The glossary

A guide to understand VCP key principles

Allele

An allele is a specific variation of a gene. A person inherits two alleles for each gene, one from each parent. Each person's gene sequence is slightly different from another person's. Blood type and eye color are examples of alleles.

Assays

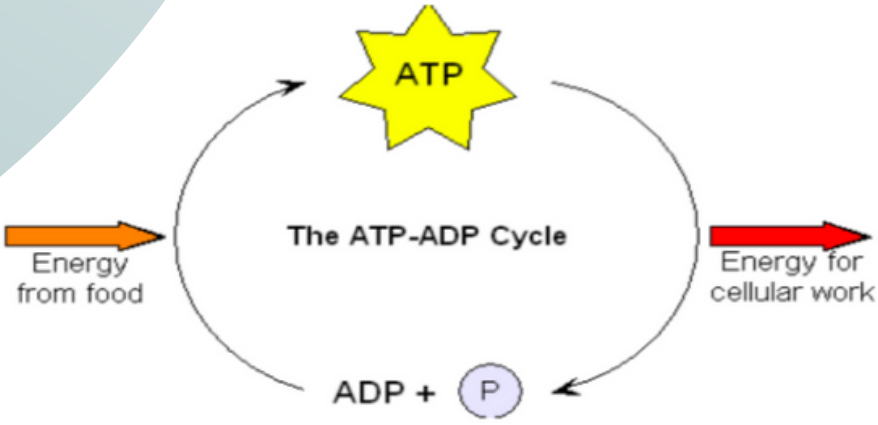
An assay is an experiment that allows us to measure the activity of a molecule or the amount of a molecule. Think of an assay as a way to test something.

FOR THE NERDS

The molecules assessed in the assay can be proteins, nucleic acids, such as an mRNA, or lipids. Each molecule present in a cell has a specific function. When its activity is measured in an experiment, it is called an activity assay. An example of an activity assay is the amount of ATP an ATPase enzyme degrades. When the molecule's function is measured, it is called a functional assay. Mechanisms like autophagy or cell proliferation are functional assays.

ATPase

ATPases are proteins that break the link between two phosphate groups in the ATP molecule. This process produces energy for the cell to use.



This reaction is reversible, so an ATP molecule can be formed back from an ADP molecule + Pi, but this time energy is being used instead of released.

From: https://slideplayer.com/slide/6882192/

AAA+

AAA+ is a superfamily of proteins that produces energy and uses it for different functions. VCP/p97 belongs to the AAA+ superfamily. AAA+ is a particular type of ATPase. AAA+ stands for ATPase Associated with diverse cellular Activities.

Autophagy

Autophagy is the body's way of removing part of a cell that is damaged. When the cell is under stress or has a shortage of nutrients, it breaks parts of the cell into pieces that can be used for other essential processes. Autophagy is a cellular process that is similar to recycling because it saves, repurposes, and reuses resources.

FOR THE NERDS

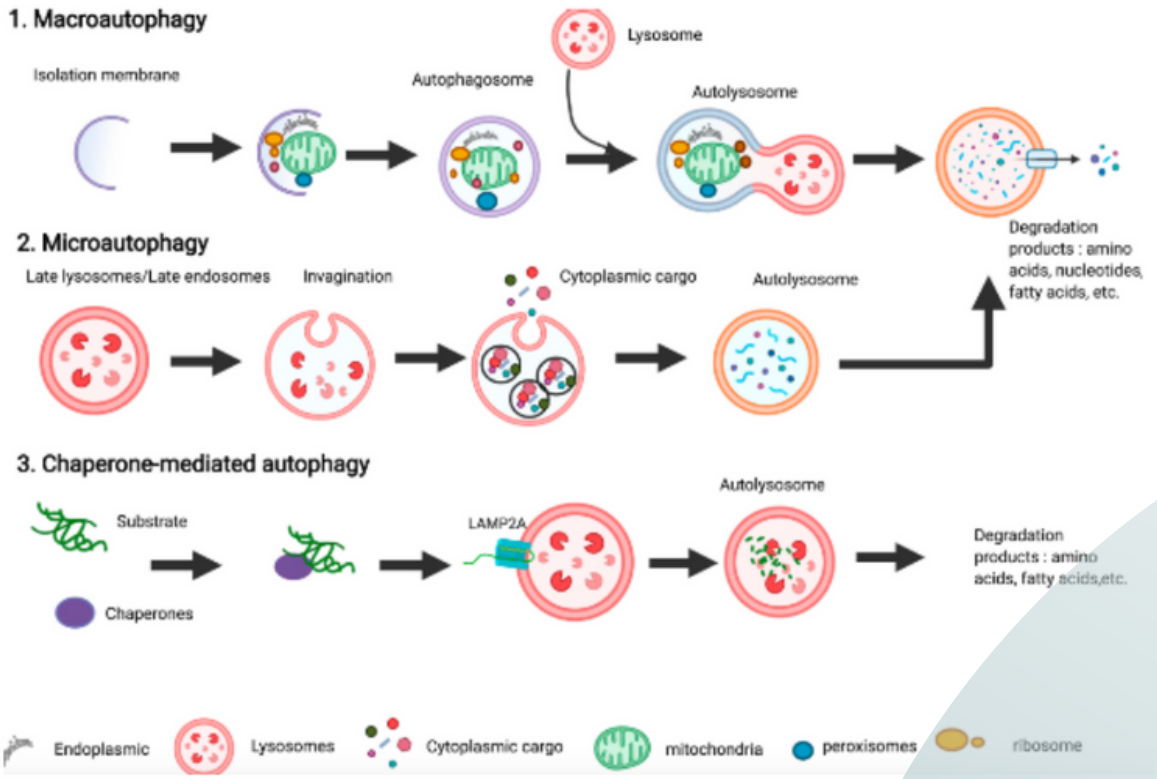
The process of breaking down cell organs and self-degrading is called autophagy ("eating itself"). There are three mechanisms of autophagy: macroautophagy, microautophagy, and chaperone-mediated autophagy.

The process is mainly done through macroautophagy, a sequence of events involving the formation of a phagosome (in the shape of an open bag) that will englobe the "cargo" and then fuse with a lysosome (a bag containing a corrosive environment) that will destroy the cargo and release it. The destruction of some specific organelles has specific names, such as mitophagy for mitochondria, as described further in this glossary.

Autophagy occurs at low basal rates in healthy cells but is rapidly upregulated during nutrient/environmental stress.

From "Autophagy in health and disease" edited by Beverly A. Rothermel, Abhinav Diwan. Academic Press Elseveir.

Autophagy Process



The figure represents 3 main autophagy process. From "Autophagy in health and disease" edited by Beverly A. Rothermel, Abhinav Diwan. Academic Press Elseveir.

Autosomal Dominant Mutation

For autosomal dominant mutations, only one parent has to have the genetic mutation to pass the mutation to an offspring. A child has a 50% chance of inheriting an autosomal dominant mutation from an affected parent. VCP disease is caused by an autosomal dominant mutation in the VCP gene.

FOR THE NERDS

Chromosomes can be of 2 types, sexual (X or Y), which gives the sex of a living animal, or nonsex (autosomal), which are the rest of the chromosomes. Autosomal chromosomes are numbered from 1 to 22 for humans. When a mutation is only present in one of the pair of chromosomes and just one mutation is sufficient to trigger a specific disease, it is said to be dominant.

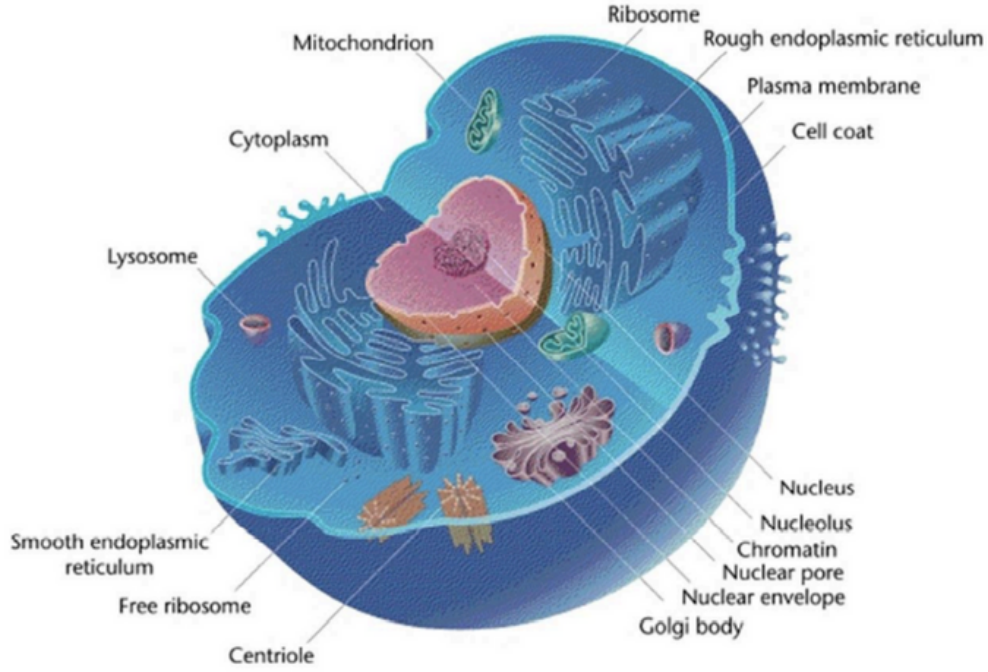
Cell

The cell is the smallest unit of life in the body. Cells are enclosed by membranes and contain small organs that allow the cell to live, work, and reproduce

FOR THE NERDS

The cell can live independently and reproduce itself if in the right conditions. In this condition, the cell is supplied with nutrients, oxygen, and CO2, and has a temperature of 37 Celsius. The cell is similar to a bag, made of a membrane of phospholipids containing different small organs called organelles, each having a specific function, allowing the cell to live and work.

