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Stem Cell

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Abstract: The cell is the basic structural, functional, and biological unit of all known organisms. Cells are the smallest units of life, and hence are often referred to as the building blocks of life. The study of cells is called cell biology, cellular biology, or cytology. Cells consist of cytoplasm enclosed within a membrane, which contains many biomolecules such as proteins and nucleic acids. Most plant and animal cells are only visible under a light microscope, with dimensions between 1 and 100 micrometres. Electron microscopy gives a much higher resolution showing greatly detailed cell structure. Organisms can be classified as unicellular or multicellular. Most unicellular organisms are classed as microorganisms. The number of cells in plants and animals varies from species to species; it has been estimated that humans contain somewhere around 40 trillion (4×10^{13}) cells. The human brain accounts for around 80 billion of these cells. Cells were discovered by Robert Hooke in 1665, who named them for their resemblance to cells inhabited by Christian monks in a monastery. Cell theory, first developed in 1839 by Matthias Jakob Schleiden and Theodor Schwann, states that all organisms are composed of one or more cells, that cells are the fundamental unit of structure and function in all living organisms, and that all cells come from pre-existing cells.[9] Cells emerged on Earth at least 3.5 billion years ago.
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The cell is the basic structural, functional, and biological unit of all known organisms. Cells are the smallest units of life, and hence are often referred to as the building blocks of life. The study of cells is called cell biology, cellular biology, or cytology. [1]

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Cells were discovered by Robert Hooke in 1665, who named them for their resemblance to cells inhabited by Christian monks in a monastery.[7][8] Cell theory, first developed in 1839 by Matthias Jakob Schleiden and Theodor Schwann, states that all organisms are composed of one or more cells, that cells are the fundamental unit of structure and function in all living organisms, and that all cells come from pre-existing cells.[9] Cells emerged on Earth at least 3.5 billion years ago.[10][11][12]

Cell biology (also **cellular biology** or **cytology**) is a branch of biology studying the structure and function of the cell, also known as the basic unit of life.[1] Cell biology encompasses both prokaryotic and eukaryotic cells and can be divided into many sub-topics which may include the study of cell metabolism, cell communication, cell cycle, biochemistry, and cell composition. The study of cells is performed using several techniques such as cell culture, various types of microscopy, and cell fractionation. These have allowed for and are currently being used for discoveries and research pertaining to how cells function, ultimately giving insight into understanding larger organisms. Knowing the components of cells and how cells work is fundamental to all biological sciences while also being essential for research in biomedical fields such as cancer, and other diseases. Research in cell biology is interconnected to other fields such as genetics, molecular genetics, biochemistry, molecular biology, medical microbiology, immunology, and cytochemistry.

Cell types

Cells are of two types: eukaryotic, which contain a nucleus, and prokaryotic, which do not. Prokaryotes are single-celled organisms, while eukaryotes can be either single-celled or multicellular.

Prokaryotic cells

Prokaryotes include bacteria and archaea, two of the three domains of life. Prokaryotic cells were the first form of life on Earth, characterized by having vital biological processes including cell signaling. They are simpler and smaller than eukaryotic cells, and lack a nucleus, and other membrane-bound organelles. The DNA of a prokaryotic cell consists of a single circular chromosome that is in direct contact with the cytoplasm. The nuclear region in the cytoplasm is called the nucleoid. Most prokaryotes are the smallest of all organisms ranging from 0.5 to 2.0 µm in diameter.[13]

A prokaryotic cell has three regions:

- Enclosing the cell is the cell envelope – generally consisting of a plasma membrane covered by a cell wall which, for some bacteria, may be further covered by a third layer called a capsule. Though most prokaryotes have both a cell membrane and a cell wall, there are exceptions such as *Mycoplasma* (bacteria) and *Thermoplasma* (archaea) which only possess the cell membrane layer. The envelope gives rigidity to the cell and separates the interior of the cell from its environment, serving as a protective filter. The cell wall consists of peptidoglycan in bacteria, and acts as an additional barrier against exterior forces. It also prevents the cell from expanding and bursting (cytolysis) from osmotic pressure due to a hypotonic environment. Some eukaryotic cells (plant cells and fungal cells) also have a cell wall.
- Inside the cell is the cytoplasmic region that contains the genome (DNA), ribosomes and various sorts of inclusions.[4] The genetic material is freely found in the cytoplasm. Prokaryotes can carry extrachromosomal DNA elements called plasmids, which are usually circular. Linear bacterial plasmids have been identified in several species of spirochete bacteria, including members of the genus *Borrelia* notably *Borrelia burgdorferi*, which causes Lyme disease.[14] Though not forming a nucleus, the DNA is condensed in a nucleoid. Plasmids encode additional genes, such as antibiotic resistance genes.
- On the outside, flagella and pili project from the cell's surface. These are structures (not present in all prokaryotes) made of proteins that facilitate movement and communication between cells.

