News & views

Cell biology

Senescent cells feed on their neighbours

Michael Overholtzer

Chemotherapy-treated cancer cells that enter a non-dividing state called senescence can nevertheless boost cancer growth. The finding that these cells eat neighbouring cells reveals a mechanism that enables senescent cells to persist.

Multicellular life requires individual cells to cooperate in a way that benefits the organism. Cells that are uncooperative because they are damaged or dysfunctional, and that pose a threat, are either eliminated by cell death or undergo a usually irreversible growth arrest called senescence[1]. Senescent cells typically never divide (although there are some rare examples of cells exiting senescence and resuming division), but they can persist in tissues and contribute to ageing and cancer progression[2,3]. Writing in the *Journal of Cell Biology*, Tonnessen-Murray *et al.*[4] reveal a deadly activity that underlies the persistence of senescent cells — they can eat their neighbours alive.

Cellular entry into senescence benefits an organism because it inhibits cancer development by preventing the division of cells that have accumulated extensive DNA damage or that express cancer-promoting genes called oncogenes[2,5]. Senescent cells are metabolically active[6], and this is characterized by their secretion of pro-inflammatory molecules as part of a phenomenon termed the senescence-associated secretory phenotype (SASP) response[2]. Senescent cells can promote cancer progression and resistance to anticancer therapy in some contexts, as a result of the secretion, through SASP, of growth factors and immune-signalling molecules called cytokines[2].

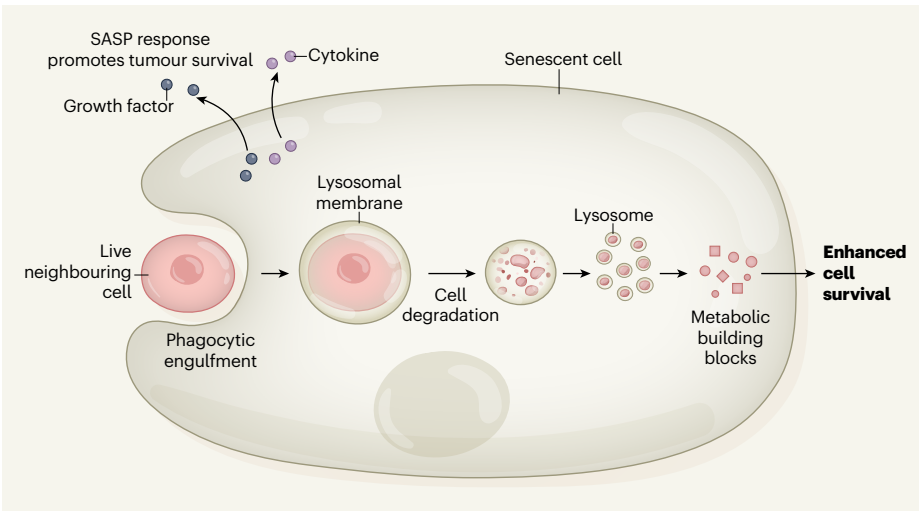

Figure 1 | Cellular cannibalism. Chemotherapy drugs can cause cancer cells to enter a state of senescence, which is usually associated with an irreversible halt to cell division. However, these cells can promote tumour survival by secreting growth factors and signalling molecules called cytokines in a process termed the senescence-associated secretory phenotype (SASP) response[2]. Tonnessen-Murray *et al.*[4] report studies of breast cancer in mice which reveal that this type of senescent cell takes up (engulfs) and digests neighbouring living cells. The cells are engulfed by a process that has molecular characteristics of phagocytosis, an engulfment process that immune cells use. Once ingested, the cells are enveloped in membrane from an organelle called the lysosome and digested. This might account for a portion of the numerous lysosomes that are a hallmark of senescent cells. This degradation provides metabolic building blocks for the cell. Senescent cells that have ingested their neighbours survive for longer than senescent cells that have not.

Chemotherapy that damages the DNA of cancer cells can result in their death or their entry into senescence. Tonnessen-Murray and colleagues investigated the effects of chemotherapy-driven senescence in breast cancer cells in mice treated with the chemotherapeutic drug doxorubicin. Under the microscope, they saw senescent cells eating and digesting entire neighbouring cells (Fig. 1). This striking observation was made in breast tumours formed of mixtures of transplanted cancer cells, which were engineered to express red or green fluorescent proteins. It can be difficult to observe a cell being internalized by another cell (a process termed engulfment) in cancer tissues. By growing tumours with mixtures of fluorescently labelled cells, the authors could clearly identify red- or green-labelled cells being taken up into neighbouring cells labelled by the other colour.

Engulfment also occurred at high rates for mouse and human breast cancer cells grown *in vitro* and treated with doxorubicin or another chemotherapeutic drug, paclitaxel. Ingestion peaked at 4–6 days after drug treatment, a time that correlated with the induction of senescence. The cells that were engulfed by the senescent cells were neighbouring senescent or non-senescent cancer cells. They showed no sign of being dead, and engulfment occurred even in the presence of a cell-death inhibitor molecule. This led the authors to conclude that the ingested cells were being eaten alive.

Ingested cells are broken down in a digestive organelle called the lysosome. Crucially, senescent cells that ate their neighbours survived longer *in vitro* than those that did not. This finding suggests that metabolic building blocks retrieved from the lysosomal digestion of neighbouring cells were being used by senescent cells to promote their survival.