Cells don't create themselves; they all derive from the division of a parent cell. The prominent organelles are the nucleus containing the genome, the endoplasmic reticulum, ER, where proteins are produced; the mitochondria, the cell's power center; and the lysosomes, the recycling factory. The organelles float in a substance called the cytosol or the cytoplasm. The structure and shape of the cell are given by a skeleton, called the cytoskeleton, which also transmits signals from outside the cell.



Mediran / Wikimedia Commons / CC-BY-SA-3.0
From: https://www.thoughtco.com/all-about-animal-cells-373379

Cell Cycle

The cell cycle is the series of events that take place in a cell as it grows and divides. The cell cycle is also referred to as the cell division cycle. To reproduce, a parent cell divides into two daughter cells.

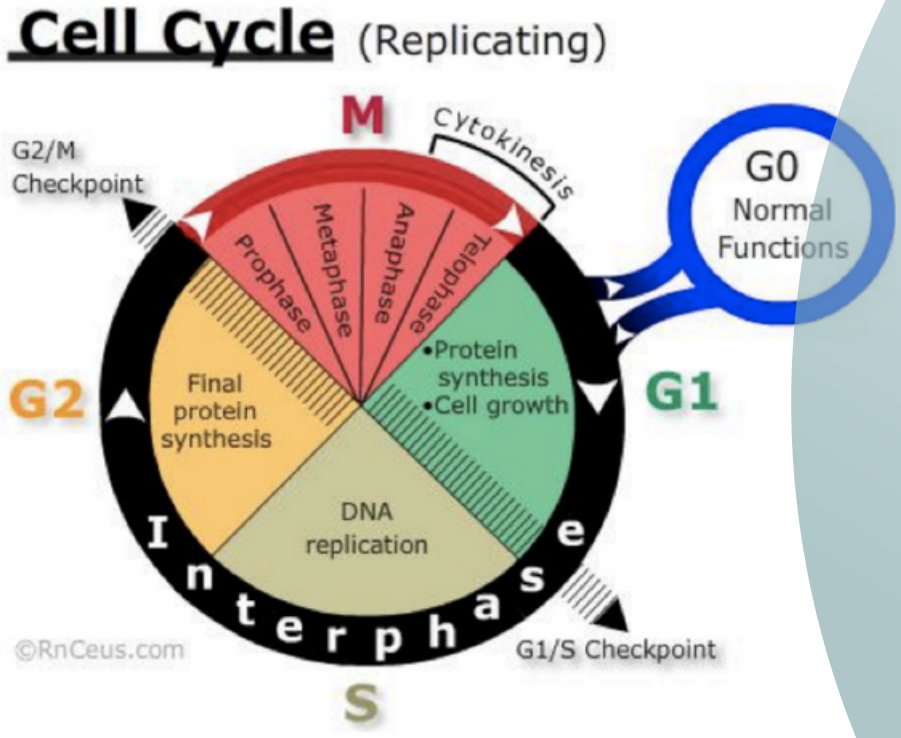


Image from: https://www.rnceus.com/chem/cycle.html

FOR THE NERDS

When the cell is born from the split of the parent cell under the process called mitosis. Epigenetic signals will either tell the cell to stay in the cell cycle and go on with the multiplication process or to exit the cell cycle to start its function in the tissue it belongs to (phase G0). Note that the G0 phase is when the cell is mature; the phase is considered a phase of "no growth but work." There are checkpoints to ensure that the replication and division can go on or be stopped if there is a problem or the conditions for a proper division are not met. Differentiated cells doing a specific function may never re-enter the cell cycle but will die by apoptosis when too damaged to function correctly, for example, this happens to neurons.

Chromosome

Chromosomes are thread-like structures that contain genetic information, called genes. Chromosomes are long chains of DNA that are compacted and rolled-up around proteins. Humans have 23 pairs of chromosomes of varying lengths in every cell.

FOR THE NERDS

DNA is only in the chromosome form when the cell splits into two new cells (cellular multiplication) under the process of mitosis. During this process, the chromosomes are duplicated and sorted out, then moved to the extremities of the cell (called the cell poles). The cell membrane will rejoin in the middle and create two new cells. It is easier to align, sort out, and move the compact chromosomes than the loose form of the DNA chain, the chromatin. Under the chromosome shape, the genes cannot be transcribed or expressed.

Structure and nomenclature: The 23 pairs of human chromosomes are named using a numerical system based on the size of the chromosome. Chromosomes 1 through 22 are the autosomal chromosomes, and chromosome 23 are the sexual chromosomes (named X and Y). Chromosomes have a centromere (a DNA construction zone which will delimit the chromosome into two parts), the short arm (called p), and the long arm (called q). The location of a gene starts with the number of the chromosome, is followed by the letter (indicating if it is on the p or q part of the chromosome), and ends with the distance to the centromere.

The VCP gene location is 9p13.3

Chromatin

Chromatin is the same as a chromosome, but it is in an unrolled form. Chromatin is a chain of DNA that is wrapped around a type of protein called histones.

Chromatin (continued)

FOR THE NERDS

DNA does not always come in the chromosome form. When the cell is not in a phase of multiplication but is working, it needs to produce precise types of proteins to perform its function. In that phase, the DNA is relatively de-compacted, called chromatin. When the genes need to be expressed to make a protein, part of the chromatin uncoils and opens, accessible to the reading machinery. In the picture below, you can see that chromatin looks like a line with small balls (the protein histones).

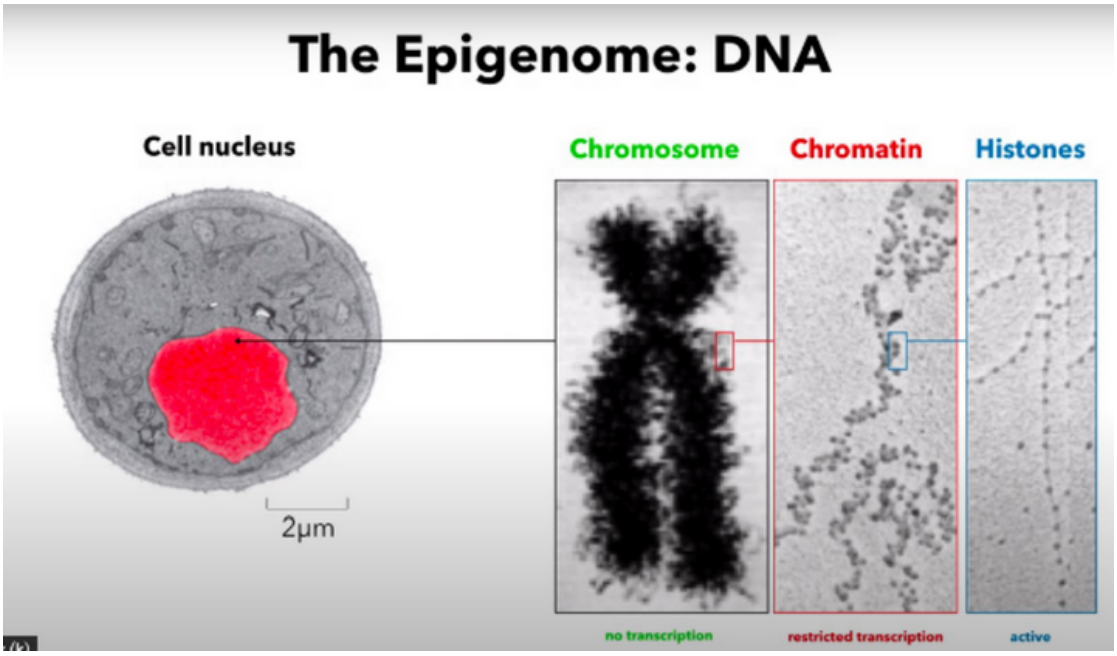


Image extracted from https://www.youtube.com/watch?v=IAu44BkOaSs

Cofactor

Some proteins need the help of another molecule, often another protein, to execute a function. The two proteins interact or bind together and change their shape to act on a third party. These are called cofactors. VCP/p97 has more than 30 cofactors, and additional ones are discovered regularly. This allows VCP/p97 to have a large variety of functions.

CRISPR-cas

CRISPR-Cas is an association of proteins and RNA from bacteria that can recognize a specific sequence of DNA and cut it open.