Eukaryotic cells

Plants, animals, fungi, slime moulds, protozoa, and algae are all eukaryotic. These cells are about fifteen times wider than a typical prokaryote and can be as much as a thousand times greater in volume. The main distinguishing feature of eukaryotes as compared to prokaryotes is compartmentalization: the presence of membrane-bound organelles (compartments) in which specific activities take place. Most important among these is a cell nucleus,[4] an organelle that houses the cell's DNA. This nucleus gives the eukaryote its name, which means "true kernel (nucleus)". Other differences include:

- The plasma membrane resembles that of prokaryotes in function, with minor differences in the setup. Cell walls may or may not be present.
- The eukaryotic DNA is organized in one or more linear molecules, called chromosomes, which are associated with histone proteins. All chromosomal DNA is stored in the cell nucleus, separated from the cytoplasm by a membrane.[4] Some eukaryotic organelles such as mitochondria also contain some DNA.
- Many eukaryotic cells are ciliated with primary cilia. Primary cilia play important roles in chemosensation, mechanosensation, and thermosensation. Each cilium may thus be "viewed as a sensory cellular antennae that coordinates a large number of cellular signaling pathways, sometimes coupling the signaling to ciliary motility or alternatively to cell division and differentiation."[15]
- Motile eukaryotes can move using motile cilia or flagella. Motile cells are absent in conifers and flowering plants.[16] Eukaryotic flagella are more complex than those of prokaryotes.[17]

Subcellular components

All cells, whether prokaryotic or eukaryotic, have a membrane that envelops the cell, regulates what moves in and out (selectively permeable), and maintains the electric potential of the cell. Inside the membrane, the cytoplasm takes up most of the cell's volume. All cells (except red blood cells which lack a cell nucleus and most organelles to accommodate maximum space for hemoglobin) possess DNA, the hereditary material of genes, and RNA, containing the information necessary to build various proteins such as enzymes, the cell's primary machinery. There are also other kinds of biomolecules in cells. This article lists these primary cellular components, then briefly describes their function.

Membrane

The cell membrane, or plasma membrane, is a biological membrane that surrounds the cytoplasm of a

cell. In animals, the plasma membrane is the outer boundary of the cell, while in plants and prokaryotes it is usually covered by a cell wall. This membrane serves to separate and protect a cell from its surrounding environment and is made mostly from a double layer of phospholipids, which are amphiphilic (partly hydrophobic and partly hydrophilic). Hence, the layer is called a phospholipid bilayer, or sometimes a fluid mosaic membrane. Embedded within this membrane is a macromolecular structure called the porosome the universal secretory portal in cells and a variety of protein molecules that act as channels and pumps that move different molecules into and out of the cell.[4] The membrane is semi-permeable, and selectively permeable, in that it can either let a substance (molecule or ion) 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.

Cytoskeleton

The cytoskeleton acts to organize and maintain the cell's shape; anchors organelles in place; helps during endocytosis, the uptake of external materials by a cell, and cytokinesis, the separation of daughter cells after cell division; and moves parts of the cell in processes of growth and mobility. The eukaryotic cytoskeleton is composed of microtubules, intermediate filaments and microfilaments. In the cytoskeleton of a neuron the intermediate filaments are known as neurofilaments. There are a great number of proteins associated with them, each controlling a cell's structure by directing, bundling, and aligning filaments.[4] The prokaryotic cytoskeleton is less well-studied but is involved in the maintenance of cell shape, polarity and cytokinesis.[19] The subunit protein of microfilaments is a small, monomeric protein called actin. The subunit of microtubules is a dimeric molecule called tubulin. Intermediate filaments are heteropolymers whose subunits vary among the cell types in different tissues. But some of the subunit protein of intermediate filaments include vimentin, desmin, lamin (lamins A, B and C), keratin (multiple acidic and basic keratins), neurofilament proteins (NF–L, NF–M).

Genetic material

Two different kinds of genetic material exist: deoxyribonucleic acid (DNA) and ribonucleic acid (RNA). Cells use DNA for their long-term information storage. The biological information contained in an organism is encoded in its DNA sequence.[4] RNA is used for information transport (e.g., mRNA) and enzymatic functions (e.g., ribosomal RNA). Transfer RNA (tRNA) molecules are used to add amino acids during protein translation.

Prokaryotic genetic material is organized in a simple circular bacterial chromosome in the nucleoid region of the cytoplasm. Eukaryotic genetic material is divided into different,[4] linear molecules called chromosomes inside a discrete nucleus, usually with additional genetic material in some organelles like mitochondria and chloroplasts (see endosymbiotic theory).

A human cell has genetic material contained in the cell nucleus (the nuclear genome) and in the mitochondria (the mitochondrial genome). In humans the nuclear genome is divided into 46 linear DNA molecules called chromosomes, including 22 homologous chromosome pairs and a pair of sex chromosomes. The mitochondrial genome is a circular DNA molecule distinct from the nuclear DNA. Although the mitochondrial DNA is very small compared to nuclear chromosomes,[4] it codes for 13 proteins involved in mitochondrial energy production and specific tRNAs.

