Second Childhood

In my beginning is my end. In my end is my beginning.
TS Elliot, *East Coker*.

Embryologists who study the beginning of life, and gerontologists who study its end, interact rather little. This is hardly surprising: the former work with growth, construction and preparation for the long life ahead, while the latter work with loss, decline, and the inevitable journey to oblivion. Sometimes, though, different sciences connect in surprising ways and, when they do, discoveries can be made that completely change our understanding of both. Just such a fruitful collision happened very recently, the critical experiments appearing in papers from two Spanish laboratories (Maneul Serrano's and Willima Keyes': see links) in November's issue of *Cell*. The groups' findings may lead to a radical shift in the way we understand why and how we age.

Ageing can be seen at all levels from whole bodies to individual cells. As cells live, they suffer many types of damage: some is quickly repaired but some cannot be. When a cell is alive but irreparably damaged, it enters a specific state called cell senescence, easily detected because it involves the continual synthesis of a set of characteristic proteins. Senescent cells relinquish their ability to multiply, leaving the task of tissue renewal to their undamaged neighbours. This makes sense, teleologically, because a cell with badly damaged chromosomes, for example, would be likely to produce daughters with incomplete genomes that might give rise to a tumour. As well as shutting off proliferation, senescent cells secrete signalling proteins that trigger local inflammation. This too makes sense: one possible cause of damage is infection, and the inflammation brings defence systems into the area. Less easy to understand is the secretion by senescent cells of proteins that cause neighbouring cells to behave in apparently unhelpful ways, remodelling healthy tissue into a scar-like mess (fibrosis), altering blood vessels and even helping cancers grow. These changes are part of bodily ageing, and may cause neighbours to suffer collateral damage and to enter the senescent state themselves, making things worse. Some scientists call this process 'inflam-ageing', to underline its unhelpful nature.

Signals that alter the behaviour of other cells are very common during embryonic development, and in this context they are useful. In the ever-changing anatomy of a developing body, specific clusters

of cells take charge of a particular aspect of body-building. A signalling centre at the end of the limb, for example, is important in making the fingers different from the wrist, the wrist different from the fore-arm etc. Similarly, signals from the roof-plate of the developing brain set up various zones of the brain, and also the cell migrations that will later make most of the face. There are many other examples of signalling centres and cells within them, though very active in communication, seldom multiply. Embryonic tissues are fresh and new, not being alive for long enough to have accumulated much damage, so they would seem an unlikely place to find senescent cells. Nevertheless, the Serrano and Keyes laboratories set out to to look for signs of senescence in the young, healthy embryos of mice, chicks and humans. They found them – in surprisingly large numbers.

The senescent cells of embryos were not scattered randomly, as would be expected if entering the senescent state were just a response to damage, but were instead located in particular tissues. Some of them were located in temporary structures that are made during development but destroyed before birth, serving the needs of a developing human rather as scaffolding serves the needs of a new building. Here, cell senescence may just be to do with cells preparing to be eliminated. The rest of the senescent cells were located in places altogether more surprising: they made up some of the embryo's key signalling centres, including the end of the limb and the roof-plate of the brain. Not only are these cells in a senescent state: they need to be for development to take place properly. Mice genetically engineered so that these cells cannot become senescent show abnormal gene expression in their developing limbs, and the limbs end up growing abnormally.

Why are cells apparently becoming senescent in signalling centres, even though they are not about to be cleared away? One important clue comes from bringing together information from embryology and from gerontology. Comparing the list of the signalling molecules released by the signalling centre of the developing limb with the list released by adult senescent cells reveals something startling: the sets overlap substantially. This raises an intriguing possibility, which would imply that we have got this whole senescence thing the wrong way round.

Researchers discovered the 'senescent' cell state in ageing research and became puzzled that, while some aspects of it were helpful in repair and in suppressing cancers, some things the cells secrete are unhelpful and cause inflam-ageing. The new data shows that 'senescent' cells are responsible for secreting very similar sets of molecules to control embryonic development. What if the original

'point' of the senescent state had nothing to do with ageing and damage, but was all about signalling to control development of primitive embryos? What it is not a 'senescent' cell state at all, but a 'signalling centre' cell state?

Small, short-lived animals do not need elaborate defences against cancer and slowly accumulating damage: they get eaten before it matters. We large, longer-lived animals do need these defences, and by the time we came to evolve, the 'signalling centre' cell state, with its automatic shut-down of multiplication and its secretion of a bunch of signalling molecules, was already there in our developmental repertoire. It may have taken only a small amount of evolutionary change to connect damage detection systems to drive activation of this cell state. With the connection achieved, our damaged, adult cells would automatically shut down and give signals that, an an adult body, are associated with repair and defence. Job done! Well, almost... some of those signals still provoke tissue modelling even in an adult body, where it is no longer appropriate. The convenience of stealing an old embryonic system for the new purpose of controlling damage, rather than going to the trouble of evolving a new purpose-built one, has its price. The price label appears in every line on our faces, every narrowing artery, every aching joint.

It is too early to say how this story will turn out when more experiments have been done, but the possibility that we have had the whole story round the wrong way is intriguing. It would mean that we need to understand inflam-ageing as an effect of unhelpfully reactivated embryonic development. Medically, that may change a lot.

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Links to the original papers:

http://www.cell.com/cell/pdf/S0092-8674(13)01295-6.pdf

http://www.cell.com/cell/pdf/S0092-8674(13)01359-7.pdf