CRISPR-cas (continued)

FOR THE NERDS

CRISPR stands for Clustered Regularly Interspaced Short Palindromic Repeats. Cas stands for CRISPR-associated protein, a family of at least 20 Cas proteins. The CRISPR-Cas system recognizes a specifically targeted sequence (CRISPR's role) and cuts the DNA (Cas's role) at that site. It is a helpful tool for molecular biology purposes. For example, multiple cuts in a gene will block its transcription, thus, knocking out the gene and preventing the formation of its protein. The consequences of the missing protein can then be studied. The cell has an efficient apparatus to repair DNA damage that, with proper guidance, can be used to repair a cut performed at a mutation site and edit the sequence. (VCP is part of this fixing team.) The system, CRISPR-Cas, is challenging to use in humans since it is too big to be delivered via an AAV vector. CRISPR-Cas requires treatments for a double infection, one with CRISPR and the other one with Cas. CRISPR-Cas is also not 100% specific, so it cuts the DNA outside the targeted sequence, destroying other genes (This is called off-target). There are cytotoxicity issues and a weak efficacy, with less than 15% of cells responding.

Watch the videos:
https://www.youtube.com/watch?v=4YKFw2KZA5o
https://www.youtube.com/watch?v=4YKFw2KZA5o&t=60s
https://www.youtube.com/watch?v=IiPL5HgPehs

Cytoplasm

The cytoplasm is a gelatinous liquid inside a cell. The organelles float in the cytoplasm. Cytoplasm is composed of water, salts, ions, and macromolecules.

Disease-Modifying Therapy

Disease-modifying therapies are therapies that do not provide a cure but can modify the course of the disease. These therapies can decrease the speed of the disease's evolution and slow down the damage caused by the disease.

DNA

DNA carries genetic instructions that allows a cell to function. DNA is made up of two long molecules, arranged in a spiral. Each cell contains almost 6 feet (1.8 meters) of DNA if it were unfolded.

DNA (continued)

FOR THE NERDS

DNA stands for DeoxyriboNucleic Acid. Humans have 46 of these chains of different lengths, present in every cell nucleus. (A circular DNA molecule is present in every mitochondrion.) The DNA chain is a double helix rolled up and compacted to form the chromatin and the chromosomes. Each chromosome has millions of bases linked together in a precise order called a sequence.

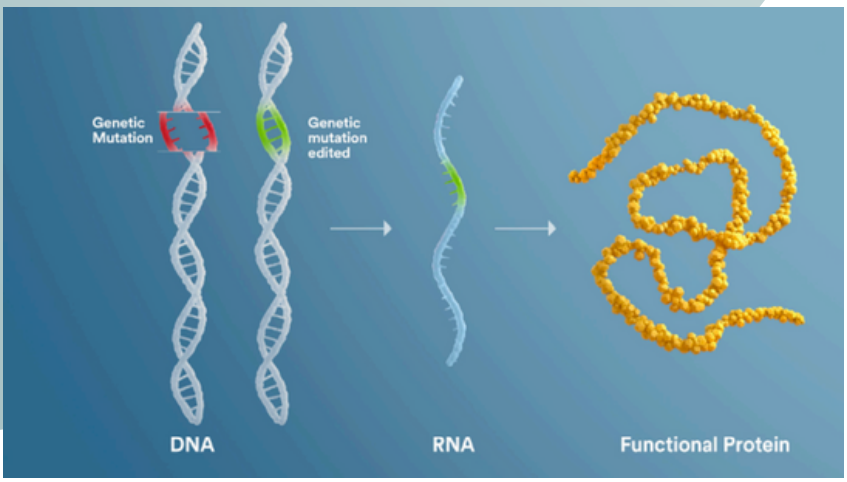
The DNA contains segments called genes, which are the instructions to build proteins. The VCP gene provides instructions to build for the VCP/p97 protein.

The information in DNA is stored as a code made up of four building blocks called nucleotide bases (A, C, G, and T). The bases are attached one after the other in a long chain in what appears to be a random sequence like ATGCCTAGCATGGTTAACC. However, the sequence order is of extreme importance to maintain the right code.

An error in the sequence, such as one missing or added nucleotide, can completely change the instructions on making the protein. This results in a protein that cannot function properly.

Editing

Editing is the process of correcting a gene mutation by changing the DNA. Editing is a modification of the DNA sequence by replacing, adding, or removing a piece of a gene.



https://www.sarepta.com/science/gene-editing

DID YOU KNOW?

The editing techniques have been revolutionized by the use of CRISPR-Cas systems. It is possible to perform gene editing in cells, but it is very difficult to achieve in an animal because of toxicity, lack of specificity, and low efficiency.

Epigenetics

Epigenetics is the link between the gene and its environment. You can think of it as the study of how the gene is switched ON or OFF by “actors” in the cells. The “actors” can be inherited from the parents or influenced by the environment, such as by food or the sun.

FOR THE NERDS

Epigenetics is the study of mechanisms that cause gene expression changes but do NOT change the DNA sequence. It includes DNA methylation, histone modification, non-coding RNA activity such as microRNAs, and the effect of non-coding repeating regions in the DNA sequence. All of these mechanisms end up acting on the physical accessibility of the gene to be transcribed and expressed in its protein. The epigenetic modifications are moving the conformation of the genome by modifying the electric charge on the complex that rolls up the genome (protein -DNA); and either repulse each other (+/+) or (-/-) and open access by de-compacting the chain of DNA, or attracting each other to condensate the DNA more tightly and prevent molecules from reading the DNA.

Watch the videos:
https://www.youtube.com/watch?v=XelGO582s4U
https://www.youtube.com/watch?v=JTBg6hqeuTg

Exon and Intron

A gene is made of a succession of blocks of DNA sequences with different functions. These blocks are called exons and introns. The exons provide instructions on the material for building the protein. The introns give the option to use or skip a part of the material.

FOR THE NERDS

The introns are non-coding sequences of the gene, while the exons are mainly coding sequences. Exons carry the codons that determine the type of aminoacid to associate in the chain building the protein; however, some parts of exons are non-coding sequences located either at the beginning or the end of an mRNA, the 5'UTR and 3'UTR to initiate or end the translation. Read also "Splicing" in that glossary.

Enzyme Replacement Therapy

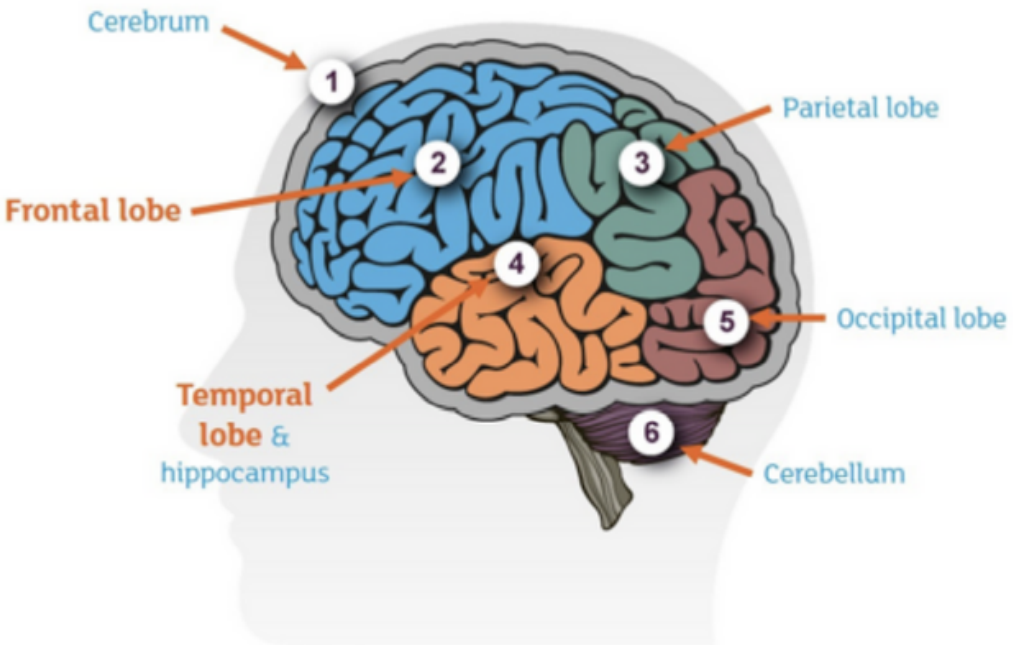
This is a medical treatment used to treat diseases when an enzyme is absent or not functional. The most common method of enzyme replacement therapy is through IV infusions containing a solution of replacement enzymes.

Frontotemporal Dementia

Dementia is a decline in mental abilities and covers several types of disabilities, depending on the type of dementia. Frontotemporal dementia (FTD) is a group of disorders characterized by a change in behavior and difficulties speaking. FTD is a progressive disorder meaning the symptoms appear over time. Frontotemporal refers to the part of the brain where the disease occurs, the front (fronto) and the sides (temporal). VCP mutations can cause frontotemporal dementia, but there are other causes of FTD as well.

FOR THE NERDS

FTD has several causes, not all of them elucidated; some are linked with ALS with an unusual mutation in the c9orf72 gene, and others are due to mutations in the GRN gene or the Tau gene. The FTD caused by VCP mutations is characterized by neurodegeneration and accumulation at the wrong place in the neurons of a protein named TDP43.



https://www.alzheimersresearchuk.org/blog/untangling-frontotemporal-dementia/

FTD (continued)

Problems in the frontal lobe trigger changes in the personality and behavior of the patient. It is our emotional control center and home to our personality. The frontal lobes are involved in motor function, problem solving, spontaneity, memory, language, initiation, judgment, impulse control, and social and sexual behavior.

