Programmed cell death
How our cells sacrifice themselves for our own good

For Social media:

As it is usual on Thursdays, today comes a new course and an opportunity for you to broaden your horizons - at least in the field of biology. This time we will delve into the world of programmed cell death. We will learn why and how it sometimes happens that our cells must die for the good of the whole organism and what the consequences can be when this process does not work as it should. And don't worry, it's even more complicated than it may seem at first!

Every day, approximately 50 – 70 billion cells of an average adult undergo programmed cell death. To many of you, this might seem quite scary – programmed cell death doesn't sound too good. But that is not the case. In order to keep our body healthy, it is necessary for the cells which can no longer function properly to sort of self-destruct in a controlled manner and thus make sure that they cannot do any damage to their other colleagues. This quite complex phenomenon is called programmed cell death and includes a variety of processes. In the beginning, I will be mostly describing the most common type of cell death – Apoptosis.

Delicate balance

The average number of cells constituting the human body is estimated to be around 37 trillion. That is quite a lot! And all of them need to be working together like a well-oiled machine in order to allow us to function in our day to day lives.

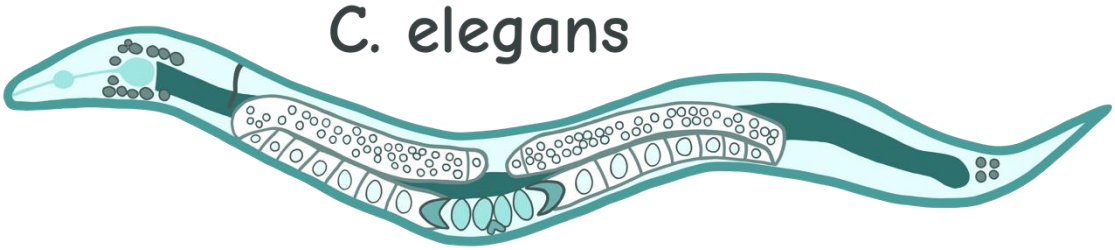
It is thus vital for the cellular composition of our bodies to be maintained. In a fully developed organism under normal conditions, the number of cells which are created through cell replication should be the fairly similar to the number of cells which die. A large decrease in the number of cells would leave us with without proper workforce to maintain the basic functions of our body while a significant increase in the number of cells might cause issues with the spatial distribution of our tissues and organs.

Programmed cell death also occurs when the cell is somehow damaged. When the damage cannot be repaired, it is safer for the cell to be removed in a controlled way, rather then leave it be and wait for it to do more damage.

The discovery – or The disappearing cells of the roundworm

Scientists have been observing and speculating about cell death for ages, but the real breakthrough came with studying a simple tubular multicellular nematode – *Caenorhabditis elegans*, or roundworm. This organism was uniquely suited to studying its development. Adult

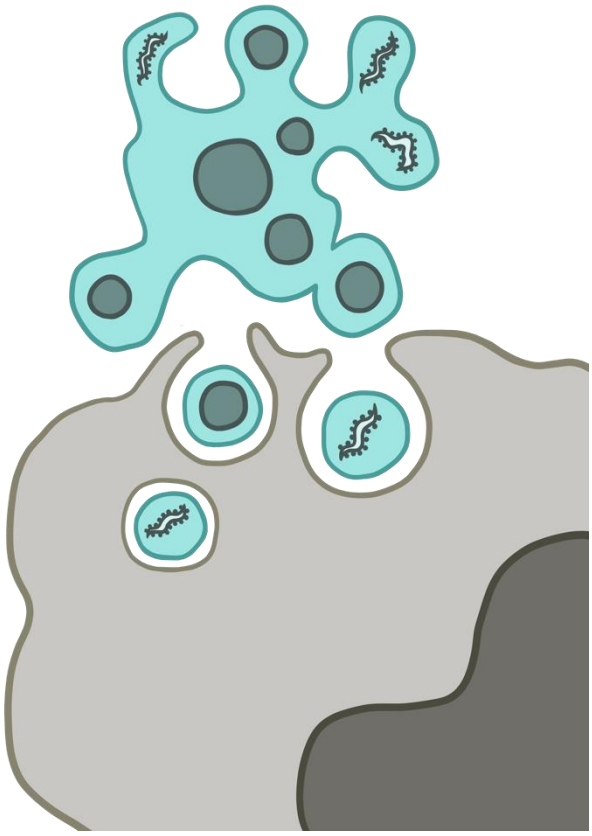
roundworm has exactly 959 cells and each of them can be observed under the microscope due to its transparent body.



