In particular, the production of reactive oxygen species during normal metabolism or in response to extracellular challenges can damage cellular constituents, leading to loss of function and necrotic cell death. In order to afford some protection, cells express chemicals and enzymes to inactivate these reactive species. Inevitably some damage occurs, and where this is to DNA there are particular risks for the cell. If a mutation results in altered control of the cell cycle, the cell may become transformed or cancerous and begin to divide in an uncontrolled fashion. Similarly, errors in DNA replication during cell division can have the same result. Cells continually screen for damaged DNA and possess mechanisms to arrest the cell cycle to prevent the replication of damaged DNA and to permit time for DNA repair; however, there is always a danger that cells will escape this check. In some instances, apoptotic cell death is required to allow a tissue to remove cells predestined to become cancerous or to remodel in response to physiological challenge. This occurs via a series of programmed intracellular responses such as the activation of proteolytic caspase enzymes. Inappropriate initiation of apoptosis may contribute to degenerative diseases.

SUMMARY

This section has outlined the principles of cell biology. Section two identifies 50 high return facts that form its core concepts and underlying principles. They are the bare bones that will focus your learning and provide an overview on which to build an understanding of cell biology. In Section three, each high return fact is fleshed out in a double-page spread to add further detail and clinical context to the core principle. Students able to learn the 50 facts with some of the fleshed out detail should have no significant gaps in their understanding of the principal workings of a cell and should have a good foundation for more detailed studies in this area.

High return facts

2

The cell

1 Eukaryotic cells range between 10 and 100 μm in length. The genetic material is packaged in the membrane-bounded nucleus. Other membrane-bounded structures, termed organelles, compartmentalize cellular functions and permit greater cellular specialization and diversity.

Organelles

2 Nuclei and mitochondria are both organelles with double membranes. The nucleus is involved in the storage and expression of genetic material; it contains two complete copies of the genomic DNA packaged as chromosomes. Mitochondria are involved in the release of energy from catabolism of fuel molecules as cellular energy currency; consequently, there are more in active tissues. The components of the electron transport chain and oxidative phosphorylation are located on the inner mitochondrial membrane. Mitochondria also contain DNA coding for 13 proteins. This DNA has a maternal pattern of inheritance as the sperm only contributes its nuclear material at fertilization.

3 Single membrane organelles have important roles in secretory and membrane protein biosynthesis, lipid biosynthesis and Ca^{2+} storage (endoplasmic/sarcoplasmic reticulum), protein modification (Golgi apparatus) and cellular digestion (lysosomes).

Genetic information

4 The genetic blueprint for the cell is carried by deoxyribonucleic acid (DNA) a polymer of four repeating chemicals called nucleotides. Chromosomes are made from two strands of DNA, intertwined to produce a double helix. DNA is organized into functional units, called genes. Within each gene are sequences that direct its expression, as well as sequences that describe the structure of the protein product itself. The bases that code for protein are read in threes, each triplet (codon) specifying the incorporation of a different amino acid. Before the information contained within the sequence of DNA can be turned into protein, it must be copied into messenger ribonucleic acid (mRNA), a process called transcription.

5 The coding information in many eukaryotic genes is organized into cassettes (exons) interrupted by regions of junk sequence called introns. Introns are removed from mRNA by splicing. Splicing provides an opportunity to increase the diversity of protein products by controlling whether or not individual exons are retained in the mature message. Amino acids attach to transfer RNAs, which carry a triplet sequence (anticodon) that is complementary to the codon specified by the mRNA. The binding of codon and anticodon brings amino acids in the correct order for assembly into a new polypeptide chain on the ribosome.

Proteins

6 Proteins are composed of a linear sequence of amino acids linked by peptide bonds, with each protein type encoded by a specific gene. Protein structure can be described as primary (linear sequence of amino acids in the polypeptide chain and the position of covalent links between chains), secondary (folding and stabilization into regular structural elements, e.g. α-helix and β-sheet), tertiary (folding and stabilization of segments of secondary structure into a three-dimensional shape and any chemical prosthetic groups) and quaternary (interaction of distinct polypeptide chains into oligomeric complexes). Protein molecules define the specific structural and functional characteristics of cells, functioning as structural proteins, receptors and enzymes.