The main functions of the temporal lobes include understanding language, memory acquisition, face recognition, object recognition, perception, and processing auditory information. The inner substructures of the temporal lobe include part of the limbic system, hippocampus for the long-term memory, and the amygdala, known as the center of emotions. The auditory cortex is also located in the temporal lobe; it is responsible for processing auditory information and is especially important in processing the semantics of language and vision. Primary Progressive Aphasia (PPA) is associated with FTD, including difficulty using or understanding words and difficulty speaking correctly (e.g., slurred speech).

Gene

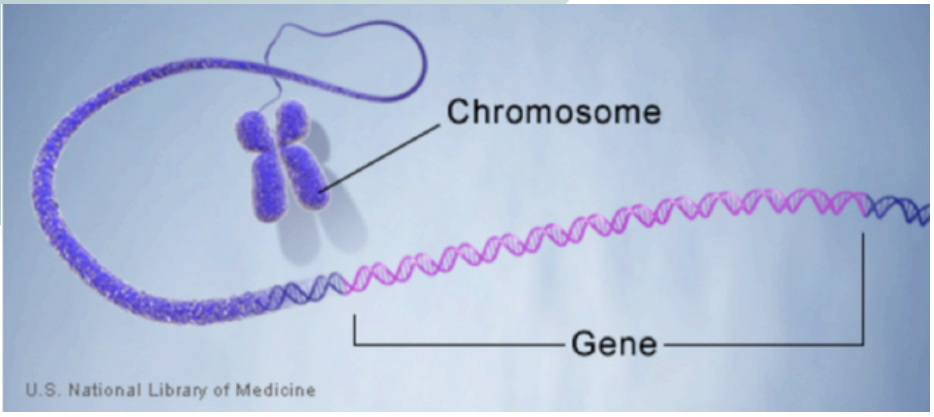
A gene is a part of the DNA chain that gives the instructions for building a protein or building a regulatory RNA.

FOR THE NERDS

The human project estimated approximately that 20,000 is the number of genes in humans. Every gene has two copies, one on each chromosome. Since genes are part of the DNA, they are hereditary; one of the two gene copies will be transmitted randomly to the offspring. The sequence of a gene can be slightly different from one person to another; the different versions of a gene are called alleles; the gene coding for the blood type has different alleles, either A, B, or O. A gene is composed of several parts, regulators sequences, and coding sequences.

FOR THE SUPER NERDS

The initiation of the transcription is regulated by a promoter, a sequence where other proteins can bind and prompt the reading of the gene, followed by the exons and introns that will be transcribed to form the pre-mRNA and then the termination signal sequence that will stop the transcription. The VCP gene promoter contains sites for: CREB, deltaCREB, GR, NF-kappaB1, Pax-5, POU3F2, POU3F2 (N-Oct-5a), POU3F2 (N-Oct-5b), RREB-1, and STAT3



Genetic Code

The genetic code is used to read the messenger of a gene and build proteins. The mRNA is the messenger of the gene.

FOR THE NERDS

The language used in the genetic code is made of groups of 3 nucleotide bases, called codons, which indicate which amino acid the ribosomes must associate in the protein's chain. The AUG codon is the Start codon; it codes for the amino acid methionine and indicates that the cell should begin synthesizing a protein from this location on the mRNA. UAA, UAG, and UGA are the STOP codons indicating that the mRNA-reading machinery must stop its protein production and remove itself from the mRNA.

You can find the genetic code information at: https://researchtweet.com/genetic-code-chart-table-definition-and-examples/

Genetic Disease

Having a genetic disease means having a gene variation that is considered an error in the genetic material, the DNA. It can be hereditary, transmitted by one or both parents, or it can be a *de novo* variant.

HOW ARE GENETIC ERRORS CREATED?

During embryonic growth cells multiply at a high rate, or during life, cells are not eternal; they are born, live and work, and then die. It is, therefore, necessary to constantly produce new cells. New cells are born from a "parent cell" division into two “daughter cells.” Before dividing into two daughter cells, the parent cell must replicate its DNA so that the set can be divided in two and equally distributed in the new daughter cells.

Copying millions of nucleotides and keeping the exact same sequence is a challenge. The cells make many mistakes, which are immediately corrected by special machinery dedicated to checking, revising, and editing the sequences. However, this proofreading is not 100% efficient, leaving some errors in the newly replicated DNA: these errors are mutations, creating **"De Novo" variants.**

Regarding genetics, cells can be separated into two broad categories: the germline which are, the reproductive cells, and the rest of the body, which are the somatic cells (soma means body in Greek). If a mutation is present in the germline it is transmissible to offspring. If a mutation is present in the soma or part of the soma, but not in the germline, it is not transmissible to the offspring.

Gene Editing Therapy

Gene-editing therapy is most often performed with the CRISPR-Cas tool (read CRISPR-Cas) to correct a mutation responsible for a disease. It is highly unspecific and toxic if used systematically (given in the whole body via the blood). However, it has been done for ocular treatment because the CRISPR-Cas system was delivered locally. New discoveries are helping to develop this tool, advancing every day.

Gene Replacement Therapy

This therapy consists of bringing a "wild type" gene to the cells of an individual. (A wild type gene is a gene without mutations.) With gene replacement therapy, the variant gene is still present in the person, but the massive addition of the functional gene brings enough protein production to cure the patient.

SPECIAL SECTION: Some Challenges with Gene Therapy

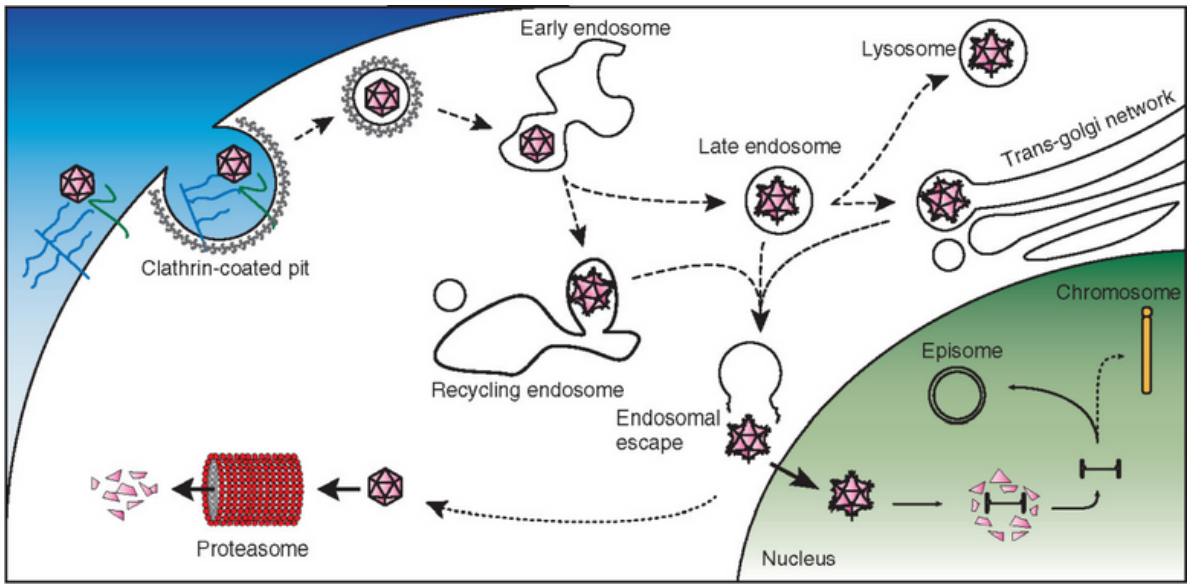
Synthesizing a gene is feasible, but then other challenges arise such as:

1. Specificity: How to get the gene in the cell of interest and its nucleus (where the DNA and its machinery lie).
2. Efficacy: How to get the gene to be transcribed into a messenger RNA and translate the information into building the functional protein.
3. Regulable therapy: How to regulate the gene expression amount and time.
4. Scalable: How to produce this therapy in a large amount.

Another concern in gene therapy is the low equivalence between mice infections and primates infection, reducing the relevance of studies on mice (more often used for their low cost and higher throughput) compared to studies on primates.

The need for a mode of transportation:
A carrier, called a vector, is used to deliver the gene into the cells to the nucleus; a virus is the most frequently used vector.

Why use viruses for gene therapy?
Because viruses can infect our organs and reproduce by injecting their DNA into our cells and highjacking the cell mechanism to express their genes into proteins. Thus, scientists utilize the virus's properties to bring another gene to a cell. Scientists genetically modify the virus so the virus cannot cause disease in humans, while still retaining their ability to inject a modified DNA into the cells it infects. Some viruses, such as retroviruses, integrate their genetic material into a chromosome in the human cell. If the cell divides, the new gene will be replicated in the two new cells. Other viruses, such as adenoviruses, introduce their DNA into the cell's nucleus, but the DNA is not integrated into a chromosome; it remains floating next to the chromosomes, and if the cell divides, the gene will not be replicated in the new cells.