Foreign genetic material (most commonly DNA) can also be artificially introduced into the cell by a process called transfection. This can be transient, if the DNA is not inserted into the cell's genome, or stable, if it is. Certain viruses also insert their genetic material into the genome.

Organelles

Organelles are parts of the cell which are adapted and/or specialized for carrying out one or more vital functions, analogous to the organs of the human body (such as the heart, lung, and kidney, with each organ performing a different function).[4] Both eukaryotic and prokaryotic cells have organelles, but prokaryotic organelles are generally simpler and are not membrane-bound.

There are several types of organelles in a cell. Some (such as the nucleus and golgi apparatus) are typically solitary, while others (such as mitochondria, chloroplasts, peroxisomes and lysosomes) can be numerous (hundreds to thousands). The cytosol is the gelatinous fluid that fills the cell and surrounds the organelles.

Eukaryotic

- **Cell nucleus**: A cell's information center, the cell nucleus is the most conspicuous organelle found in a eukaryotic cell. It houses the cell's chromosomes, and is the place where almost all DNA replication and RNA synthesis (transcription) occur. The nucleus is spherical and separated from the cytoplasm by a double membrane called the nuclear envelope. The nuclear envelope isolates and protects a cell's DNA from various molecules that could accidentally damage its structure or

interfere with its processing. During processing, DNA is transcribed, or copied into a special RNA, called messenger RNA (mRNA). This mRNA is then transported out of the nucleus, where it is translated into a specific protein molecule. The nucleolus is a specialized region within the nucleus where ribosome subunits are assembled. In prokaryotes, DNA processing takes place in the cytoplasm.[4]

- **Mitochondria and chloroplasts**: generate energy for the cell. Mitochondria are self-replicating organelles that occur in various numbers, shapes, and sizes in the cytoplasm of all eukaryotic cells.[4] Respiration occurs in the cell mitochondria, which generate the cell's energy by oxidative phosphorylation, using oxygen to release energy stored in cellular nutrients (typically pertaining to glucose) to generate ATP. Mitochondria multiply by binary fission, like prokaryotes. Chloroplasts can only be found in plants and algae, and they capture the sun's energy to make carbohydrates through photosynthesis.
- **Endoplasmic reticulum**: The endoplasmic reticulum (ER) is a transport network for molecules targeted for certain modifications and specific destinations, as compared to molecules that float freely in the cytoplasm. The ER has two forms: the rough ER, which has ribosomes on its surface that secrete proteins into the ER, and the smooth ER, which lacks ribosomes.[4] The smooth ER plays a role in calcium sequestration and release.
- **Golgi apparatus**: The primary function of the Golgi apparatus is to process and package the macromolecules such as proteins and lipids that are synthesized by the cell.
- **Lysosomes and peroxisomes**: Lysosomes contain digestive enzymes (acid hydrolases). They digest excess or worn-out organelles, food particles, and engulfed viruses or bacteria. Peroxisomes have enzymes that rid the cell of toxic peroxides. The cell could not house these destructive enzymes if they were not contained in a membrane-bound system.[4]
- **Centrosome**: the cytoskeleton organiser: The centrosome produces the microtubules of a cell – a key component of the cytoskeleton. It directs the transport through the ER and the Golgi apparatus. Centrosomes are composed of two centrioles, which separate during cell division and help in the formation of the mitotic spindle. A single centrosome is present in the animal cells. They are also found in some fungi and algae cells.
- Vacuoles: Vacuoles sequester waste products and in plant cells store water. They are often described as liquid filled space and are surrounded by a membrane. Some cells, most notably Amoeba, have contractile vacuoles, which can pump water out of the cell if there is too much water. The vacuoles of plant cells and fungal cells are usually larger than those of animal cells.

Eukaryotic and prokaryotic

- **Ribosomes**: The ribosome is a large complex of RNA and protein molecules.[4] They each consist of two subunits, and act as an assembly line where RNA from the nucleus is used to synthesise proteins from amino acids. Ribosomes can be found either floating freely or bound to a membrane (the rough endoplasmatic reticulum in eukaryotes, or the cell membrane in prokaryotes).[20]

Structures outside the cell membrane

Many cells also have structures which exist wholly or partially outside the cell membrane. These structures are notable because they are not protected from the external environment by the semipermeable cell membrane. In order to assemble these structures, their components must be carried across the cell membrane by export processes.

Cell wall

Many types of prokaryotic and eukaryotic cells have a cell wall. The cell wall acts to protect the cell mechanically and chemically from its environment, and is an additional layer of protection to the cell membrane. Different types of cell have cell walls made up of different materials; plant cell walls are primarily made up of cellulose, fungi cell walls are made up of chitin and bacteria cell walls are made up of peptidoglycan.