In the 70s, scientists Sulston and Horovitz started tracking the fate of each cell of this nematode from its conception. Soon, they noticed something interesting – 1090 cells come to be during the embryonal development of *C. elegans*, but only 959 cells can be observed in the adult specimen. So, what happens to the extra 131 cells? If the answer isn't clear to you, you probably weren't paying attention to the title of this article. They undergo programmed cell death of course. As the absence of these 131 cells did not bother the roundworm and was a regular occurrence, it was clear that it is normal and even necessary step in its embryonal development.

Although cell death had been observed and described before, this was the first concrete evidence of it happening under standard circumstances in animals. In the 80s, Horovitz and colleagues managed to identify one of the genes, which regulated this process and named it ced-3. When this gene was rendered non-functional, the 131 cells remained.

Let's take a look inside



As a well-regulated physiological process, apoptosis has a typical "look". DNA of the cell is cut up into smaller pieces and the cell itself shrinks and then splits into many small fragments, which remain wrapped in the cell membrane. At this stage, specific molecules get displayed on the surface of the membrane, which signals for macrophages to engulf and digest the fragments of the cell.

This ensures, that no harmful or disruptive substances get released outside of the apoptotic cell.

It's all about control

Now we should understand the importance of programmed cell death and what this process looks like. No less important however is the way in which programmed cell death is triggered and regulated.

Programmed cell death requires precise and complex regulation as the process cannot be reversed once it has begun. There are also many different circumstances and conditions which can trigger the event. Even the type of the cell can somewhat influence the way in which cell death occurs.

Dying cell can also disturb its neighbours so it is important to maintain control not only when initiating the process but also while its happening.

Proceed with caution

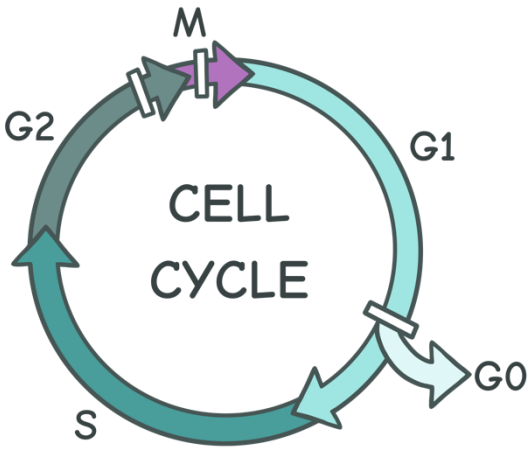
First let's take a look at how apoptosis can be triggered by damaged genetic material.

The life of a cell can be expressed as a cell cycle – newly formed cell must grow, replicate its DNA and then divide itself to create a new daughter cell. Not all cells go through this process. A majority of fully differentiated cells, whose composition and structure has been changed to perfectly suit their specific function, are in the G0 phase of the cell cycle. These cells remain as they are and do not replicate themselves. The cells which do replicate must go through four phases of the cell cycle.

Before the cell divides into two, it must make sure that it has enough genetic material and important organelles to provide both cells with a good starting point. In G1, the cell can rest,

produce important substances and ensure that everything is ready for S phase. In S phase, all DNA molecules in the nucleus of the cell must be duplicated to make sure that each daughter cell receives a complete set of chromosomes. In G2, the cell can recuperate after demanding process of DNA replication and get ready for M phase. M phase is the main event! The cell undergoes mitosis and divides into two daughter cells.

When the cell enters M phase, there aren't many ways to stop its completion so at this point, everything must be in order. When going from one phase to another, there is always a checkpoint where the cell evaluates its condition and decides whether it should proceed. If the cell fails some of these checks, it can either go into G0 phase where it simply remains stagnant or, if the damage is too severe, apoptosis can be triggered.