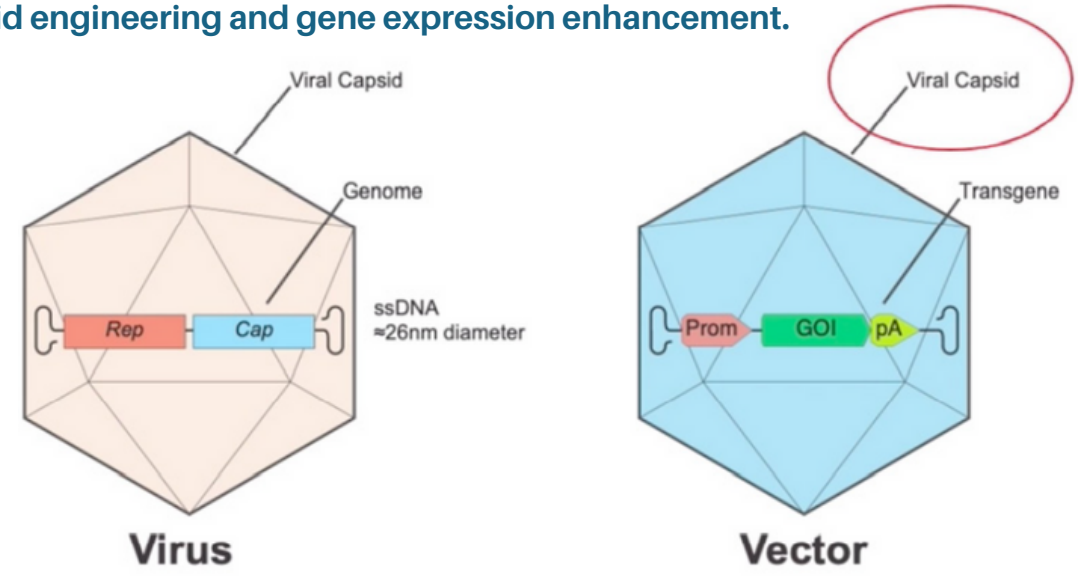
The virus infection:
The most commonly used virus is the Adeno-associated virus (AAV), which does not cause disease in humans or non-human primates. The genetic material of a virus is enveloped and protected by the capsid. Receptors specific to particular cells and tissues recognize labels on the surface of the capsid. The virus is recognized and taken up by receptors on the cell surface and sticks to the cell membrane, which triggers the virus internalization inside the cell. The AAV is carried inside the cell by elements called endosomes into the nucleus of the cell.

One of the most critical issues of gene therapy is the target delivery to cells of interest. Several delivery systems are utilized today, such as viral vectors, nanoparticles, and liposomes. Viral vectors are considered one of the most promising gene delivery systems due to the vast diversity of cell attachment and entry mechanisms.

Adeno-associated viruses (AAVs) have a remarkable safety profile, and this is crucial for the successful clinical application of gene therapy. Among the AAVs, AAV9 demonstrates the capacity to bypass the blood-brain barrier (BBB), making it a leading capsid for the transduction of the central nervous system (CNS) via systemic administration.

Tissue tropism:
Viruses will not infect all cell types in the same way; some viruses infect preferentially intestine epithelial cells while others infect neurons. AAV tissue tropism varies depending on the type of strain, as different virus strains may have different receptors that different cell types will recognize. The composition of the capsid, and its labels, are crucial to having a higher degree of infection in the specific cells where it is necessary to correct the gene. For VCP, the adhesion of the virus to muscle cells, neurons, and motor neurons is fundamental.

Thus, the severe limitation of gene therapy is the specificity of tissue delivery and the low level of expression in the targeted cells, which triggers intensive research in capsid engineering and gene expression enhancement.



Genotype

The genotype is the sequence of a gene. The same gene can have variations among individuals. These variations define the different genotypes of the gene.

Germline

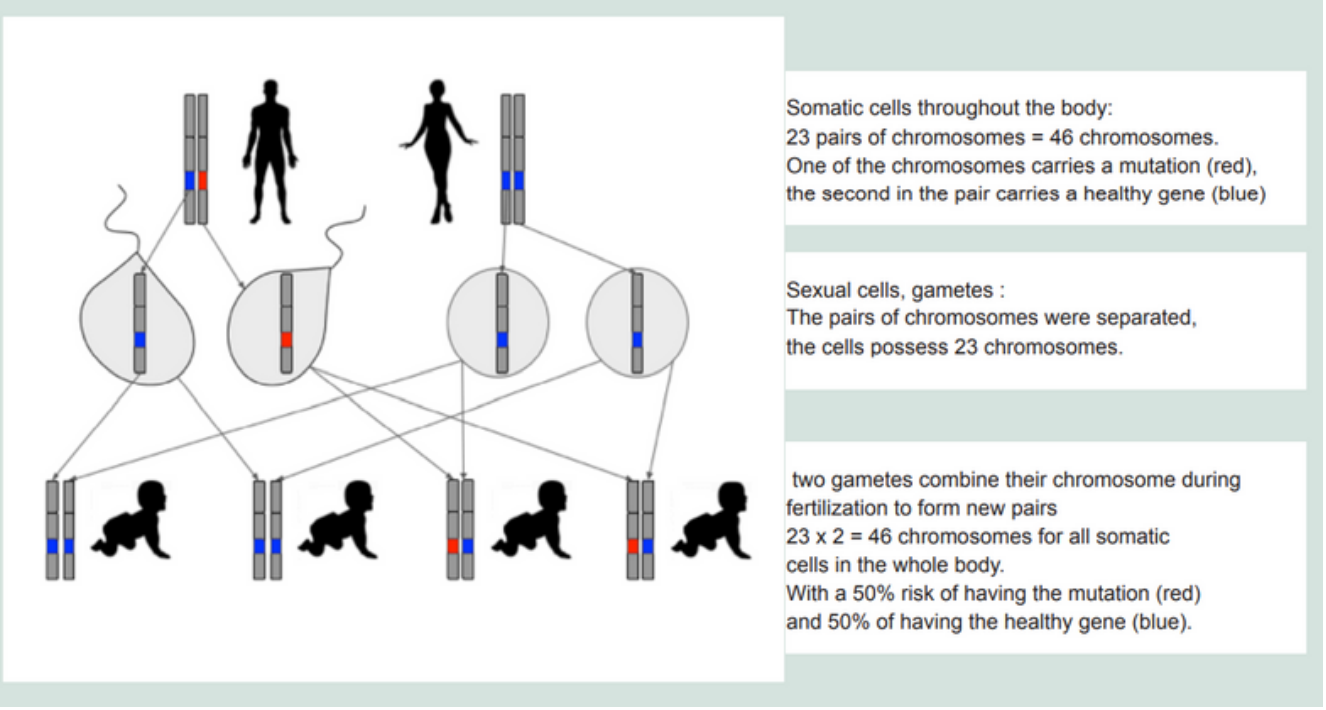
The germline are the reproductive cells, including the egg and sperm. All the rest of the cells are the somatic cells (soma means body in Greek). A mutation in the soma rather than the germline will therefore determine whether the mutationit is transmissible to offspring.

Hereditary

When a mutation is already present in the genome of the sperm or egg that formed an embryo, it is said to be inherited or hereditary.

FOR THE NERDS

A mutation will be hereditary, transmitted from parent to child, only if the parent has the mutation in all the cells of his/her body, including sperm or eggs (called gametes in a general term) or at least in a part of the body including the gametes.



HOW IS A MUTATION TRANSMITTED?

During fertilization, each parent's chromosomes are added up. Therefore, the gametes must have only half the number of chromosomes to avoid doubling the number of chromosomes at each generation. For that purpose, the cells creating the gametes follow a different process of division, a meiotic division. The daughter cells will not be genetically identical to the parent cells at the meiotic division. The initial cells will split by randomly separating their pairs of chromosomes (one from the father and one from the mother) in the two daughter cells, receiving only one chromosome.

Thus, there is a 50% chance of getting one or the other. When fertilization occurs, the two gametes come together and give each their single chromosomes, allowing the embryo to be back with pairs of chromosomes. If the mutation is present on one of the two chromosomes of the pair, there is a one in two chance that the gamete has the chromosome with a mutation and a one in two chance that it receives the healthy chromosome. So when a parent has a mutation on a chromosome, there is a 50% chance of transmitting it to a child.

Homeostasis

Homeostasis is the process of maintaining a stable and healthy status for the cell's chemical and physical characteristics. Homeostasis can be applied to the whole body, a compartment (like is the blood), an organ, or a cell. In homeostasis, the composition of salt, proteins, ions, etc. is maintained in equilibrium.