Prokaryotic

Capsule

A gelatinous capsule is present in some bacteria outside the cell membrane and cell wall. The capsule may be polysaccharide as in pneumococci, meningococci or polypeptide as *Bacillus anthracis* or hyaluronic acid as in streptococci. Capsules are not marked by normal staining protocols and can be detected by India ink or methyl blue; which allows for higher contrast between the cells for observation.[21]:87

Flagella

Flagella are organelles for cellular mobility. The bacterial flagellum stretches from cytoplasm through the cell membrane(s) and extrudes through the cell wall. They are long and thick thread-like appendages, protein in nature. A different type of flagellum is found in archaea and a different type is

found in eukaryotes.

Fimbriae

A fimbria (plural fimbriae also known as a pilus, plural pili) is a short, thin, hair-like filament found on the surface of bacteria. Fimbriae are formed of a protein called pilin (antigenic) and are responsible for the attachment of bacteria to specific receptors on human cells (cell adhesion). There are special types of pili involved in bacterial conjugation.

Cellular processes

Replication

Cell division involves a single cell (called a *mother cell*) dividing into two daughter cells. This leads to growth in multicellular organisms (the growth of tissue) and to procreation (vegetative reproduction) in unicellular organisms. Prokaryotic cells divide by binary fission, while eukaryotic cells usually undergo a process of nuclear division, called mitosis, followed by division of the cell, called cytokinesis. A diploid cell may also undergo meiosis to produce haploid cells, usually four. Haploid cells serve as gametes in multicellular organisms, fusing to form new diploid cells.

DNA replication, or the process of duplicating a cell's genome,[4] always happens when a cell divides through mitosis or binary fission. This occurs during the S phase of the cell cycle.

In meiosis, the DNA is replicated only once, while the cell divides twice. DNA replication only occurs before meiosis I. DNA replication does not occur when the cells divide the second time, in meiosis II.[22] Replication, like all cellular activities, requires specialized proteins for carrying out the job.[4]

DNA repair

In general, cells of all organisms contain enzyme systems that scan their DNA for damages and carry out repair processes when damages are detected.[23] Diverse repair processes have evolved in organisms ranging from bacteria to humans. The widespread prevalence of these repair processes indicates the importance of maintaining cellular DNA in an undamaged state in order to avoid cell death or errors of replication due to damages that could lead to mutation. *E. coli* bacteria are a well-studied example of a cellular organism with diverse well-defined DNA repair processes. These include: (1) nucleotide excision repair, (2) DNA mismatch repair, (3) non-homologous end joining of double-strand breaks, (4) recombinational repair and (5) light-dependent repair (photoreactivation).

Growth and metabolism

Within the nucleus of the cell (*light blue*), genes (DNA, *dark blue*) are transcribed into RNA. This RNA is then subject to post-transcriptional modification and control, resulting in a mature mRNA (*red*) that is then transported out of the nucleus and into the cytoplasm (*peach*), where it undergoes translation into a protein. mRNA is translated by ribosomes (*purple*) that match the three-base codons of the mRNA to the three-base anti-codons of the appropriate tRNA. Newly synthesized proteins (*black*) are often further modified, such as by binding to an effector molecule (*orange*), to become fully active.

Between successive cell divisions, cells grow through the functioning of cellular metabolism. Cell metabolism is the process by which individual cells process nutrient molecules. Metabolism has two distinct divisions: catabolism, in which the cell breaks down complex molecules to produce energy and reducing power, and anabolism, in which the cell uses energy and reducing power to construct complex molecules and perform other biological functions. Complex sugars consumed by the organism can be broken down into simpler sugar molecules called monosaccharides such as glucose. Once inside the cell, glucose is broken down to make adenosine triphosphate (ATP),[4] a molecule that possesses readily available energy, through two different pathways.

Protein synthesis

Cells are capable of synthesizing new proteins, which are essential for the modulation and maintenance of cellular activities. This process involves the formation of new protein molecules from amino acid building blocks based on information encoded in DNA/RNA. Protein synthesis generally consists of two major steps: transcription and translation.

Transcription is the process where genetic information in DNA is used to produce a complementary RNA strand. This RNA strand is then processed to give messenger RNA (mRNA), which is free to migrate through the cell. mRNA molecules bind to protein-RNA complexes called ribosomes located in the cytosol, where they are translated into polypeptide sequences. The ribosome mediates the formation of a polypeptide sequence based on the mRNA sequence. The mRNA sequence directly relates to the polypeptide sequence by binding to transfer RNA (tRNA) adapter molecules in binding pockets within the ribosome. The new polypeptide then folds into a functional three-dimensional protein molecule.

Motility

Unicellular organisms can move in order to find food or escape predators. Common mechanisms of motion include flagella and cilia.

