activates the WNT pathway downstream of the site of NOTUM action[7] – NOTUM secretion by cells with an *Apc* mutation does not affect the mutant cells themselves, but has a negative effect on wild-type cells. Thus, cells with *Apc* mutations not only outcompete their neighbours by driving them to differentiate, but they are also shielded from NOTUM-mediated adverse effects. Activating the WNT pathway using molecules such as lithium chloride (as done by Van Neerven and colleagues) or a NOTUM inhibitor (used by Flanagan *et al.*), thus levelling the playing field between wild-type intestinal cells and those with mutant *Apc*, reduced cancer formation in the mouse intestine mediated by mutant *Apc*; this suggests a possible approach in developing innovative anticancer therapies.

Together, these three studies reveal how malignant intestinal stem cells can win competitive battles in the gut by promoting neighbouring stem cells to differentiate into specialized and less-proliferative cell types (Fig. 1). Other studies using models for the formation of leukaemia have similarly shown that malignant cells secrete factors, such as pro-inflammatory cytokine molecules, that impair the fitness of competing normal cells and boost the fitness of the malignant cells[8,9].

Although cell competition is a process that is clearly involved in the progression of malignancy, it also serves as a quality-control mechanism for maintaining tissue health. For example, during embryonic development, defective cells are eliminated to ensure healthy growth through a process that involves factors secreted from normal cells[10]; this phenomenon has echoes of the mechanism described in these three studies.

There are numerous other examples of cellular competition processes affecting health and disease. One study[11] reported that the expression of the protein COL17A1 regulates basal (stem) cell divisions in the skin. Damage to a cell results in the downregulation of COL17A1 expression, which drives the differentiation of these stem cells into mature cells of the outer skin layer. This results in healthy basal cells replacing damaged ones. Moreover, normal cells can 'evict' mutant cells; for example, normal epithelial cells force the extrusion of cells with a cancer-promoting mutation from the skin layer, thereby preventing cancer initiation[12]. Beyond tumour-suppressive roles, the efficient recognition and elimination of 'loser' cells during cell competition is also crucial for the longevity of *D. melanogaster*[13].

The incidence of colon cancer rises exponentially in old age, and the expression of NOTUM increases with ageing, too[14]. This raises the question of whether the processes reported in these studies might be some of the ways in which ageing creates an environment that promotes cancer initiation. Numerous studies over the past decade have described how cells with cancer-promoting mutations become increasingly abundant in our tissues as we age[15]. Given that the papers by Yum *et al.*, Van Neerven *et al.* and Flanagan *et al.* indicate that such cells can impair the maintenance of neighbouring stem cells, such pre-malignant clones could hypothetically contribute to both tissue ageing (by reducing tissue maintenance) and ageing-associated cancers (through selection for cancer-promoting mutations that might resist, and perhaps even reinforce, pro-differentiation forces).

Current developments in cancer therapeutics often focus on exploiting our own natural systems of defence against the disease. The focus so far has been on the promotion of defences mediated by the immune system. However, we are now gaining an appreciation of how stem cells and aspects of the tissue environment are important for tumour progression. Hence, interventions might be developed that promote stem cells and tissue contexts that are unfavourable to the evolution of malignancy. Given the ability of healthy tissues to eliminate malfunctional or malignant cells[12], these three studies should further encourage the development of therapeutic strategies in which cancer is halted by counteracting the pro-differentiative influences of malignant cells, thus boosting the fitness of the competing normal cells.

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Neuroscience

Attraction and repulsion in brain-circuit wiring

Yajun Xie & Corey Harwell

Examination of the molecular interactions that govern the assembly of neural circuits in a brain region called the hippocampus reveals that neuronal projections are guided to their targets by both attractive and repulsive cues.

Our ability to sense and navigate the world requires the precise assembly and function of neural circuits in the brain. During development, neuronal-cell projections called axons are guided by molecular cues to extend away from non-target regions of the brain and towards their target regions[1], where axons make synaptic connections with partner neurons. Over the past few decades, several candidate molecular cues have been identified[2]; however, questions remain as to whether distinct sets of cell-surface molecules mediate attraction to targets and avoidance of non-target regions. Writing in *Science*, Pederick *et al.*[3] show in mice that axon attraction and repulsion are guided by the same cell-surface molecule during circuit assembly in the hippocampus, a brain region involved in spatial memory and navigation[4].

