News & views

Cancer

Heartbeat of brain tumours targeted

Benjamin Deneen

Analysis of an invasive brain cancer reveals that networks of tumour cells are linked to small groups of 'pacemaker' cells in which levels of calcium ions pulse periodically, driving a signal through the network that causes tumour growth. **See p.179**

Malignant glioma is an almost universally lethal form of brain cancer for which therapies have not changed markedly over the past 20 years, highlighting the need to find new approaches. As part of the burgeoning field of cancer neuroscience, studies have shown that glioma cells adopt some core properties of healthy brain cells[1]. Hausmann *et al.*[2] reveal on page 179 that small groups of glioma cells also borrow a communication tool from pacemaker cells in the heart, and show that this mechanism might be a target for future treatments.

Gliomas originate in non-neuronal cells, called glial cells, that have a key role in supporting neuronal function in healthy brains. Some glial cells, called astrocytes, are physically connected to one another through intercellular channels called gap junctions[3]. Glioma cells are similarly interconnected, through a series of channels called tumour microtubes[4]. This microtube 'highway' is known to propagate calcium-ion (Ca^{2+}) signals across the glioma network, enabling the cells to resist therapeutic intervention, and contributing to drug resistance and cancer recurrence[4]. However, the microtube highway's structure, and how it aids the flow of information across the glioma network, are unknown. Also unknown are how this highway contributes to tumour expansion, and whether it might be vulnerable to therapeutics.

Hausmann and colleagues address these issues using state-of-the-art imaging of Ca^{2+} movement across microtube networks in a host of glioma systems (including *in vitro* models and mice harbouring cells from human gliomas). They find that Ca^{2+} moves between glioma cells along the microtube highways, and that blocking this movement by inhibiting the formation of gap junctions slows glioma-cell proliferation. They also note that, when they block intercellular Ca^{2+} movement, a small subset of glioma cells maintains Ca^{2+} oscillations that are highly synchronized, periodic and cell-intrinsic, similar to a cardiac pacemaker cell (Fig. 1). This feature is not static, because removing those glioma 'pacemaker' cells causes other cells to acquire this periodicity.

Delving more deeply into the network's dynamics using mathematical modelling of intercellular Ca^{2+} movement, the authors find that the pacemaker cells have 'hub'-like properties. Specifically, the patterns of Ca^{2+} movement reveal that the cells in which Ca^{2+} oscillates are more highly connected with other cells in the network than is the average glioma cell.

These hub-like properties raise the question of how network dynamics contribute to glioma-cell proliferation. Using *in vitro* systems and precise laser removal of pacemaker and non-pacemaker cells, Hausmann *et al.* find that removing only the pacemaker cells disrupts the network dynamics. Strikingly, ablating the pacemakers also causes the death of non-pacemaker cells in the network, whereas ablating non-pacemaker cells has no effect on the survival of other network cells. All of this suggests that maintaining a rhythmic flow of Ca^{2+} across the network from the pacemaker cells contributes to the proliferation of glioma cells and hence expansion of the glioma.

To uncover the molecular mechanisms governing the pacemaker cells, Hausmann and colleagues screen a series of pharmacological inhibitors that suppress Ca^{2+} oscillations, and find that the molecules TRAM-34 and senicapoc prevent the periodic activity. These inhibitors block the activity of the Ca^{2+}-activated potassium-channel protein KCa3.1. Using imaging, the authors demonstrate that KCa3.1 is essential for the oscillations and associated proliferation of glioma-network cells. Importantly, culturing cells that lack KCa3.1 with a small number of