In multicellular organisms, cells can move during processes such as wound healing, the immune

response and cancer metastasis. For example, in wound healing in animals, white blood cells move to the wound site to kill the microorganisms that cause infection. Cell motility involves many receptors, crosslinking, bundling, binding, adhesion, motor and other proteins.[24] The process is divided into three steps – protrusion of the leading edge of the cell, adhesion of the leading edge and de-adhesion at the cell body and rear, and cytoskeletal contraction to pull the cell forward. Each step is driven by physical forces generated by unique segments of the cytoskeleton.[25][26]

Navigation, control and communication

In August 2020, scientists described one way cells – in particular cells of a slime mold and mouse pancreatic cancer–derived cells – are able to navigate efficiently through a body and identify the best routes through complex mazes: generating gradients after breaking down diffused chemoattractants which enable them to sense upcoming maze junctions before reaching them, including around corners.[27][28][29]

Multicellularity

Cell specialization/differentiation

Multicellular organisms are organisms that consist of more than one cell, in contrast to single-celled organisms.[30]

In complex multicellular organisms, cells specialize into different cell types that are adapted to particular functions. In mammals, major cell types include skin cells, muscle cells, neurons, blood cells, fibroblasts, stem cells, and others. Cell types differ both in appearance and function, yet are genetically identical. Cells are able to be of the same genotype but of different cell type due to the differential expression of the genes they contain.

Most distinct cell types arise from a single totipotent cell, called a zygote, that differentiates into hundreds of different cell types during the course of development. Differentiation of cells is driven by different environmental cues (such as cell–cell interaction) and intrinsic differences (such as those caused by the uneven distribution of molecules during division).

Origin of multicellularity

Multicellularity has evolved independently at least 25 times,[31] including in some prokaryotes, like cyanobacteria, myxobacteria, actinomycetes, *Magnetoglobus multicellularis* or *Methanosarcina*. However, complex multicellular organisms evolved only in six eukaryotic groups: animals, fungi, brown algae, red algae, green algae, and plants.[32] It evolved repeatedly for plants (Chloroplastida), once or twice for animals, once for brown algae, and perhaps several times for fungi, slime molds, and red algae.[33] Multicellularity may have evolved from colonies of interdependent organisms, from cellularization, or from organisms in symbiotic relationships.

The first evidence of multicellularity is from cyanobacteria-like organisms that lived between 3 and 3.5 billion years ago.[31] Other early fossils of multicellular organisms include the contested Grypania spiralis and the fossils of the black shales of the Palaeoproterozoic Francevillian Group Fossil B Formation in Gabon.[34]

The evolution of multicellularity from unicellular ancestors has been replicated in the laboratory, in evolution experiments using predation as the selective pressure.[31]

Origins

The origin of cells has to do with the origin of life, which began the history of life on Earth.

Origin of the first cell

There are several theories about the origin of small molecules that led to life on the early Earth. They may have been carried to Earth on meteorites (see Murchison meteorite), created at deep-sea vents, or synthesized by lightning in a reducing atmosphere (see Miller–Urey experiment). There is little experimental data defining what the first self-replicating forms were. RNA is thought to be the earliest self-replicating molecule, as it is capable of both storing genetic information and catalyzing chemical reactions (see RNA world hypothesis), but some other entity with the potential to self-replicate could have preceded RNA, such as clay or peptide nucleic acid.[35]

Cells emerged at least 3.5 billion years ago.[10][11][12] The current belief is that these cells were heterotrophs. The early cell membranes were probably more simple and permeable than modern ones, with only a single fatty acid chain per lipid. Lipids are known to spontaneously form bilayered vesicles in water, and could have preceded RNA, but the first cell membranes could also have been produced by catalytic RNA, or even have required structural proteins before they could form.[36]

Origin of eukaryotic cells

The eukaryotic cell seems to have evolved from a symbiotic community of prokaryotic cells. DNA-bearing organelles like the mitochondria and the chloroplasts are descended from ancient symbiotic oxygen-breathing proteobacteria and cyanobacteria, respectively, which were endosymbiosed by an ancestral archaean prokaryote.

There is still considerable debate about whether organelles like the hydrogenosome predated the origin of mitochondria, or vice versa: see the hydrogen hypothesis for the origin of eukaryotic cells.

Stem Cells

In multicellular organisms, stem cells are undifferentiated or partially differentiated cells that can differentiate into various types of cells and proliferate indefinitely to produce more of the same stem cell. They are the earliest type of cell in a cell lineage. They are found in both embryonic and adult organisms, but they have slightly different properties in each. They are usually distinguished from progenitor cells, which cannot divide indefinitely, and precursor or blast cells, which are usually committed to differentiating into one cell type.

In mammals, roughly 50–150 cells make up the inner cell mass during the blastocyst stage of embryonic development, around days 5–14. These have stem-cell capability. *In vivo*, they eventually differentiate into all of the body's cell types (making them pluripotent). This process starts with the differentiation into the three germ layers – the ectoderm, mesoderm and endoderm – at the gastrulation stage. However, when they are isolated and cultured *in vitro*, they can be kept in the stem-cell stage and are known as embryonic stem cells (ESCs).

Adult stem cells are found in a few select locations in the body, known as niches, such as those in the bone marrow or gonads. They exist to replenish rapidly lost cell types and are multipotent or unipotent, meaning they only differentiate into a few cell types or one cell type. In mammals, they include, among others, hematopoietic stem cells, which replenish blood and immune cells, basal cells, which maintain the skin epithelium, and mesenchymal stem cells, which maintain bone, cartilage, muscle and fat cells. Adult stem cells are a small minority of cells; they are vastly outnumbered by the progenitor cells and terminally differentiated cells that they differentiate into.