The hippocampus contains the subfields CA1, CA2 and CA3, and neurons in the CA1 subfield project to a target region in an adjacent brain structure called the subiculum. CA1 projections to the subiculum are organized along a medial-to-lateral anatomical axis. In this way, in the medial part of the network, neurons in the proximal CA1 (located near the border with the CA2 region) project to the distal subiculum (the part farthest from the CA1 border), whereas, in the lateral part of the network, distal CA1 neurons project to the proximal subiculum (Fig. 1).

A previous study by Pederick and colleagues' laboratory showed[5] that a cell-surface molecule called teneurin-3 (Ten3) is expressed both by proximal CA1 neurons and by neurons in their target region, the distal subiculum. The study showed that molecules of Ten-3

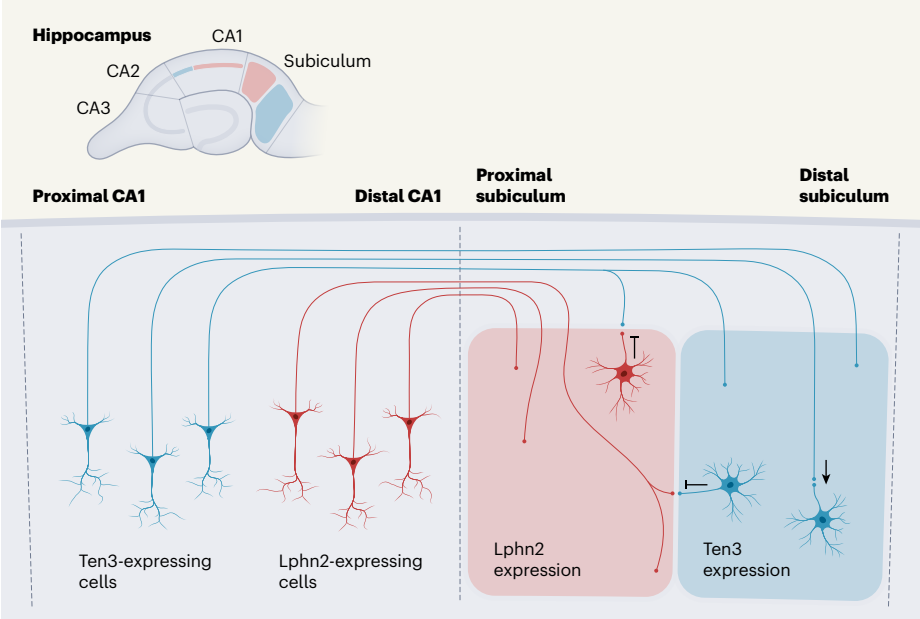

Figure 1 | Attractive and repulsive interactions mediate neuronal-circuit assembly. The hippocampus, a brain structure involved in memory, contains the CA1, CA2 and CA3 subfields. During development, neurons in the CA1 region extend projections called axons to another brain region, called the subiculum, to form two networks. In the medial network, neurons in the proximal part of CA1 (proximal CA1) express the cell-surface molecule teneurin-3 (Ten3) and project to the distal subiculum, a region where other neurons express Ten3. In the lateral network, neurons in distal CA1 express latrophilin 2 (Lphn2) and project to the proximal subiculum, which also is rich in Lphn2. Previous work[4] revealed that Ten3-expressing axons are attracted to Ten3-expressing regions (arrow). Pederick *et al.*[3] manipulated Ten3 and Lphn2 expression in CA1 and the subiculum to reveal that Ten3-expressing axons of proximal CA1 are also repelled (blocking symbol) by Lphn2-expressing neurons in the proximal subiculum — and that, similarly, Lphn2-expressing axons from distal CA1 are repelled by Ten3-expressing cells in the distal subiculum.

adhere to each other, and that this binding leads to attraction between neurons expressing this protein. Through this interaction, Ten3-expressing projections are attracted to target regions that express Ten3. Pederick *et al.* hypothesized that a similar mechanism — in which protein binding causes projections expressing that protein to be attracted to target regions expressing the same protein — might be involved in directing the formation of the lateral hippocampal network.

Using a technique called single-cell RNA sequencing to profile gene expression in individual cells from the developing mouse hippocampus, Pederick *et al.* found that the cell-surface protein latrophilin 2 (Lphn2) was expressed both in distal CA1 projections and in proximal-subiculum target neurons of the lateral hippocampal network. They initially investigated whether Lphn2–Lphn2 adhesion and attraction might, in a similar way to Ten3–Ten3 adhesion and attraction, direct the formation of hippocampal circuits. However, this was not the case: when the authors overexpressed Lphn2 in a non-adhesive cell line, the cells did not adhere to each other. By contrast, Lphn2-expressing cells readily formed aggregates with Ten3-expressing cells, consistent with previous reports of Lphn2–Ten3 binding[6].