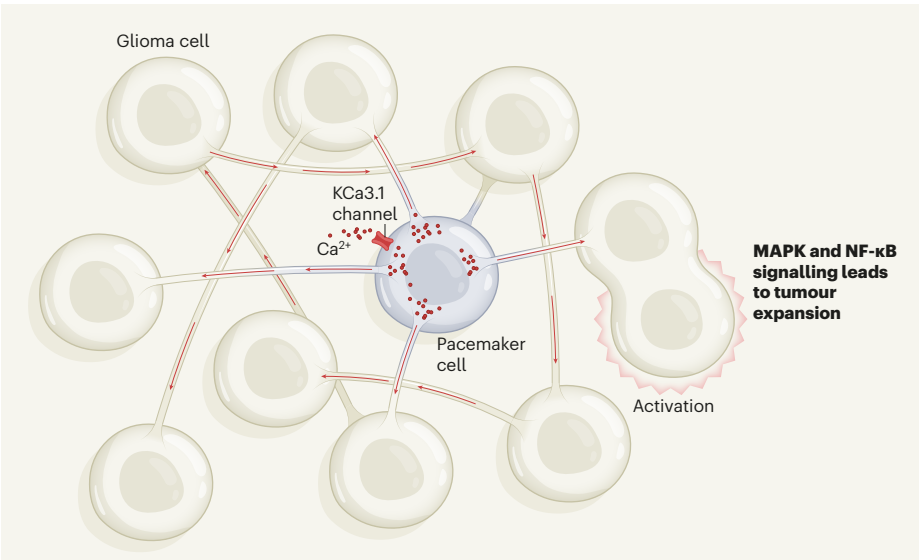

Figure 1 | Network dynamics in a deadly brain cancer. Glioma cells are connected through tumour 'microtubes', which propagate calcium-ion (Ca^{2+}) signals across the cell network[4]. Hausmann *et al.*[2] find that these network-wide Ca^{2+} signals are driven by small groups (or hubs) of highly connected glioma cells with central 'pacemaker' cells. A membrane-spanning KCa3.1 potassium-channel protein drives oscillation of Ca^{2+} levels in a periodic fashion in the pacemakers. These oscillations, in turn, drive the activation of the MAPK and NF-κB signalling pathways in other cells. This signalling promotes the proliferation of glioma cells and expansion of the tumour.

KCa3.1-expressing glioma cells restores both periodic activity and proliferation. It therefore seems that these pacemaker cells and the associated network are self-organizing, and that a small number of such cells can restore network properties and glioma expansion.

These results raise the question of how the patterns of Ca^{2+} oscillation are converted into proliferative signals. Here, Hausmann *et al.* take advantage of research that links the activities of key intracellular signalling pathways to distinct Ca^{2+} oscillation frequencies[5,6]. Their analysis reveals that the frequency of the oscillations in pacemaker cells lies in the range that activates the MAPK and NF-κB cascades – two key pathways implicated in cancer-cell proliferation. When the researchers co-culture KCa3.1-deficient glioma cells with cells that have activated MAPK and NF-κB pathways, they find that the activated cells can restore network activity and proliferation.

Finally, the authors test directly whether inhibiting KCa3.1 affects tumour growth. They find that when transplanted into mouse brains, glioma cells with reduced expression of KCa3.1 form tumours at a much slower rate than do normal glioma cells. Extending these genetic studies towards prospective therapeutic approaches, they show that TRAM-34 and senicapoc also suppress glioma growth in mice. Together, these results indicate that KCa3.1 is essential for glioma formation, and suggest a potential therapeutic strategy rooted in targeting the glioma pacemaker cells.

Hausmann and colleagues' work expands on the group's previous observations of the glioma-cell microtube highway[4], demonstrating the use of Ca^{2+} to orchestrate the flow of information across the network. The activity of Ca^{2+} has a clearly defined role in neuronal signalling, but in glia it is used as a proxy for overall physiological activity, and its contributions to glial-cell function are enigmatic[7]. Extended to glioma, these observations raise questions about what else is being transported between cells, and how these signals are encoded in pacemaker cells and deciphered in adjoining network cells.

These pacemaker cells are rare and exhibit a degree of functional plasticity (characteristics that are reminiscent of tumour-initiating glioma stem cells[8]). This plasticity – in terms of the ability to interconvert between pacemaker and non-pacemaker oscillation states – could present a therapeutic challenge, because non-pacemaker cells can re-establish the network. The cells' properties should also stimulate research into how the pacemaker's periodic activity is acquired, the associated biology of KCa3.1 channels in gliomas, and the sources of Ca^{2+} that seem to drive the network.

Nonetheless, the demonstration that pharmacological inhibition of KCa3.1 activity can suppress glioma development is exciting, because it suggests that disrupting these glioma pacemakers has clinical potential. Given the dearth of therapeutic options for people with malignant glioma, these studies offer hope that strategies rooted in the tenets of cancer neuroscience might pave the way to improved treatment of this deadly disease.