Research into stem cells grew out of findings by Canadian biologists Ernest McCulloch, James Till and Andrew J. Becker at the University of Toronto in the 1960s. As of 2016, the only established medical therapy using stem cells is hematopoietic stem cell transplantation, first performed in 1958 by French oncologist Georges Mathé. Since 1998 however, it has been possible to culture and differentiate human embryonic stem cells (in stem-cell lines). The process of isolating these cells has been controversial, because it typically results in the destruction of the embryo. Sources for isolating ESCs have been restricted in some European countries and Canada, but others such as the UK and China have promoted the research. Somatic cell nuclear transfer is a cloning method that can be used to create a cloned embryo for the use of its embryonic stem cells in stem cell therapy. In 2006, a Japanese team led by Shinya Yamanaka discovered a method to convert mature body cells back into stem cells. These were termed induced pluripotent stem cells (iPSCs).

In practice, stem cells are identified by whether they can regenerate tissue. For example, the defining test for bone marrow or hematopoietic stem cells (HSCs) is the ability to transplant the cells and save an individual without HSCs. This demonstrates that the cells can produce new blood cells over a long term. It should also be possible to isolate stem cells from the transplanted individual, which can themselves be transplanted into another individual without HSCs, demonstrating that the stem cell was able to self-renew.

Properties of stem cells can be illustrated *in vitro*, using methods such as clonogenic assays, in which single cells are assessed for their ability to differentiate and self-renew. Stem cells can also be isolated by their possession of a distinctive set of cell surface markers. However, *in vitro* culture conditions can alter the behavior of cells, making it unclear whether the cells shall behave in a similar manner *in vivo*. There is considerable debate as to whether some proposed adult cell populations are truly stem cells.

Embryonic stem cells (ESCs) are the cells of the inner cell mass of a blastocyst, formed prior to implantation in the uterus. In human embryonic development the blastocyst stage is reached 4–5 days after fertilization, at which time it consists of 50–150 cells. ESCs are pluripotent and give rise during development to all derivatives of the three germ layers: ectoderm, endoderm and mesoderm. In other words, they can develop into each of the more than 200 cell types of the adult body when given sufficient and necessary stimulation for a specific cell type. They do not contribute to the extraembryonic membranes or to the placenta.

During embryonic development the cells of the inner cell mass continuously divide and become more specialized. For example, a portion of the ectoderm in the dorsal part of the embryo specializes as 'neurectoderm', which will become the future central nervous system. Later in development, neurulation causes the neurectoderm to form the neural tube. At the neural tube stage, the anterior portion undergoes encephalization to generate or 'pattern' the basic form of the brain. At this stage of development, the principal cell type of the CNS is considered a neural stem cell.

The neural stem cells self-renew and at some point transition into radial glial progenitor cells (RGPs). Early-formed RGPs self-renew by symmetrical division to form a reservoir group of progenitor cells. These cells transition to a neurogenic state and start to divide asymmetrically to produce a large diversity of many different neuron types, each with unique gene expression, morphological, and functional characteristics. The process of generating neurons from radial glial cells is called neurogenesis. The radial glial

cell, has a distinctive bipolar morphology with highly elongated processes spanning the thickness of the neural tube wall. It shares some glial characteristics, most notably the expression of glial fibrillary acidic protein (GFAP). The radial glial cell is the primary neural stem cell of the developing vertebrate CNS, and its cell body resides in the ventricular zone, adjacent to the developing ventricular system. Neural stem cells are committed to the neuronal lineages (neurons, astrocytes, and oligodendrocytes), and thus their potency is restricted.

Nearly all research to date has made use of mouse embryonic stem cells (mES) or human embryonic stem cells (hES) derived from the early inner cell mass. Both have the essential stem cell characteristics, yet they require very different environments in order to maintain an undifferentiated state. Mouse ES cells are grown on a layer of gelatin as an extracellular matrix (for support) and require the presence of leukemia inhibitory factor (LIF) in serum media. A drug cocktail containing inhibitors to GSK3B and the MAPK/ERK pathway, called 2i, has also been shown to maintain pluripotency in stem cell culture. Human ESCs are grown on a feeder layer of mouse embryonic fibroblasts and require the presence of basic fibroblast growth factor (bFGF or FGF-2). Without optimal culture conditions or genetic manipulation, embryonic stem cells will rapidly differentiate.

A human embryonic stem cell is also defined by the expression of several transcription factors and cell surface proteins. The transcription factors Oct-4, Nanog, and Sox2 form the core regulatory network that ensures the suppression of genes that lead to differentiation and the maintenance of pluripotency. The cell surface antigens most commonly used to identify hES cells are the glycolipids stage specific embryonic antigen 3 and 4, and the keratan sulfate antigens Tra-1-60 and Tra-1-81. The molecular definition of a stem cell includes many more proteins and continues to be a topic of research.

