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> ONE MONTH, ONE PROTEIN <

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delayed

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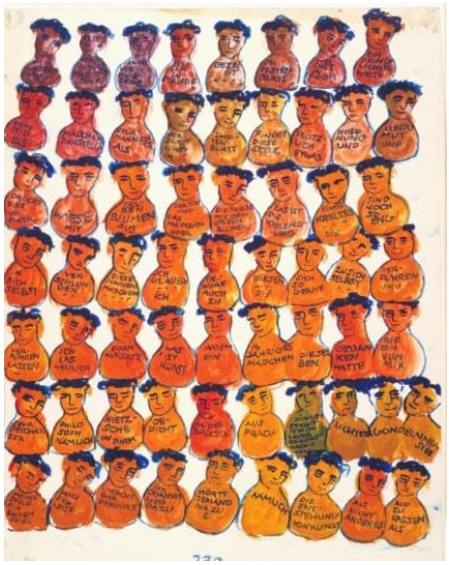
Better safe than sorry. Leaving – whatever or whoever it may be – is always better when executed with some forethought and organisation. Cells sometimes behave similarly. Many are the occasions when our bodies decide to get rid of cells for the sake of health and equilibrium. The notion is easy to grasp when you consider cells that have either aged or been infected; our system is better off without them. Organisms have several ways of removing cells or, in other words, of programming cell death. Sometimes, though, an ongoing programme moves too fast and, rather like writing a will, the cell needs more time to arrange a few important things before its passing. So, a temporary reanimation mechanism kicks in. Enzymes known as caspases are frequently involved in programmed cell death. One particular caspase however, caspase-7, is actually engaged in repairing self-inflicted holes in a cell's membrane so that the cell has time to prepare a cleaner exit, that is to say without being detrimental to the environment.



Charlotte Salomon (1917-1943)

from her book "Leben? Oder Theater?: Ein Singspiel"

Programmed Cell Death, or PCD, is a form of cell suicide. At the level of the cell, the outcome is final, but when considering its existence as part of a tissue in which there are millions – if not billions – of cells, the death of one cell, or even a few hundred, will go pretty much unnoticed. Tissues regenerate in this way, discarding cells that have aged or are not working properly anymore, so that they and their contents can be recycled. Tissues also defend themselves in this way. If cells lining our gut, for instance, are infected by bacteria or a virus, the infected cells may simply opt to wither and die, thus helping to prevent further infection in the neighbouring cells, while our immune system fires off an arsenal to deal with the microbes themselves.

Caspases – for **c**ysteine-**asp**artic prote**ases** – were discovered in the early 1990s as was their role in PCD. To date, about 20 different mammalian caspases are known as is their involvement in supporting processes as diverse as inflammation, cell-fate, ageing, neural development, cell proliferation and tissue regeneration – all of which are tightly linked to cell death. Caspases assemble into active heterodimers of one large and one small subunit, or heterotetramers composed of two heterodimers, and have cysteine protease activity, where the cysteine in their active site only attacks and cleaves a target protein after an aspartic acid residue – hence their name.

Since its discovery, caspase-7 was considered to be rather an idle fellow, a sort of inefficient back-up to other caspases, until recently when researchers observed that, like its companions, caspase-7 is also involved in cell death but perhaps in a more subtle way. Caspase-7 actually prevents a cell from dying too fast so that it can prepare a cleaner exit. An illustration: consider having to dispose of toxic waste. You would need to put the waste into a sealed container so that the contents cannot seep out and contaminate the environment. When a cell is infected, as a means of quick defence it may choose to pepper its membrane with holes, or pores, which will gradually kill it. However, besides letting harmful

foreign components enter the cell it would also encourage some of the cell's insides to flow out – which could be detrimental to surrounding cells. In intestinal and liver cells, caspase-7 has been shown to hinder this form of PCD by promoting pore repair while the cell prepares for an alternative – and less messy – way to die.

Cell extrusion is a form of PCD, which takes place in epithelia. During cell extrusion, unwanted cells are slowly squeezed out of the epithelium much in the way you would pick a bad pea out of a pile of others. Like the sealed container with toxic waste, cell extrusion rids a tissue of unwanted matter by keeping it closed tightly within an intact membrane while preserving tissue integrity. Because membrane pore formation following infection is a spontaneous reaction, the cell may begin by perforating its membrane long before extrusion can take place. In so doing, molecules such as ATP could leak out and deprive the cell of precious energy it needs to complete the alternative process: extrusion. This is exactly where caspase-7 comes in.

A caspase, other than caspase-7, triggers the initial formation of pores, which are known as gasdermin pores in intestinal cell membranes. The same caspase also activates caspase-7 which goes on to activate yet another enzyme called acid sphingomyelinase, or ASM. Sphingomyelin is one of the main building blocks of the lipid bilayer observed in cell membranes. Once activated, ASM beheads sphingomyelin, which gives rise to a modified lipid molecule known as ceramide. This change in lipid structure creates a sort of disharmony within the cell membrane, causing both invagination and spontaneous endocytosis exactly where a new gasdermin pore has formed – so the pore is swallowed up inside the cell and the membrane repaired.

This may sound straightforward enough but scientists could not understand how caspase-7 managed to reach its target protein ASM in the first place. ASM is found in intracellular lysosomes and there is little chance caspase-7 can wriggle its way through the lysosomal membrane to reach it. So how does it do it? An elegant hypothesis suggests that when undesired pores form in a membrane, calcium flows into the cell which causes lysosomes to migrate towards the sites of damage and undergo exocytosis. While this is going on, caspase-7 would use the newly-formed gasdermin pores to join – and activate – ASM now situated in the extracellular environment. The hypothesis is supported by the fact that ASM is spontaneously activated when cell membrane damage occurs. What caspase-7 does is enhance AMS's role in the repair process, thus giving time to the cell to extrude.

We seem to be going round in circles. In response to damage, an epithelial cell initiates one kind of PCD before the programme is slowed down to give time to a second PCD to reach completion. Cell extrusion is a clean way of dealing with cell damage – that is understood – so why let a cell riddle its membrane with pores in the first place? Is this not counter-productive? Energy-consuming? The thing is, when a cell membrane is damaged – whether the damage is self-inflicted or not – the cell will spontaneously set out to repair the damage regardless of how it was initiated. This obviously hinders the more intricate and tidy form of programmed cell death such as cell extrusion, which appeared later in evolutionary terms. So, perhaps the fastest and least energy-consuming way to support cell death by extrusion would be to reduce as much as possible any harm caused by the less refined, but spontaneous, cell death programme via pore formation. It is like emptying seawater rapidly leaking into a damaged hull so that the ship can at least sink in the harbour.

Cross-references to UniProt

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Caspase-7, *Homo sapiens* (Human): P55210

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