7 Misfolded or damaged proteins are potentially harmful to the cell. Degradation signals tell the cell which proteins to remove. These proteins are modified by covalent addition of ubiquitin, which targets them for degradation by proteasomes.

Biological membranes

8 Biological membranes comprise a phospholipid bilayer with associated proteins; the proteins may penetrate the bilayer or be associated with one side. Membranes permit enclosed environments to be formed (compartmentalization) and mediate information flow between these compartments (communication).

9 Biosynthesis of secretory and membrane proteins begins on ribosomes in the cytoplasm. Recognition of a newly synthesized N-terminal signal sequence by a signal recognition particle arrests synthesis. Interaction of the signal recognition particle with its receptor on the endoplasmic reticulum allows protein synthesis to recommence; nascent protein is directed into the lumen of the endoplasmic reticulum through a protein translocator complex.

10 Non-polar molecules, such as O_2, CO_2, N_2, urea and, importantly, water, are able to dissolve in and diffuse across the hydrophobic domain of lipid bilayers, whereas the diffusion of ions and small hydrophilic molecules is not favoured. Movement of ions and hydrophilic molecules across biological membranes is mediated by specific membrane transport systems or channels. Transport processes may occur spontaneously (passive transport) or may be driven by the input of energy (active transport).

11 ATP-dependent ion pumps and ion exchangers play important roles in maintaining cellular ion concentrations and, thereby, provide the basis for the regulation of many cellular processes. Ion pumps derive the energy to transport ions across membranes against their electrochemical gradient by using the energy of ATP hydrolysis directly. Exchangers use energy from the movement of one ion down its electrochemical gradient to move another ion or molecule up its gradient.

12 Transmembrane ion transport contributes to the regulation of intracellular pH, volume and nutrient uptake. In the plasma membrane, the energy for these processes is often derived from the inward electrochemical gradient for Na^+. Anion exchange in red blood cells is responsible for their buffering capacity and contributes to their ability to transport O_2 and CO_2 in the circulation. Transport mechanisms for Na^+ in the kidney play an important role in the regulation of circulating Na^+ concentrations.

13 Proteins are targeted either to specific cellular destinations by structural signals within the protein or to a default destination in the absence of a specific signal. Secretory proteins enter either a constitutive (e.g. extracellular matrix proteins) or a regulated (e.g. insulin) secretory pathway.

14 Mature proteins are transported into mitochondria and nuclei via complex ATP-driven mechanisms. Proteins must be unfolded before translocation into mitochondria can commence and cytosolic chaperone proteins help to stabilize the unfolded protein during transfer. Transfer to the nucleoplasm from the cytoplasm occurs through selective nuclear pore structures in the nuclear envelope.

15 Internalization of particulate matter (phagocytosis) and solutes (pinocytosis) occurs by invagination of the plasma membrane to form transport vesicles. Transport between organellar compartments is achieved by the budding off of transport vesicles and movement of these to their destination. Transport vesicle formation is driven by the association of coat proteins, and correct targeting of a transport vesicle is achieved by 'targeting molecules' (SNAREs) in both the transport vesicles (vSNAREs) themselves and the cognate target organelle (tSNAREs). Both vesicle budding and vesicle fusion are governed by small GTP-binding regulatory proteins.

16 Substances too large to enter cells via carrier transport proteins may enter, bound to specific receptors, via receptor-mediated endocytosis. Functions of receptor-mediated endocytosis include metabolite uptake, protein turnover, receptor desensitization and transcellular transport.

Electrical signalling

17 All cells have an electrical potential difference across their plasma membrane (membrane potential); this is expressed as the voltage inside relative to that on the outside of the membrane. The resting membrane potential is established predominantly by the selective permeability of the plasma membrane to K^+, which exits cells through voltage-insensitive K^+ channels until electrochemical equilibrium is reached.