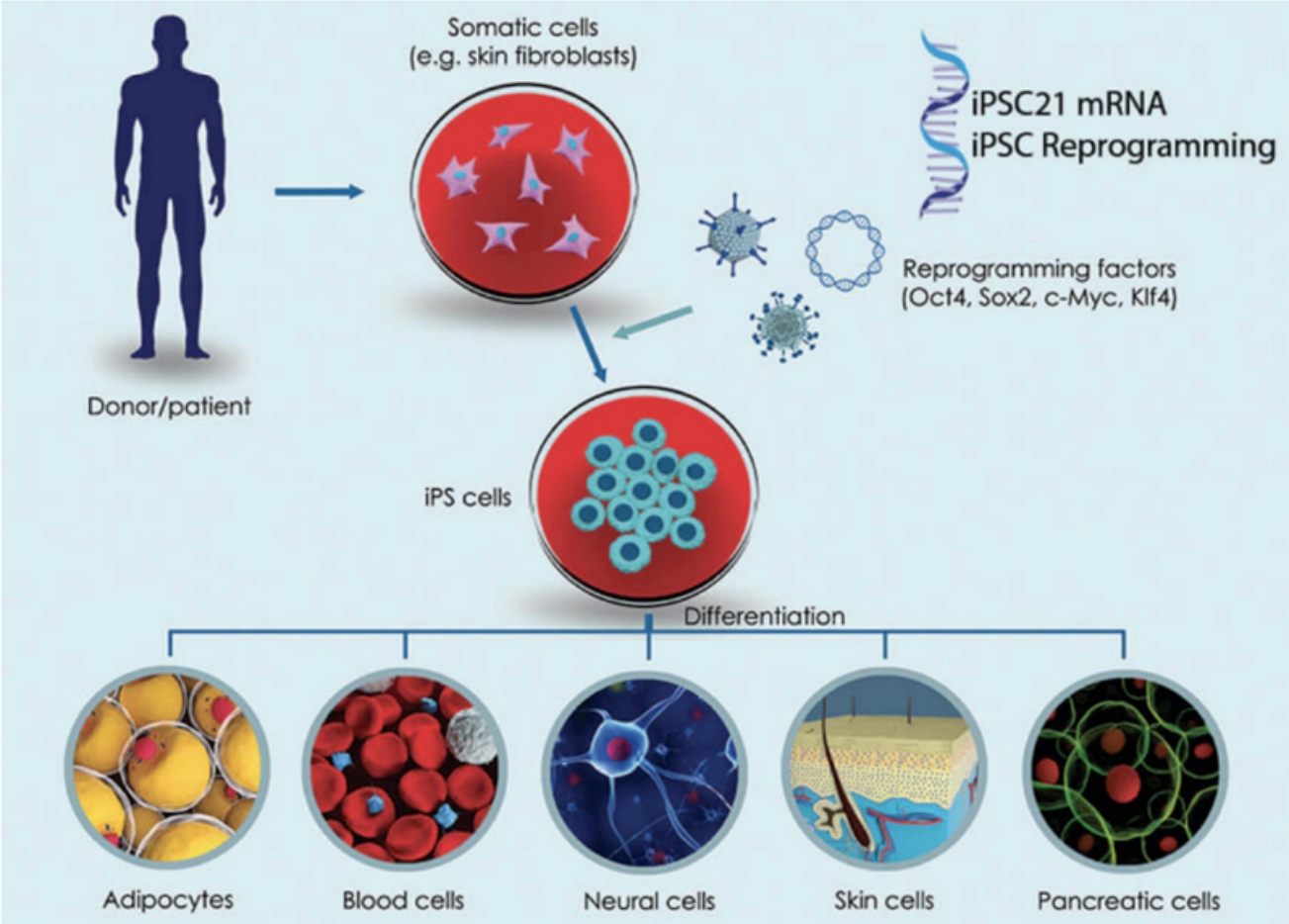
IPSC

IPSC stands for Induced Pluripotent Stem Cells. IPSC are cells from the body, like skin cells that are artificially transformed back to embryonic stem cells. Embryonic stem cells exist at the early stages of development after the egg fertilization and are able, under precise treatments, to become any cell type. IPSC cells can be used to create neurons, muscle, or cardiac cells. Thanks to this artificial process, a person's skin cell can be transformed into a neuron with the exact same genes without opening a person's brain.

IPSC (continued)

FOR THE NERDS

Dr. Yamanaka received the Nobel prize for his work leading to the discovery of the transcription factors allowing the reprogramming of differentiated cells such as fibroblasts from the skin to undifferentiated pluripotent stem cells, Oct4, Sox2, cMyc, and Klf4. The combination of iPSC and gene editing technologies opens the door to personalized treatments for patients that would have their iPSC created from a skin biopsy, then corrected by CRISPR-Cas, and re-infused to the patient to correct their disease.



https://www.ipsc21.com/ipsc-generation-stem-cell-reprogramming/

Lysosome

Lysosomes break down damaged or excess cells. A lysosome is an organelle of the cell that contains digestive enzymes to proceed to the decomposition of cell material.

Lysosome (continued)

FOR THE NERDS

The lysosomes are part of the process of autophagy but can also participate in the immune response and destroy viruses and bacteria. They are called the suicidal bags of the cell because when the cell is damaged and no longer able to function, lysosomes can burst open and release their digestive enzymes, destroying the cell.

VCP maintains lysosomal homeostasis and stability and helps in the process of bringing the cargo to destroy the lysosomes.

Mitochondria

Mitochondria are organelles that produce energy for the cell using oxygen. The singular of mitochondria is the mitochondrion.

FOR THE NERDS

Mitochondria are different from the other cell organelles; they are thought to derive from bacteria because they contain their own circular DNA, which encodes for a part of the machinery necessary to read and produce some of the mitochondrial proteins. Mitochondria produce the fuel used for energy in the form of ATP by breaking down fatty acids and carbohydrates in an oxidative phosphorylation process. The mitochondria are inherited from the mother.

Mitophagy

Mitophagy is the destruction of damaged mitochondria through autophagy.

mRNA:

The mRNA is the messenger carrying the coded sequence from a gene into the cytoplasm of the cell for protein synthesis. The mRNa is the product of the rearrangement of a pre-mRNA through the process of alternative splicing.

For more information see "splicing" and watch the video:
https://www.youtube.com/watch?v=gG7uCskUOrA

Multi-system proteinopathy type 1

Multi-system proteinopathy type 1 (MSP-1) is the new designation for IBMPFD because the disease is caused by a protein and affects multiple body-systems.

Mutation

A mutation is a difference or error in the sequence of the DNA. Now, a mutation may be referred to as a "variation." A mutation triggers "variants."

There are more than 50 variants identified in the p97/VCP gene. Sometimes, misdiagnosed patients are genetically tested and reveal new mutations. Most mutations in VCP patients are punctual missense mutations (which means that only one nucleotide is changed). A rare deletion (meaning several nucleotides are missing) at the end of the gene has also been discovered in one family.

For how mutations are created, see page 15.

Myoblast

Myoblasts are progenitor cells (cells at the origin of mature cells) not fully differentiated and will fuse together to form muscle fibers.

FOR THE NERDS

Myoblasts are present in the periphery of muscle fibers, even in adults. Their fusion allows muscles to grow in embryonic and childhood development as well as during regeneration of mature muscle and to increase muscle mass. The huge myofibers formed after fusion still contain all the nuclei from the myoblasts, forming multi-nuclei long cells.

Myopathy

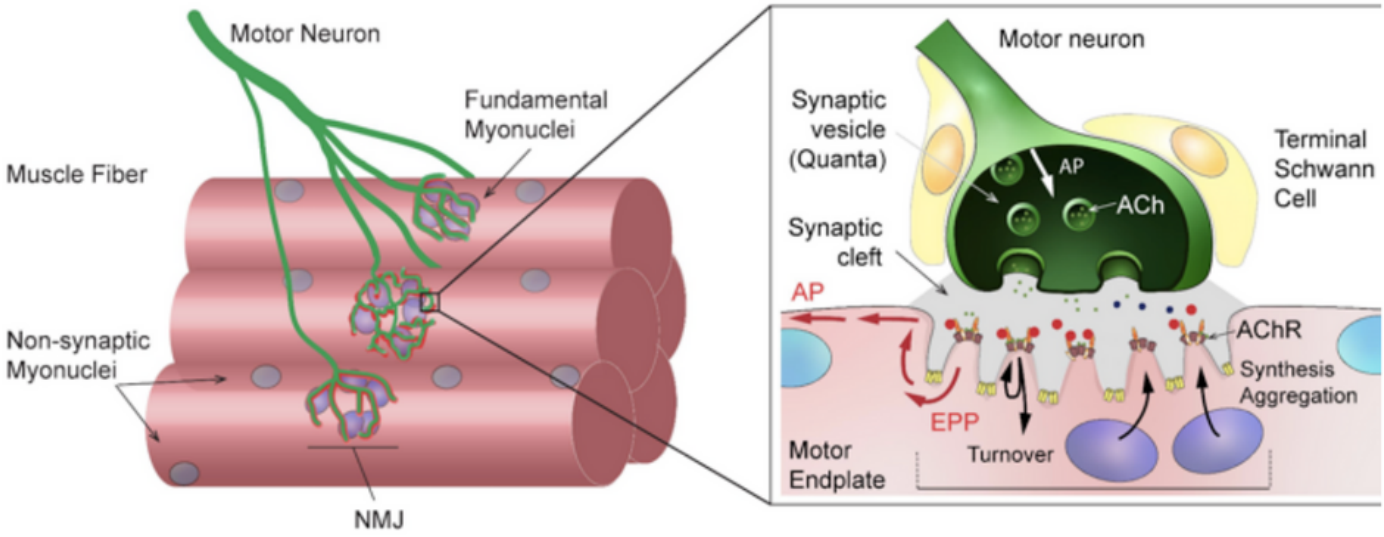
Myopathies are characterized by muscle weakness, muscle cramps, spasms, or stiffness. Myopathies are disorders of muscle fibers. The origin of a myopathy can be neuronal or muscular, distributed among twelve big groups of disorders.

Neuro-muscular Disease

Neuromuscular diseases are a group of disorders that affect your neuromuscular system. Neuromuscular diseases can cause problems with your muscles, nerves, and communication between your muscles and nerves. Symptoms include muscle weakness, muscle loss, balance problems, among others.