By using human embryonic stem cells to produce specialized cells like nerve cells or heart cells in the lab, scientists can gain access to adult human cells without taking tissue from patients. They can then study these specialized adult cells in detail to try to discern complications of diseases, or to study cell reactions to proposed new drugs.

Because of their combined abilities of unlimited expansion and pluripotency, embryonic stem cells remain a theoretically potential source for regenerative medicine and tissue replacement after injury or disease, however, there are currently no approved treatments using ES cells. The first human trial was approved by the US Food and Drug Administration in January 2009. However, the human trial was not initiated until October 13, 2010 in Atlanta for spinal cord injury research. On November 14, 2011 the company conducting the trial (Geron Corporation) announced that it will discontinue further development of its stem cell programs. Differentiating ES cells into usable cells while avoiding transplant rejection are just a few of the hurdles that embryonic stem cell researchers still face. Embryonic stem cells, being pluripotent, require specific signals for correct differentiation – if injected directly into another body, ES cells will differentiate into many different types of cells, causing a teratoma. Ethical considerations regarding the use of unborn human tissue are another reason for the lack of approved treatments using embryonic stem cells. Many nations currently have moratoria or limitations on either human ES cell research or the production of new human ES cell lines.

Embryonic stem cells (ESCs) have the ability to divide indefinitely while keeping their pluripotency, which is made possible through specialized mechanisms of cell cycle control. Compared to proliferating somatic cells, ESCs have unique cell cycle characteristics—such as rapid cell division caused by shortened G1 phase, absent G0 phase, and modifications in cell cycle checkpoints—which leaves the cells mostly in S phase at any given time. ESCs' rapid division is demonstrated by their short doubling time, which ranges from 8 to 10 hours, whereas somatic cells have doubling time of approximately 20 hours or longer. As cells differentiate, these properties change: G1 and G2 phases lengthen, leading to longer cell division cycles. This suggests that a specific cell cycle structure may contribute to the establishment of pluripotency.

Particularly because G1 phase is the phase in which cells have increased sensitivity to differentiation, shortened G1 is one of the key characteristics of ESCs and plays an important role in maintaining undifferentiated phenotype. Although the exact molecular mechanism remains only partially understood, several studies have shown insight on how ESCs progress through G1—and potentially other phases—so rapidly.

The cell cycle is regulated by complex network of cyclins, cyclin-dependent kinases (Cdk), cyclin-dependent kinase inhibitors (Cdkn), pocket proteins of the retinoblastoma (Rb) family, and other accessory factors. Foundational insight into the distinctive regulation of ESC cell cycle was gained by studies on mouse ESCs (mESCs). mESCs showed a cell cycle with highly abbreviated G1 phase, which enabled cells to rapidly alternate between M phase and S phase. In a somatic cell cycle, oscillatory activity of Cyclin-Cdk complexes is observed in sequential action, which controls crucial regulators of the cell cycle to induce unidirectional transitions between phases: Cyclin D and Cdk4/6 are active in the G1 phase, while

Cyclin E and Cdk2 are active during the late G1 phase and S phase; and Cyclin A and Cdk2 are active in the S phase and G2, while Cyclin B and Cdk1 are active in G2 and M phase. However, in mESCs, this typically ordered and oscillatory activity of Cyclin-Cdk complexes is absent. Rather, the Cyclin E/Cdk2 complex is constitutively active throughout the cycle, keeping retinoblastoma protein (pRb) hyperphosphorylated and thus inactive. This allows for direct transition from M phase to the late G1 phase, leading to absence of D-type cyclins and therefore a shortened G1 phase. Cdk2 activity is crucial for both cell cycle regulation and cell-fate decisions in mESCs; downregulation of Cdk2 activity prolongs G1 phase progression, establishes a somatic cell-like cell cycle, and induces expression of differentiation markers.

In human ESCs (hESCs), the duration of G1 is dramatically shortened. This has been attributed to high mRNA levels of G1-related Cyclin D2 and Cdk4 genes and low levels of cell cycle regulatory proteins that inhibit cell cycle progression at G1, such as $p21^{CipP1}$, $p27^{Kip1}$, and $p57^{Kip2}$. Furthermore, regulators of Cdk4 and Cdk6 activity, such as members of the Ink family of inhibitors (p15, p16, p18, and p19), are expressed at low levels or not at all. Thus, similar to mESCs, hESCs show high Cdk activity, with Cdk2 exhibiting the highest kinase activity. Also similar to mESCs, hESCs demonstrate the importance of Cdk2 in G1 phase regulation by showing that G1 to S transition is delayed when Cdk2 activity is inhibited and G1 is arrest when Cdk2 is knocked down. However unlike mESCs, hESCs have a functional G1 phase. hESCs show that the activities of Cyclin E/Cdk2 and Cyclin A/Cdk2 complexes are cell cycle-dependent and the Rb checkpoint in G1 is functional.

