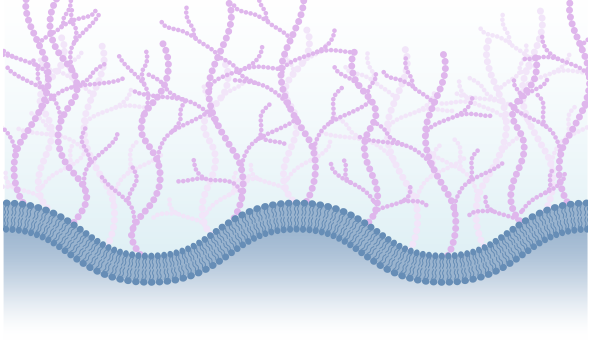
MEMBRANE DYNAMICS

Bend it like glycocalyx



Credit: V. Summersby/ Springer Nature Limited

Glycocalyx is a layer of glycolipids and glycoproteins on the surface of various cell types, which functions in cell–cell recognition, communication and adhesion. Shurer et al. show that the glycoproteins of the glycocalyx also have the capacity to shape the plasma membrane.

Important components of the glycocalyx are mucins — transmembrane, elongated and flexible glycoprotein polymers that extend from the cell surface. Overexpression of mucins in epithelial cells resulted in the emergence of tubular plasma membrane projections. Such membrane tubulation was not observed following overexpression of rigid glycoproteins and could be reversed by removing mucins from the cell surface. Furthermore, mucins could bend synthetic membranes in vitro. Thus, mucins induce membrane bending and tubulation, which rely on their molecular flexibility.

The extent of membrane tubulation correlated with the levels of mucin expression, both in epithelial cells overexpressing mucins and in human carcinoma cell lines, which are known to upregulate mucin expression. At higher levels of expression, mucins acquired more extended conformations, suggesting that the repulsion between the polymer chains resulting from their crowding is the source of free energy for membrane bending.

Tubules formed by mucin overexpression typically contained an F-actin core. Disruption of F-actin assembly led to the emergence of undulating membrane protrusions harbouring multiple pearl-like structures, which could undergo spontaneous fission to generate extracellular vesicles. Medium isolated from mucin-overexpressing epithelial cells contained large amounts of extracellular vesicles. Higher propensity for generating extracellular vesicles correlated with mucin expression also in human carcinoma cells. Thus, membrane protrusions induced by the glycocalyx can serve as a source of extracellular vesicles following the disassembly of their F-actin core.

> “mucins induce membrane bending and tubulation”

In the future, it will be interesting to study the importance and implications of glycocalyx-induced membrane shaping in different cellular contexts. Specifically, in light of the frequent changes in the glycocalyx associated with tumorigenesis, these studies could provide new insights into cancer development.

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ORIGINAL ARTICLE Shurer, C. R. et al. Physical principles of membrane shape regulation by the glycocalyx. *Cell* https://doi.org/10.1016/j.cell.2019.04.017 (2019)

Journal Club

CELLULAR SENESCENCE CAUSES AGEING

In my view, the study published by the van Deursen group in 2011 (Baker et al.), reporting that the elimination of senescent cells can delay ageing-associated disorders, transformed this research field. First, it provided evidence for cellular senescence having a role in ageing, a hypothesis that had been around for about 50 years. But also crucially, it exposed the unexpected potential for the selective elimination of senescent cells to be of benefit for treating diseases as diverse as cancer, atherosclerosis, osteoarthritis and glaucoma — taking research on cellular senescence to new heights.

Senescence defines a stable growth arrest that is induced when cells reach the end of their replicative potential or are exposed to various stressors. This cell state was discovered serendipitously by Leonard Hayflick when culturing primary human fibroblasts to grow viruses. He stumbled upon something unexpected: primary cells could be cultured for a while but eventually stopped proliferating. This was the first suggestion that cellular senescence might be linked to ageing. But the excitement was followed by high levels of scepticism. Could cell senescence be just an artefact resulting from non-physiological cell culture conditions rather than a defined physiological cell state?

In 1997, the discovery by Serrano et al. that cellular senescence can be ‘prematurely’ triggered by the expression of oncogenic Ras sparked new interest as it suggested that senescence is associated with cancer. But, the physiological relevance of oncogene-induced senescence (OIS) was disputed. It was not until 2005 that senescent cells were identified in premalignant lesions but not in more advanced lesions; an observation consistent with OIS being a mechanism for tumour suppression. This breakthrough led researchers to refocus on the role of senescence in cancer rather than ageing.

Not only did Baker et al. settle a looming question of half a century; they also provided a tool (the *INK-ATTAC* mouse model to eliminate senescent cells) to validate the causative role of senescence in a myriad of diseases. In addition, the paper also formulated a new concept: that the elimination of senescent cells has widespread benefits. It is not often that a paper spearheads such a revolution. A decade has not yet passed and there are already multiple investments in therapeutic strategies based on the idea that selective elimination of senescent cells can improve healthspan. We can safely say, more than 60 years since senescence was first discovered, that research on cellular senescence looks anything but arrested.

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J.G. owns equity and is a consultant for Unity Biotechnology. Unity Biotechnology funds research on senolytics in J.G.’s laboratory. J.G is a named inventor in a filed MRC patent related to senolytic therapies (PCT/GB2018/051437) that has been licensed to Unity Biotechnology.

ORIGINAL ARTICLES Baker, D. J. et al. Clearance of p16^{Ink4a}-positive senescent cells delays ageing-associated disorders. *Nature* **479**, 232–236 (2011) | Hayflick, L. & Moorhead, P. S. The serial cultivation of human diploid cell strains. *Exp. Cell Res.* **25**, 585–621 (1961) | Narita, M. & Lowe, S. W. Senescence comes of age. *Nat. Med.* **11**, 920–922 (2005) | Serrano, M. et al. Oncogenic *ras* provokes premature cell senescence associated with accumulation of p53 and p16^{INK4a}. *Cell* **88**, 593–602 (1997)