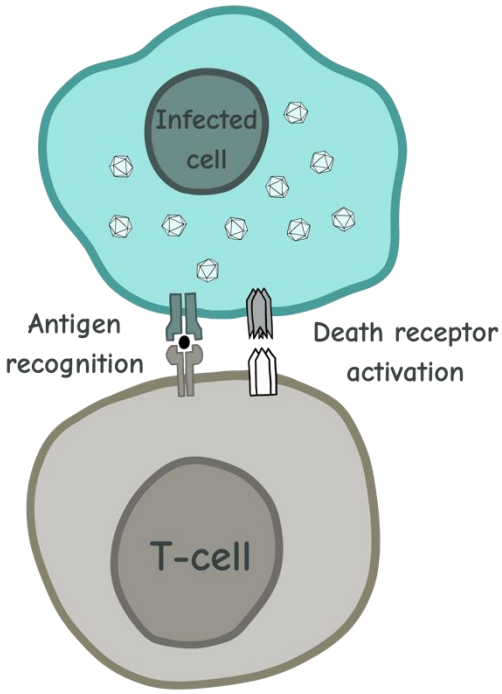


Communication is key

Another common reason for cell death is simply the absence of communication.
The cells of a complex multicellular organism are always passing signals between themselves. They are telling each other that they belong in this tissue, they are passing along important substances, they are ordering each other to change their behaviour or to begin replicating and – most importantly – they are being told stay alive.

In the absence of these signals, the abandoned cell does not really know what to do with itself or where it belongs and thus cell death is triggered. And with a good reason – a wrong cell type at a wrong place can really mess things up.

Orders from above



Our immune system can recognise when a cell has been infected with a virus and subsequently give it an order to "kill itself" in order to stop the virus from replicating.

A type of white blood cell called T-lymphocyte can recognise signal molecules displayed on the cell membrane of infected cells. It binds to them, which allows the proteins on the surface of the T-cell to interact with and activate death receptors – molecules embedded in the membrane of the infected cell which trigger apoptosis.

Viral infections need a living eukaryotic cell to replicate themselves. So, by triggering cell death of infected cells, T-lymphocytes are significantly slowing the progress of the infection.

To make an omelette you need to break a few eggs

At times, a cell might just happen to be no longer needed.

This happens to the secretion cells of mammary glands at the end of breastfeeding period or to the cells forming interdigital webbing which develops and then gets removed during foetal development.

Another event you might not have known to be a form of cell death is cornification. The top layers of our skin are actually composed of dead cells. As our skin cells keratinocytes mature, they migrate closer to the surface of our body. During this process, the cell produces a huge amount of keratin filaments which are then densely packed inside the cell. This makes the cell more compact and dehydrated. Full keratinized cells also cover greater surface area. These cells thus form an ideal layer of protection, but they cannot survive the process. This process looks rather different from the process of apoptosis described above – the body of the cell remains intact, there is no fragmentation of cytoplasm and it does not get eaten up by macrophages – but it is also a form of programmed cell death.

Survival of the fittest

Some cells undergo a form of selection as they develop. Previously mentioned T-lymphocytes need to be able to identify and strongly react with certain antibodies which are alien to the organism. Each T-cell displays a specific receptor on its surface, which then gets tested. If it does not react strongly enough or if it reacts with molecules displayed on healthy cells in our bodies, the T-cell is deemed unfit, and programmed death is triggered.

Similarly, many neurons which fail to connect to others while migrating during the development of the brain undergo apoptosis. This ensures that only neurons which are

a meaningful part of the complex neuronal network remain. More than 50% of neurons die during embryonal development of vertebrates.

Casting a net

Another strange form of cell death, associated with our immune response is NETosis. Some white blood cells are able to create neutrophile extracellular traps or NETs. Modified DNA molecules and their associated proteins create a net which catches bacteria. Bactericidal proteins are attached to this net and they can kill the bacteria which were caught. The white blood cell however does not survive the expulsion of this NET so this is another form of programmed cell death.

Every road leads to caspases

No matter the initial impulse, the final step of triggering apoptosis is carried out by proteolytic enzymes called caspases. These proteins have the ability to cut off a part of another protein. There are many different caspases – some activate other proteins or even themselves by severing the part of the molecule which was previously blocking its active site, or it can help move along the process of cell death by cutting up important cellular structures, for example its cytoskeleton.

When it gets out of control

Now you should have an idea about what programmed cell death looks like, when it is working as it's supposed to. But what if it gets out of control?

Die another day

The ability to undergo apoptosis is encoded in the cell's DNA and as such it can be disrupted by mutations. We've already talked about many different components which interact during this process and a mutation which renders just one of them non-functional can prevent the cell from dying. At a first glance, this might not seem like such a bad thing but in reality, it can have catastrophic consequences.