ESCs are also characterized by G1 checkpoint non-functionality, even though the G1 checkpoint is crucial for maintaining genomic stability. In response to DNA damage, ESCs do not stop in G1 to repair DNA damages but instead, depend on S and G2/M checkpoints or undergo apoptosis. The absence of G1 checkpoint in ESCs allows for the removal of cells with damaged DNA, hence avoiding potential mutations from inaccurate DNA repair. Consistent with this idea, ESCs are hypersensitive to DNA damage to minimize mutations passed onto the next generation.

Stem cell division and differentiation A: stem cell; B: progenitor cell; C: differentiated cell; 1: symmetric stem cell division; 2: asymmetric stem cell division; 3: progenitor division; 4: terminal differentiation. Adult stem cells, also called somatic (from Greek σωματικός, "of the body") stem cells, are stem cells which maintain and repair the tissue in which they are found. They can be found in children, as well as adults.

Stem cells can also be taken from umbilical cord blood just after birth. Of all stem cell types, autologous harvesting involves the least risk. By definition, autologous cells are obtained from one's own body, just as one may bank his or her own blood for elective surgical procedures.

Pluripotent adult stem cells are rare and generally small in number, but they can be found in umbilical cord blood and other tissues. Bone marrow is a rich source of adult stem cells, which have been used in treating several conditions including liver cirrhosis, chronic limb ischemia and endstage heart failure. The quantity of bone marrow stem cells declines with age and is greater in males than females during reproductive years. Much adult stem cell research to date has aimed to characterize their potency and self-renewal capabilities. DNA damage accumulates with age in both stem cells and the cells that comprise the stem cell environment. This accumulation is considered to be responsible, at least in part, for increasing stem cell dysfunction with aging.

Adult stem cells have limitations with their potency; unlike embryonic stem cells (ESCs), they are not able to differentiate into cells from all three germ layers. As such, they are deemed multipotent.

However, reprogramming allows for the creation of pluripotent cells, induced pluripotent stem cells (iPSCs), from adult cells. These are not adult stem cells, but somatic cells (e.g. epithelial cells) reprogrammed to give rise to cells with pluripotent capabilities. Using genetic reprogramming with protein transcription factors, pluripotent stem cells with ESC-like capabilities have been derived. The first demonstration of induced pluripotent stem cells was conducted by Shinya Yamanaka and his colleagues at Kyoto University. They used the transcription factors Oct3/4, Sox2, c-Myc, and Klf4 to reprogram mouse fibroblast cells into pluripotent cells. Subsequent work used these factors to induce pluripotency in human fibroblast cells. Junying Yu, James Thomson, and their colleagues at the University of Wisconsin–Madison used a different set of factors, Oct4, Sox2, Nanog and Lin28, and carried out their experiments using cells from human foreskin. However, they were able to replicate Yamanaka's finding that inducing pluripotency in human cells was possible.

Induced pluripotent stem cells differ from embryonic stem cells. They share many similar properties, such as pluripotency and differentiation potential, the expression of pluripotency genes, epigenetic patterns, embryoid body and teratoma formation, and viable chimera formation, but there are many differences within these properties. The chromatin of iPSCs appears to be more "closed" or methylated than that of ESCs. Similarly, the gene expression pattern between ESCs and iPSCs, or even iPSCs sourced from different origins. There are thus

questions about the "completeness" of reprogramming and the somatic memory of induced pluripotent stem cells. Despite this, inducing somatic cells to be pluripotent appears to be viable.

As a result of the success of these experiments, Ian Wilmut, who helped create the first cloned animal Dolly the Sheep, has announced that he will abandon somatic cell nuclear transfer as an avenue of research.

IPSCs has helped the field of medicine significantly by finding numerous ways to cure diseases. Since human IPSCc has given the advantage to make vitro models to study toxins and pathogenesis.

Furthermore, induced pluripotent stem cells provide several therapeutic advantages. Like ESCs, they are pluripotent. They thus have great differentiation potential; theoretically, they could produce any cell within the human body. Moreover, unlike ESCs, they potentially could allow doctors to create a pluripotent stem cell line for each individual patient. Frozen blood samples can be used as a valuable source of induced pluripotent stem cells. Patient specific stem cells allow for the screening for side effects before drug treatment, as well as the reduced risk of transplantation rejection. Despite their current limited use therapeutically, iPSCs hold create potential for future use in medical treatment and research.

The key factors controlling the cell cycle also regulate pluripotency. Thus, manipulation of relevant genes can maintain pluripotency and reprogram somatic cells to an induced pluripotent state. However, reprogramming of somatic cells is often low in efficiency and considered stochastic.

With the idea that a more rapid cell cycle is a key component of pluripotency, reprogramming efficiency can be improved. Methods for improving pluripotency through manipulation of cell cycle regulators include: overexpression of Cyclin D/Cdk4, phosphorylation of Sox2 at S39 and S253, overexpression of Cyclin A and Cyclin E, knockdown of Rb, and knockdown of members of the Cip/Kip family or the Ink family. Furthermore, reprogramming efficiency is correlated with the number of cell divisions happened during the stochastic phase, which is suggested by the growing inefficiency of reprogramming of older or slow diving cells.

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