Motor Neurons

Skeletal muscles contract under the stimulation of nerves called motor neurons. The site where the motor neurons touch the muscle is named the neuromuscular junction.



https://www.frontiersin.org/files/Articles/568236/fnmol-13-00162-HTML/image_m/fnmol-13-00162-g001.jpg

Nucleus

The nucleus is an organelle inside the cell and contains the genome, which is made of DNA. The genes are located on the DNA and transcribed into RNA. RNA leaves the nucleus through pores to build proteins or regulate processes in the rest of the cell.

FOR THE NERDS

The nucleus contains molecules other than the DNA, such as proteins and RNA. The nucleus is the location where the cycle of the cell is regulated, and the process of cell division called mitosis is initiated and conducted.

Paget's Disease of Bone

Bones are not inert matter; they are constantly renewed, following a cycle of destruction and reconstruction. In Paget's disease of bone, the balance between the processes is disrupted, leading to the point of destruction and weakness in bones.

Phenotype

A phenotype is different characteristics observed in a person as a result of genetic make-up or the environment. A phenotype can be caused by a gene variant.

Protein

Proteins are present in all living organisms. Proteins have critical functions in the cell. Proteins can work alone or grouped with other proteins, called complexes. VCP is a protein that works in a complex of six identical units (monohexamers).

An enzyme is a type of protein that can create and accelerate a chemical reaction in the body.

FOR THE NERDS

Protein is one of the four macromolecules of the living environment (lipids, carbohydrates, proteins, and nucleic acid). Proteins are made of units (named amino acids) linked together in a chain and can have one or several chains. The chain of amino acids is the beginning of protein formation, they are folded and modified adding different chains together and other elements such as glycogenation, giving a three-dimensional conformation for the protein to operate and function.

There are 20 amino acids available.

Watch the video:

https://www.youtube.com/watch?v=gG7uCskUOrA

Protein Unfolding

Proteins have a 3D structure by folding the chain of amino acids. It is sometimes necessary to change the 3D structures by unpacking the protein, either to degrade the protein or to ensure its function. Some examples of the functions of protein are adhesion, muscle contraction, or cytoskeleton protein communicating tensions to the rest of the cell.

p97

p97 is another name for the VCP protein in humans.

FOR THE NERDS

The nomenclature p97 originates from the weight of the VCP protein, which is around 97 kilo Dalton (Dalton is the international unit to measure the weight of a protein).

RNA

RNA is a chain of nucleotides similar to the DNA, but RNA is a single strand, and DNA is a double strand. RNA stands for RiboNucleic Acid.

FOR THE NERDS

The roles of RNAs are in protein synthesis and gene expression. RNAs come from the DNA transcription used as a template. The RNAs can leave the nucleus and enter the rest of the cell. There are different types and roles of RNAs, indicated by one or several small letters, such as mRNA, rRNA, tRNA, miRNA, etc. Interestingly, RNA has one nucleotide base different from DNA, the U in RNA chain corresponding to the T in DNA chain.

There is a distinction between the coding RNA that will code for protein synthesis (pre-mRNA and mRNA and some rare circRNA) and the non-coding RNAs involved either in the machinery to synthesize protein, such as the ribosomic RNAs and transfer RNA, or in the gene expression regulator, such as micro RNA, long non-coding RNAs, or circular RNAs.

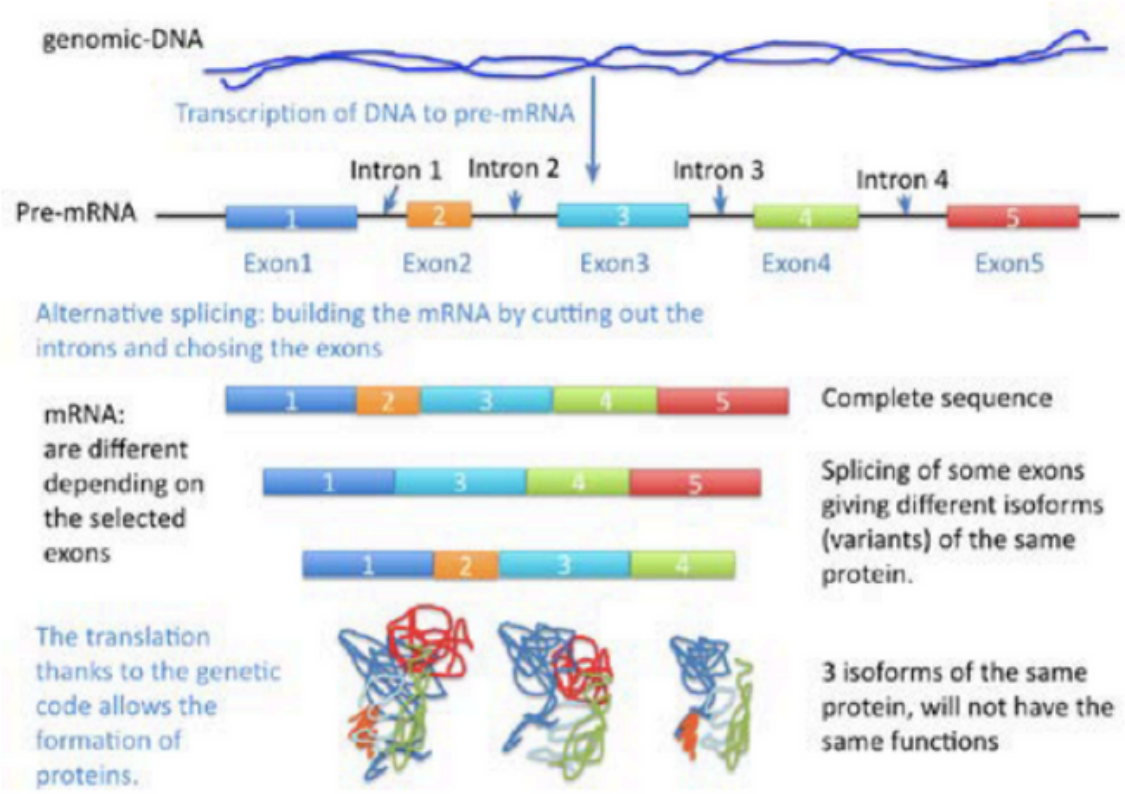
Splicing (Gene)

Gene splicing is the process of selecting some sections in a gene, cutting it out and re-gluing them together. Splicing allows a single gene to code for multiple proteins that are very similar, named subtypes or variants.

FOR THE NERDS

The DNA is located in one particular part of the cell, the nucleus, and cannot leave this structure. However, proteins are needed throughout the cell. The coding sequence on the DNA will be, therefore "transcribed" on another carrier, an RNA. This messenger will carry the sequence, the instructions for making the protein, out of the nucleus into the rest of the cell. This messenger is the messenger RNA (mRNA) transporting the information in the form of a code. Logically, the code reading to make the protein will be called the "translation" of the mRNA.

DNA Gene splicing is performed before translating the mRNA code into protein. This process excludes non-coding introns by cutting them out and forming a coding sequence by linking (sticking) the exons together in a new chain



Splicing (continued)

However, the selection of exons can vary depending on the cell type, the stage of development of the embryo, or the age of a person. Gene splicing is an essential source of protein diversity. In a typical gene splicing event, the transcribed pre-mRNA of a gene can lead to different mature mRNA molecules that generate multiple functional proteins.

Thus, gene splicing allows a single gene to increase its coding capacity, synthesizing structurally and functionally distinct protein isoforms. This phenomenon is observed in a high proportion of genes; in human cells, approximately 40-60% of genes are known to exhibit alternative splicing.

Watch the video:
https://www.youtube.com/watch?v=t5jroSCBBwk

Stress Granules

Stress granules are mRNA and protein from the protein machinery building that aggregate during cell stress. VCP regulates the formation of stress granules.

Transcription (DNA)

Transcripting is the transfer of information from a piece of DNA into another molecule called RNA. The transfer of information is made by creating an RNA as an exact copy of the sequence of DNA.

WHY IS THERE A NEED FOR TRANSCRIPTION?

DNA cannot leave the nucleus of a cell, but RNA can. When DNA needs to give a message to the rest of the cell, like giving instructions on how to build a protein, the message needs to go through transcription so that RNA can deliver the instructions to the rest of the cell.

Transcription (continued)

FOR THE NERDS

The transcription is performed by a complex that opens the double strand of DNA, reads the sequence, and builds an RNA chain of complementary sequence to the DNA with the enzyme RNA polymerase. The complementary nucleotides are specific, and coupling A to U, T to A, C to G, and G to C reproduces a mirror of the DNA sequence. The transcription is regulated by transcription factors that bind to the DNA before the gene to a sequence named a promoter or an enhancer.