18 Changes in the permeability of a membrane to particular ions (Na^+, K^+, Ca^{2+}, Cl^-) results in a change in the membrane potential and is the basis of electrical signalling. In electrically excitable cells, electrical signals are encoded and propagated in action potentials. In the initial depolarizing phase of the action potential, Na^+ enters the cell through the opening of voltage-gated Na^+ channels. During the repolarization phase, Na^+ channels inactivate and slowly activating K^+ channels open, resulting in the efflux of K^+ and repolarization of the membrane.

19 Ion channels permit the gated movement of ions across membranes in the direction of the electrochemical gradient. Channels may be open constitutively or may be gated by the binding of a ligand or by a voltage change across the membrane. Accessory subunits can alter the kinetic properties of the channel and help to target and anchor it. Mutations affecting channel or accessory proteins are involved in a number of disorders (e.g. cystic fibrosis).

20 Conduction of a nerve impulse is achieved by local currents induced by an action potential in an active region of membrane, which raise adjacent resting regions of the nerve membrane to threshold for firing of an action potential. Myelination of nerves, by decreasing the electrical capacitance of the membrane, speeds up nerve impulse conduction by permitting salutatory conduction where action potentials fire only at nodes of Ranvier. Retrograde conduction of a nerve impulse is prevented by inactivation of ion channels, which makes the nerve refractory to further action potentials until the membrane is reprimed by repolarization.

Chemical signalling

21 For a cell to respond to any chemical messenger, it must produce specific receptor proteins that recognize and produce a response to the signalling molecule. Interaction of the signalling molecule with its specific receptor must then result in the activation of a cellular process; this often involves an amplification cascade. Intercellular chemical signals can be hormones, local mediators or neurotransmitters. A receptor protein is functionally silent unless activated by interaction with an agonist. Binding of an antagonist prevents the action of agonist molecules.

22 Receptors are classified according to the specific physiological signalling molecule (agonist) that they recognize (e.g. acetylcholine receptors). Further subclassification is made on the basis of their ability to be selectively activated by agonist molecules (e.g. nicotinic and muscarinic types). Subclassification is also often made on the basis of the affinity (a measure of tightness of binding) of a series of antagonists. Receptor families employ a variety of mechanisms to transduce agonist binding into a cellular event, (e.g. integral ion channel, integral enzyme activity, coupling to effectors through transducing proteins, regulation of gene expression).

23 Many membrane-bound receptors employ intermediary proteins to transduce the events of receptor activation to effector molecules in the cell. Agonist-induced conformational changes in the receptor are transmitted to transducing proteins on the cytoplasmic face of the plasma membrane, which then activate the first effector(s) of intracellular signalling pathway cascades. Examples of transducing proteins include insulin receptor substrates (IRS-1) and GTP-binding regulatory proteins (G-proteins).

24 In many instances, the response to receptor activation is the activation of an enzyme effector, which produces a small intracellular messenger molecule or 'second messenger'. Second messengers are normally maintained at low concentration, are produced only in response to specific receptor activation in proportion to the size of the signal and are degraded rapidly to ensure transiency in signalling pathways.

25 Many cellular responses are controlled by changes in the concentration of cytosolic Ca^{2+} ($[Ca^{2+}]_i$). Cells expend a great deal of energy to maintain extremely low resting $[Ca^{2+}]_i$ by extruding it out of the cell or sequestering it into intracellular vesicular stores. On appropriate stimulation, $[Ca^{2+}]_i$ may be raised by re-entry through plasma membrane channels or by release from intracellular stores.

26 Regulation of enzyme and protein activity is often achieved by phosphorylation or dephosphorylation: the directed covalent modification of the protein by the transfer onto or removal of a phosphate moiety, respectively. Protein phosphorylation is catalysed by a family of protein kinases that transfer the terminal phosphate from ATP onto the target residue. Dephosphorylation is catalysed by a family of protein phosphatases that facilitate the hydrolysis of the phosphate bond. There is considerable cross-talk between signalling pathways, which allows pathways to modulate each other and enables an integrated response to extracellular signals.