For example, let's say that the DNA of a cell has been damaged and now carries some mutations as a result. Normally, this cell would not be allowed to divide itself and apoptosis would most likely be triggered. But when the cell refuses to die, more mutations can accumulate and maybe one of these mutations will allow the cell to bypass the checks in the cell cycle and replicate itself. Maybe, one of these mutations will also render the cell unresponsive to other cells telling it to die. So now we have two cells, which do not fulfil their function, don't listen to its surroundings and can divide themselves uncontrollably. Soon, there will be more of them, often with many more mutations in their genetic material. And that probably sounds familiar as what I've just described is the beginning stage of most tumours.

A solid tumour, growing in one place might not be a great tragedy – as long as it is contained to one location and is identified soon enough for it to be safely removed. Oftentimes, the real

trouble starts with metastasis. When a cell leaves its niche – the location where it belongs – programmed cell death is triggered. But if we are talking about a tumour cell, which is already quite rebellious, it might refuse to die and end up somewhere else in the organism. This makes treatment extremely difficult, as we never really know, where a small group of tumour cells might be growing.

Many mutations which are typically associated with cancer (you might have heard about the protein p53) affect proteins which directly contribute to the process of cell death because only the cell which cannot die when they are damaged can form a tumour.
The other end of the spectrum

So now we understand that cells stubbornly clinging to life can cause a lot of trouble. But what about cells which die for no good reason?

Excess cell death is present in several neurodegenerative diseases and neuronal anomalies. Apoptotic fragments of cells can also stimulate T-cells and lead to chronic inflammation, which can then develop into an autoimmune disease. Autoimmune disease can however also happen when stimulated cell of our immune system refuse to die when they are no longer needed and thus our immune system remains overactive even when the danger is over.

Excessive cell death in disease is however simply a response to prolonged exposure to non-optimal conditions, which would cause issues even if the cells stayed alive.

Curiosities:

In conclusion
It should now be clear that programmed cell death is an important process through which an organism deals with aberrant cells as well as a necessary step in the development of many structures of our bodies. There are many ways of triggering this process and even the outcome might vary slightly, but in the end it's all about our cells dying so the rest of the organism can live on.

Not so planned
Apart from programmed cell death, there is also necrosis. This term refers to a situation in which a cell dies in an unregulated and unplanned manner. Necrosis is always pathological and a result of something going wrong. The cell typically swells up and its membrane bursts, releasing all its contents. This can get quite messy and end up damaging neighbouring cells. Necrosis typically happens, when the damage is too quick and too severe, so proper pathways leading to programmed cell death cannot be triggered.

When cells get homesick
The phenomenon of cells undergoing programmed cell death as a result of losing contact with their niche actually has its own name – it's called anoikis, which is derived from Greek and it roughly corresponds to "the state of being without a home".

Naming conventions

The name NETosis has two justifications. One is quite obvious – the trap does resemble a net quite a bit, so this term is rather easy to remember. But that is not scientific enough so of course it must have been made into an acronym. The letters in NET stand for Neutrophil Extracellular Trap as it was originally assumed that neutrophils were the only cells capable of casting these traps. It was however later discovered that it's not the case, so the acronym is technically not correct. But hey! NET fits quite well so why change it?

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Quiz:

1. **How many cells are removed during embryonic development of Roundworm:**

a) 131

b) 956

c) 87

2. **Necrosis is:**

a) planned and regulated

b) unplanned but regulated

c) unplanned and unregulated

3. **Most often, programmed cell death is disrupted:**

a) mutations

b) by bacteria

c) water

4. **Autoimmune diseases are caused by cells…**

a) cancer cells that divide uncontrollably

b) immune systems that live longer than they need to

c) that die prematurely

5. **Mature keratinocytes are dead cells…**

a) in the lining of the intestines

b) on the surface of the skin

c) of cancerous growth

6. **Cell death is associated with caspases. But what is it?**

a) name for dying cells

b) parts of DNA

c) enzymes

7. **Cell death research has advanced largely because of this model organism. This is a...**

a) Caterpillar

b) Roundworm

c) Earthworm

8. How many cells in our body succumb to programmed cell death each day?

a) 5-7x 10^{10} cells

b) 1500 cells

c) 90 x 10^{10} cells

9. NETosis is:

a) internet network

b) type of cell death performed by neutrophile

c) group of enzymes

10. Anoikis is:

a) a Greek dish

b) species of roundworm

c) cell death from homesickness