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1. Monje, M. *et al. Cell* **181**, 219–222 (2020).
2. Hausmann, D. *et al. Nature* **613**, 179–186 (2023).
3. Khakh, B. S. & Deneen, B. *Annu. Rev. Neurosci.* **42**, 187–207 (2019).
4. Osswald, M. *et al. Nature* **528**, 93–98 (2015).
5. Wacquier, B., Voorsluijs, V., Combettes, L. & Dupont, G. *Semin. Cell Dev. Biol.* **94**, 11–19 (2019).
6. Parekh, A. B. *Trends Biochem. Sci.* **36**, 78–87 (2011).
7. Shigetomi, E., Patel, S. & Khakh, B. S. *Trends Cell Biol.* **26**, 300–312 (2016).
8. Prager, B. C., Bhargava, S., Mahadev, V., Hubert, C. G. & Rich, J. N. *Trends Cancer* **6**, 223–235 (2020).

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Ageing

Senescent cells damage the body throughout life

David J. Glass

Cells in a state of arrested growth, called senescence, have been characterized in skeletal muscle in mice. Senescent cells promote inflammation and block regeneration, and thus might induce harmful changes in aged muscle. **See p.169**

Ageing was long thought to be inevitable, but treatment to forestall it is increasingly argued to be feasible. Of particular interest for such treatments are the 'senescent' cells that accumulate with age – cells that have stopped dividing and instead become seemingly dormant, in a state of arrested growth[1]. But it has proved challenging to isolate senescent cells, preventing researchers from fully understanding their behaviour throughout life. On page 169, Moiseeva *et al.*[2] present an approach to isolate senescent cells from mice. Their subsequent analyses reveal that the cells cause inflammation, preventing skeletal-muscle regeneration even in young animals (a setting in which the cells were previously assumed to be beneficial). The work adds weight to the idea that removing senescent cells could help to combat ageing.

Senescent cells make up a small percentage of the body, even in older individuals, and yet they cause major damage by secreting signalling proteins through a process called the senescence-associated secretory phenotype (SASP)[3]. The SASP induces fibrosis – the thickening and scarring of tissue – and blocks the functions of healthy neighbouring cells. As such, senescent cells are thought to contribute to many diseases and unwanted side effects of ageing.

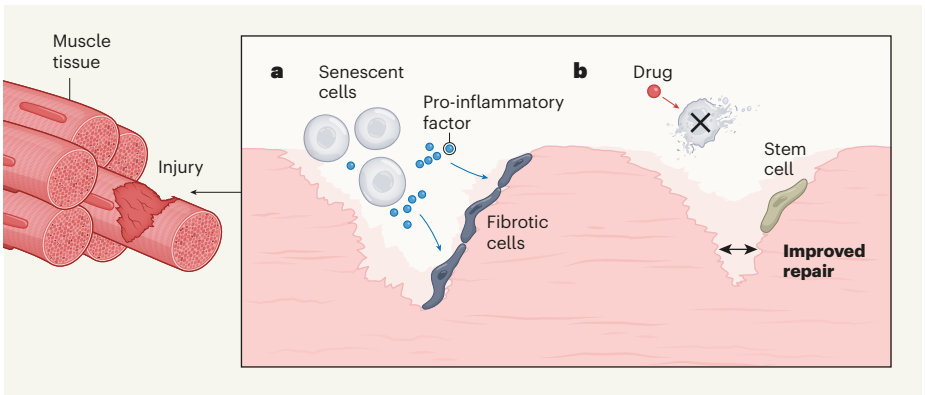

Figure 1 | Senescent cells inhibit recovery from injury. Moiseeva *et al.*[2] have analysed populations of senescent cells in injured muscle from mice of various ages. **a**, They found that, regardless of age, injury leads to an increase in the number of senescent cells (with the increase much more pronounced in older animals, not shown). The cells produce factors that trigger inflammation of the tissue and lead to the formation of fibrotic (scar) tissue, preventing muscle regeneration. **b**, When the authors gave the animals drugs that kill senescent cells, they found improved muscle repair by stem cells.