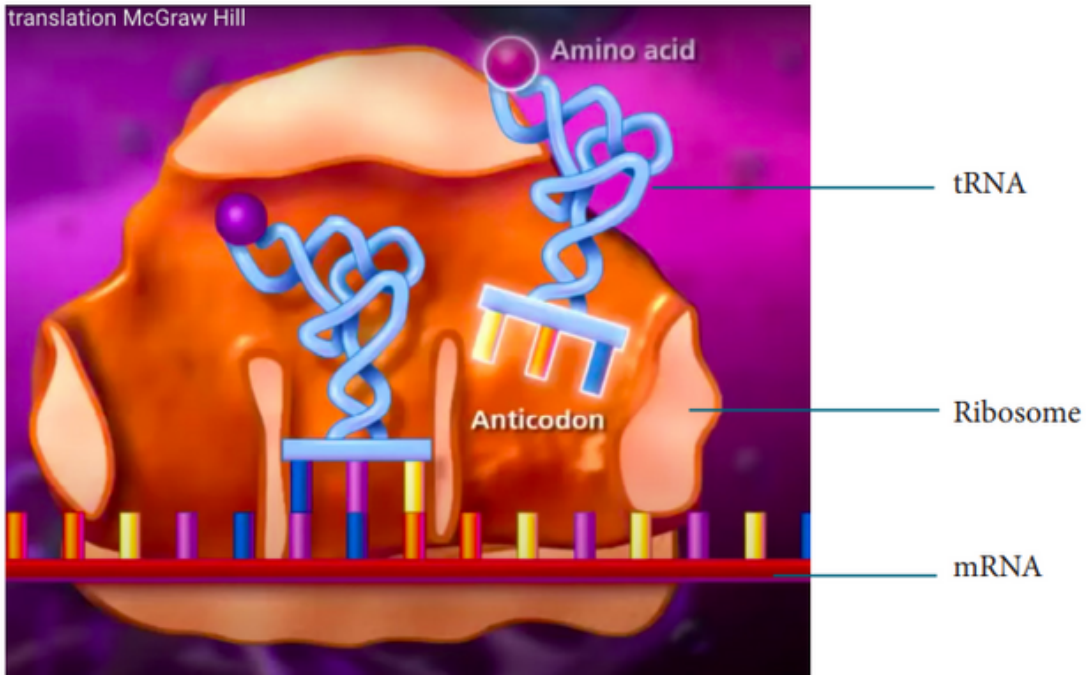
Watch the video:
https://www.youtube.com/watch?v=gG7uCskUOrA .

Transcriptome

The transcriptome is the set of all RNAs resulting from the transcription of a cell's DNA.

Translation (RNA)

Translation is the reading of instructions contained in an mRNA to build a protein block by block. The instructions are coded by the genetic code. To build a protein, aminoacids are linked in a chain. This chain is called polypeptide.



https://www.youtube.com/watch?v=gG7uCskUOrA

Translation (continued)

FOR THE NERDS

The skeleton of a protein is a long chain of amino acids linked together. The translation process starts with a complex of proteins named ribosome. The ribosome binds to the mRNA, reads the sequence on the mRNA and, at the same time, reaches for the aminoacid transporter (tRNA) corresponding to the sequence the ribosome is reading.

The reading strictly follows the genetic code. Groups of 3 nucleotide bases, called codons, will indicate which amino acid the ribosomes must associate in the chain forming the protein. For example, there are three bases of the codon CAG code for the aminoacid named Glutamine. In the genetic code, there is a start codon for the beginning of the synthesis and 3 STOP codons that will indicate that the ribosomes should stop making the protein chain. There are several codons coding for the same amino acid, and each amino acid has between two and six codons to represent it (see genetic code table).

The chain of amino acids is built by attaching one amino acid to the other. The gene coding sequence will tell which type of amino acid to link among the 20 types that can compose a protein.

Watch the video: https://www.youtube.com/watch?v=IAu44BkOaSs

Variant

A variant is a difference in the sequence of the DNA. The new term, “variants,” replaces the previous term, “mutations”.

VCP

VCP stands for valosin-containing-protein. Also known as p97, VCP is a member of the AAA+ ATPase protein family.

VCP is the name of the gene and the protein. The gene provides instructions for producing the protein. VCP is a basic protein that makes up 1% of all the protein in your body.

VCP is an enzyme involved in the replication of the cell, in the clearance and recycling of material in the cell, as well as reparation of damaged DNA.

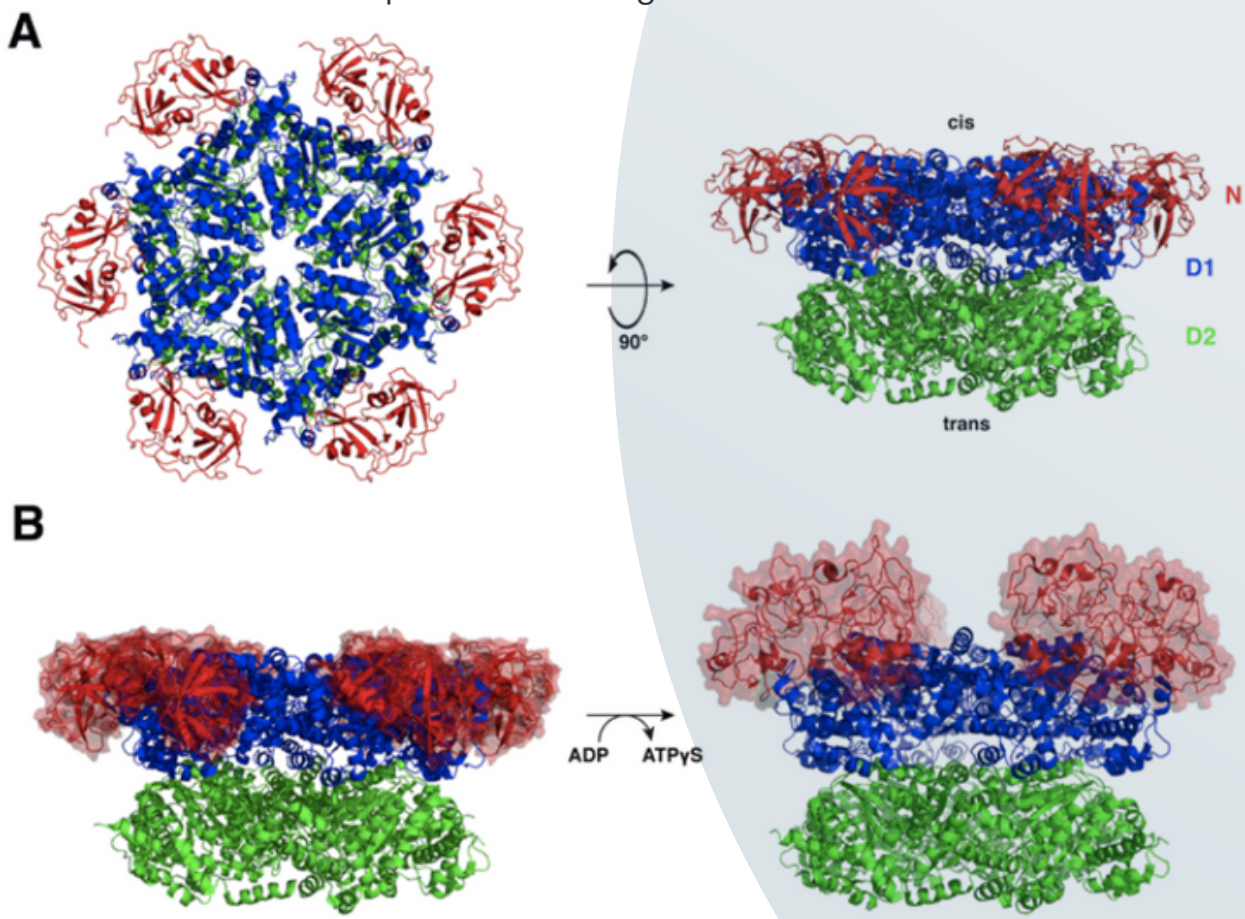


Figure from: Bodnar N and Rapoport T. Toward an understanding of the Cdc48/p97 ATPase]. F1000Research 2017, 6(F1000 Faculty Rev):1318 (https://doi.org/10.12688/f1000research.11683.1)
A) Cdc48 is a homohexamer, and each monomer comprises an N-terminal (N) domain (red) and two AAA ATPase domains: D1 (blue) and D2 (green). The N-terminal (D1) side of the central pore is referred to as the cis side, and the C-terminal (D2) side as the trans side. (B) ATP binding produces an upward rotation of the N domains into a so-called “up conformation”, in which they are positioned above the plane of the D1 ring. Left, ADP-bound state (PDB code 5FTK); right, ATPγS-bound state (PDB code 5FTN). PDB, Protein Data Bank.

VCP (continued)

FOR THE NERDS

VCP is present in the cytoplasm and the cell's nucleus. It is ubiquitous, which means expressed in the whole body. It functions as hexamers, which are six VCP proteins binded together (or sometimes as a dodecamer, which is 12 VCP proteins). The VCP hexamer forms a cylinder where other proteins will pass through and be modified, unfolded, or de-complexed from others.

VCP has been shown to be associated with some types of cancer. Treatments based on VCP inhibition are under development for cancer applications.

Mutations of the VCP gene trigger MPS-1, also known as IBMPFD. Other names for VCP/p97 are cdc48 in yeast and Ter94 in drosophila.

Zygote

A zygote is the first cell formed after the fertilization of an egg and a sperm cell. All cells of a body derive from the zygote.

General Biology Videos

DNA animation (2002-2014) by Drew Berry and Etsuko Uno
https://www.youtube.com/watch?v=7Hk9jct2ozY

Gene Silencing by microRNA
https://www.youtube.com/watch?v=t5jroSCBBwk

Empowering our Community with Knowledge

This glossary was created to help patients and families understand critical knowledge in the field of VCP science. The intent is to enrich patients' understanding of genetics and emerging technologies. We selected concepts and terms relevant to potential future therapies in VCP.

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Special thank you to Julie Nebel-Dooley

CURE VCP DISEASE, INC.