27 When cells are exposed continuously to an extracellular messenger or drug, they can often become increasingly resistant to stimulation. This loss of sensitivity is known as desensitization or tachyphylaxis when it occurs acutely over a few minutes and tolerance or resistance when occurring over a period of days or weeks.

Integration of signalling mechanisms

28 Transmission of information between excitable cells commonly occurs at specialized junctions called synapses. In response to depolarization and the resulting influx of Ca^{2+}, a chemical neurotransmitter is released from the presynaptic structure of the signalling cell. The neurotransmitter molecule diffuses across the synaptic cleft, binds to a specific receptor molecule on the postsynaptic cell and elicits a response in the postsynaptic cell.

29 Stimulus–secretion coupling in beta-cells of the islets of Langerhans is mediated by ATP-sensitive K^+ (K_{ATP}) channels, which close in response to ATP generated during glucose metabolism; a specialized glucose transporter ensures that the glucose concentration in the cell, and hence the ATP generated, reflects the plasma glucose levels. The resulting membrane depolarization results in Ca^{2+} influx through voltage-sensitive Ca^{2+} channels and stimulation of the insulin secretory machinery.

Cell adhesion

30 The development and function of tissues is dependent on the physical interaction of one cell with another. These physical interactions are mediated by members of several families of membrane-spanning proteins, called adhesion molecules. Adhesion molecules also play important roles in more transient interactions between cells, including those involved in cellular migration and the interactions between cells of the immune system.

31 Many of the cells of the body are grouped together to form tissues, structures or organs, where they function collectively. In order to maintain the structural integrity of tissues and to help individual cells to function in an organized and concerted manner, adhesion molecules on one cell link to similar molecules on adjacent cells, or to the extracellular matrix, forming cellular junctions of differing properties.

32 Much of the human body is made up of connective tissue, which contains few cells and is chiefly made from extracellular matrix; this is a mass of specialized proteins and polysaccharides mainly secreted by fibroblasts. It is the extracellular matrix that gives connective tissue the ability to resist shear, tensile and pressure forces.

33 The extracellular matrix does not simply provide a protective framework; it also has a profound influence on the behaviour of individual cells. The extracellular matrix imparts spatial information that is crucial for development, differentiation, normal cellular function and resistance to apoptosis.

The cytoskeleton

34 The cytoskeleton is a complex dynamic framework of structural protein filaments that defines the shape of a cell and contributes to changes in cell shape and organelle and cell movement. Microfilaments and microtubules are formed from globular actin and tubulin subunits, respectively. They can be rapidly assembled and disassembled as required by the cell.

35 Filamentous protein strands form the structural basis of cell cytoskeletons and contribute to the mechanical stability of cells. Although a heterogeneous group of proteins is involved, each type of filament is composed of a defined protein or combination of proteins.

36 In contractile muscle cells, the cytoskeleton is modified to provide the contractile machinery. Shortening in muscle cells is mediated by the progressive overlap of interdigitated thick and thin filaments composed predominantly of myosin and actin, respectively.

37 Stimulating action potentials are transmitted rapidly deep into skeletal muscle fibres by transverse tubules formed from specialized regions of the sarcolemma. The t-tubular L-type Ca^{2+} channels act as voltage sensors and transmit information physically to ryanodine-sensitive Ca^{2+} channels in the sarcoplasmic reticulum. These channels open to release Ca^{2+} over the sarcomere structures that will initiate contraction. Different muscles types have modifications of this basic method.

38 Transport of organelles and membrane-bound vesicles in eukaryotic cells is directed along 'tracks' of single microtubules by a 'walking' mechanism. The molecular motors for this movement are myosin-like ATPases. Kinesin drives movement from the (–)-end (centrosome end) of the microtubule to the (+)-end, while cytoplasmic dynein drives movement in the opposite direction.

39 Microfilamentous actomyosin structures also occur in non-muscle cells where contractile properties are required (e.g. in cellular locomotion and in the cell cycle to form the contractile ring). Microvilli increase the surface area of epithelial tissues by folding the apical membrane into numerous finger-like projections. Cilia and flagella are specialized surface appendages of cells that have a beating function.

