Molecular biology

Faking cellular suicide could help control inflammation

And that could help treat everything from hay fever to arthritis

AS PARACELSUS first pointed out in the 16th century, it is the dose that makes the poison. Inflammation, in particular, is vital to fighting infection or healing wounds. If it lingers, however, it can cause more harm than good. Chronic inflammation often impedes the very healing that it is meant to promote. Many drugs have been invented to combat that problem, but none is as effective as doctors would like. Now, as they describe in a paper in *ACS Macro Letters*, a team led by Mitsuhiro Ebara at the National Institute for Materials Science in Japan have come up with a new approach. They have worked out how to persuade cells in inflamed tissues to believe that other cells nearby have just committed suicide.

Cells can suffer chaotic deaths or orderly ones. Chaotic deaths are the end result of a process called necrosis, in which toxins, pathogens or other forms of damage cause a cell to fail catastrophically and rupture, spilling its contents in the process. The detection of this detritus by the immune system leads to an inflammation response.

Graceful death, known as apoptosis, is a sort of pre-planned cellular suicide. It happens naturally throughout life and is vital for many developmental events (like the separation of fingers before birth). Unlike necrosis, the leftovers of apoptosis are mostly tolerated by the immune system. Dr Ebara knew from previous research that this is because cells cover their membranes in an immune-suppressing compound called phosphatidyl-serine just before they break up. Collecting cellular fragments coated in phosphatidylserine and introducing them to areas of inflammation can dramatically improve healing by persuading the immune system to stand down.

But harvesting those remnants is tricky, since they degrade quickly. Instead, Dr Ebara wondered whether he could build polymers decorated with artificial phosphatidylserine. These impostors could then be used to dupe overactive immune cells into believing that apoptosis rather than necrosis was taking place.

The researchers worked with mouse immune cells that had been treated either with lipopolysaccharide, a bacterial compound that reliably triggers an aggressive immune

response, or with inoffensive saline solution and left as controls. Once the bacterial lure had created the expected inflammatory response, Dr Ebara and his colleagues treated the immune cells with either saline solution (again, as a control) or with the specially coated polymers.

Throughout the experiment the team collected immune cells from their Petri dishes and monitored them under a microscope. They knew from earlier work that macrophages, a particular type of immune cell, change shape depending on what they are doing. Those that drive inflammation spout long pseudopods from their bodies. Those that do not look roundish.

The team report that more than 80% of the macrophages treated with lipopolysaccharide and then saline grew long pseudopods. Less than 10% of the macrophages treated solely with saline had pseudopods. But when the cells were dosed with both the agitating lipopolysaccharide and then with Dr Ebara's polymer, less than 20% ended up in pro-inflammation mode.

It is a long way from the lab to the medicine cupboard. But a better way to damp down chronic inflammation would be welcome. Some of its consequences, like hay fever, are merely annoying. But it can also constrict the arteries, cause arthritis and even raise the odds of contracting forms of cancer. Too much of a good thing, in other words, can kill you outright.

Sources: The Economist