This surprising finding that cell death supports the survival of senescent cells highlights the complexity of cell-death regulation in multicellular animals. Numerous mechanisms of cell death occur in animal tissues. These include forms of cell suicide, such as apoptosis, which leads to the fragmentation of individual cells, and regulated forms of necrotic cell death that induce cell rupture[7]. Some cell deaths are also carried out as 'murders'[7,8]. These typically

involve the presence of engulfing cells, and occur by at least two distinct mechanisms[9].

One is a form of cell death called entosis, in which living cells that are destined to die invade a neighbouring cell and become engulfed[10]. Another mechanism is cellular cannibalism, in which living cells that will be ingested are targeted by a type of engulfment that resembles phagocytosis — the process typically used by immune-system cells such as macrophages to ingest and destroy dying cells[9]. Such cellular murders can support the survival of particular cells in a population that benefit from the metabolic banquet derived from ingesting and degrading whole cells[11,12].

The authors examined the mechanism of senescence-associated engulfment and found that, although entosis could occur in the type of tumour cell studied, the engulfment of senescent cells did not involve the proteins required for entosis[10]. The authors analysed the gene-expression profile of cancer cells treated with chemotherapy drugs (most of these cells were senescent), and found that genes characteristic of phagocytosis were expressed. This gene expression peaked within a timeframe that correlated with the cellular engulfment. Senescent cells were also observed to engulf dead cells added *in vitro*, providing further evidence for the authors' model that senescent cells engulf cells by phagocytosis.

Cell cannibalism in cancers has been reported previously[9,12]. However, Tonnessen-Murray *et al.* specifically identify an association between cannibalism and senescence, and show that this phenomenon might make a substantial contribution to the persistence of senescent cells in cancer tissues. The authors observed that cannibalism by senescent breast cancer cells occurs irrespective of whether or not the cell has functional p53, a notable tumour-suppressor protein that can control entry into senescence[13]. The authors tested chemotherapy-induced senescent cells of other types of cancer, including lung cancer and a bone cancer called osteosarcoma, and found that these cells also cannibalize neighbouring cells. Together, these findings suggest that cell cannibalism might be an activity that is broadly associated with the induction of senescence, rather than being linked to particular types of cancer or to the status of proteins such as p53. It will be important to investigate whether cannibalism is linked to senescence in other contexts, for example during tissue development when senescence can occur[14,15], or in aged tissues that accumulate senescent cells[3].

Entosis in cancer-cell populations can promote competition between individual cells in which 'winner' cells ingest and kill neighbouring 'loser' cells, removing them from the population[16]. Whether cells behave as winners or losers depends on certain cellular characteristics, for example differences in the tension of the internal cellular framework called the cytoskeleton[16]. It would be interesting to investigate whether senescent cells choose particular target cells to cannibalize in a competitive fashion. In cancers, complex mixtures of cells coexist in the tumour microenvironment, and this cellular composition changes over time or in response to anticancer therapy. The authors propose that cell cannibalism might affect cancer progression by supporting the SASP response. However, it is worth considering whether it might also contribute directly to cancer progression by removing particular cells from the tumour microenvironment. And if normal cells are found to be removed by senescent cells in aged tissues, this depletion might contribute directly to tissue degeneration.

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Palaeoclimate

Fresh evidence in the glacial-cycle debate

Eric W. Wolff

An analysis of air up to 2 million years old, trapped in Antarctic ice, shows that a major shift in the periodicity of glacial cycles was probably not caused by a long-term decline in atmospheric levels of carbon dioxide. **See p.663**

During the past 2.6 million years, Earth's climate has alternated between warm periods known as interglacials, when conditions were similar to those of today, and cold glacials, when ice sheets spread across North America and northern Europe. Before about 1 million years ago, the warm periods recurred every 40,000 years, but after that, the return period lengthened to an average of about 100,000 years. It has often been suggested that a decline in the atmospheric concentration of carbon dioxide was responsible for this fundamental change. On page 663, Yan *et al.*[1] report the first direct measurements of atmospheric CO_2 concentrations from more than 1 million years ago. Their data show that, although CO_2 levels during glacials stayed well above the lows that occurred during the deep glacials of the past 800,000 years, the maximum CO_2 concentrations during interglacials did not decline. The explanation for the change must therefore lie elsewhere.

Understanding what caused the shift in periodicity, known as the mid-Pleistocene transition (MPT), is one of the great challenges of palaeoclimate science. The 40,000-year periodicity that dominated until about 1 million years ago is easily explained, because the tilt of Earth's spin axis relative to its orbit around the Sun varies between 22.1° and 24.5° with the same period. In other words, before the MPT, low tilts led to cooler summers that promoted the growth and preservation of ice sheets.

But after the MPT, glacial cycles lasted for two to three tilt cycles. Because the pattern of variation in Earth's orbit and tilt remained unchanged, this implies that the energy needed to lose ice sheets[2] had increased. One prominent explanation[3] is that atmospheric levels of CO_2 were declining, and eventually crossed a threshold value below which the net cooling effect of the decline allowed ice sheets to persist and grow larger.

Ancient air trapped in Antarctic ice can be extracted from cores drilled from the ice sheet, allowing the CO_2 concentration to be measured directly, but the ice-core record extends to only 800,000 years ago[4]. Estimates of CO_2 concentrations from earlier periods have been made by measuring the ratio of boron isotopes in shells found in ancient marine sediments[5,6]. This proxy measurement depends on a chemical equilibrium controlled by ocean acidity, which, in turn, is closely related to the atmospheric CO_2 concentration.