Cell locomotion

40 Cell locomotion is important for a range of processes including infiltration of tissues by specialized cells in inflammation and immunity, fertilization, embryological development and tissue repair and turnover. The forward movement of cells is driven by the 'treadmilling' of actin microfilaments.

Cell division

41 The process of cell division is cyclical and unidirectional. The period between successive divisions is termed interphase; this begins with a period of rapid biosynthesis and cell growth (gap, G_1 phase). Cells can enter a resting phase (G_0) before moving into G_1. After G_1, there is a period when the complete genomic DNA is duplicated (S phase), a second gap phase (G_2 phase), then the division of nuclear material (mitosis) and cytoplasmic division (cytokinesis; M phase with mitosis). Progression through the cell cycle is controlled at 'checkpoints' between stages.

42 DNA replication occurs in the 5′ to 3′ direction against a 3′ to 5′ template strand and is initiated by synthesis of a short strand of RNA, which acts as a primer for DNA polymerase. To ensure that the whole genome is replicated within a short time period, DNA is divided into replicons, each with a replication fork; these are activated in clusters.

43 The cell cycle may be arrested at two points (G_1–S and G_2–M) if DNA is damaged. Unrepaired damage can lead to mutation and loss of information so cells express several enzymes that can repair damaged DNA before it is replicated.

44 Mitosis is cell division that produces two diploid cells (containing two copies of each chromosome) from a diploid progenitor cell and occurs in dividing somatic cells. This form of cell division is employed to permit normal growth and repair of all tissues apart from cells involved in the production of gametes.

45 Meiosis is a specialized form of cell division that produces four genetically distinct haploid cells (containing only a single copy of each chromosome) from a diploid progenitor cell (containing two copies of each chromosome). This reductive form of cell division is found only in gamete production: oogenesis and spermatogenesis.

46 The fusion of egg and sperm at fertilization, and the mixing of their haploid genomes, restores the diploid genotype in the resulting zygote. Interaction of sperm with the zona pellucida of the oocyte causes a massive influx of Ca^{2+} and activation of hydrolytic enzymes, which facilitate fusion of the gametes. On fusion, enzymes released from cortical granules modify the zona pellucida to prevent the penetration of further sperm.

47 A cancer is the uncontrolled growth and division of cells that have escaped the normal regulatory mechanisms of the cell cycle. Cancers arise because of mutations in the genome of somatic cells as a result of inaccuracies in gene replication or chromosomal rearrangement at mitosis. Oncogenes are modified genes that result in the loss of host cell growth control. Proto-oncogenes are local host cell genes that normally do not have oncogenic or transforming properties but are involved in the regulation or differentiation of cell growth. If they are disrupted, they can alter control of key regulatory genes leading to unregulated cell division.

Cell damage and death

48 Free radicals are highly reactive species that produce a range of damaging modifications to cellular molecules and thereby contribute to a wide range of disease processes. Normally, cells are protected from excessive free radical damage by the presence of dietary free radical scavengers or antioxidants (e.g. vitamins C and E), the expression of a variety of enzymes (e.g. catalase, superoxide dismutase) and the production of redox active chemicals (e.g. glutathione).

49 Two types of cell death can be distinguished. 'Accidental' cell death or necrosis occurs after severe and sudden injury. It is characterized by the swelling of organelles, loss of the integrity of the plasma membrane and leakage of cellular contents. This leads to an inflammatory response. Programmed cell death or apoptosis occurs in response to physiological triggers in development (tissue remodelling), defence, homeostasis and ageing. It is a controlled dismantling of the cell leading to small apoptotic vesicles, which are then engulfed and digested by macrophages.

50 Most cells in an adult are terminally differentiated. However, we develop from a single cell, so early embryonic cells must have the potential to become any adult cell type. Undifferentiated cells like these are called stem cells. Many adult tissues may also contain cells with the potential to differentiate into one of a limited range of cell types (oligopotent stem cells). The ability to use stem cells to replace or repair damaged or diseased tissues would offer hope for the treatment of many disorders.

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