The binding of Lphn2 to Ten3 could potentially trigger the activation of signalling pathways inside an axon, resulting in it moving towards or away from the region in which the interaction takes place. Because the areas targeted by Ten3-expressing axons and Lphn2-expressing axons do not overlap, Pederick and colleagues reasoned that Ten3–Lphn2 interactions might result in repulsion. To test this, the authors used a clever approach that involved injecting engineered viruses into the hippocampus to manipulate the expression of Lphn2 and Ten3 by CA1 neurons, and by neurons in their subiculum target regions.

The authors injected a virus expressing Lphn2 into the distal part of the developing subiculum, where Lphn2 levels are normally low, to increase Lphn2 levels there. Once the hippocampus had developed fully, the authors injected a virus expressing a fluorescent protein into the proximal CA1, where Ten3 expression is high, to visualize the axons from that region that had innervated the subiculum. These axons avoided the regions where Lphn2 was artificially expressed. The authors then performed the converse experiment: reducing Lphn2 expression in the developing proximal subiculum, where expression of this protein is usually high. In this case, Ten3-expressing axons from the proximal CA1 region invaded the regions where Lphn2 expression was reduced. Together, these results suggest that Lphn2–Ten3 interactions are necessary and sufficient for repulsive guidance of Ten3-expressing axons.

Crucially, the authors assessed the relative contributions of Ten3-mediated attraction and Lphn2-mediated repulsion of Ten3-expressing proximal CA1 axons, by reducing the expression of both Ten3 and Lphn2 across the entire subiculum. This manipulation led to an increase in axon projections in non-target regions and reduced innervation of the target region. Therefore, the precise targeting of Ten3-expressing proximal CA1 axons seems to require both Lphn2-mediated repulsion away from non-target regions and Ten3-mediated attraction.

How do Lphn2-expressing CA1 axons respond to target regions containing high levels of Ten3? Deletion of Ten3 expression from cells in the distal subiculum led to greater innervation of Lphn2-expressing axons from neurons in more-distal parts of CA1 into more-distal subiculum than was observed in hippocampi from control mice; this indicated that target-derived Ten3 repels Lphn2 axons.

Cooperation between attraction and repulsion of axon projections is a familiar theme in the development of neural circuits[2]. This study demonstrates that the connectivity between CA1 axons and subiculum neurons in the hippocampal network tightly follows a 'Ten3 axon to Ten3 target, Lphn2 axon to Lphn2 target' rule, instructed by reciprocal repulsions between Ten3-expressing and Lphn2-expressing cells.

Pederick *et al.* beautifully demonstrate how the binding interactions between cell-surface molecules depend on cellular context: on CA1 projections, Ten3 acts as a receptor for both attractive (Ten3) and repulsive (Lphn2) target-derived cues, whereas in the subiculum, it serves to repel Lphn2-expressing axons (Fig. 1). The importance of developmental context for the mechanisms that guide circuit assembly is further indicated by another study[7] showing that coincident binding of Lphn2, Ten3 and another cell-surface molecule, Flrt2, is required for the formation of neuronal synaptic connections between CA1 neurons and their partners upstream in the hippocampal circuit, rather than for axon guidance.

Further research is needed to identify the signalling cascades that are triggered by cell-surface molecules such as Ten3 and Lphn2, and that determine whether and how an axon is attracted to or repulsed by a given molecular cue. Also, if attraction and repulsion are both necessary for precise circuit assembly, what is the identity of the cell-surface molecule that mediates the attraction of Lphn2-expressing axons?

Given that the number of cell-surface molecules encoded by the genome is limited but the circuitry of the mammalian brain is

highly complex, each cell-surface molecule that is involved in guiding axons to their appropriate targets probably serves multiple such functions in different circuits, depending on the cellular and developmental context. It will be crucial to account for each molecule's context-dependent roles during the assembly of diverse neuronal circuits.

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Astronomy

Great Dimming of Betelgeuse explained

Emily M. Levesque

Observations suggest that an unexpected dimming of the massive star Betelgeuse resulted from dust forming over a cold patch in the star's southern hemisphere. This finding improves our understanding of such massive stars. **See p.365**

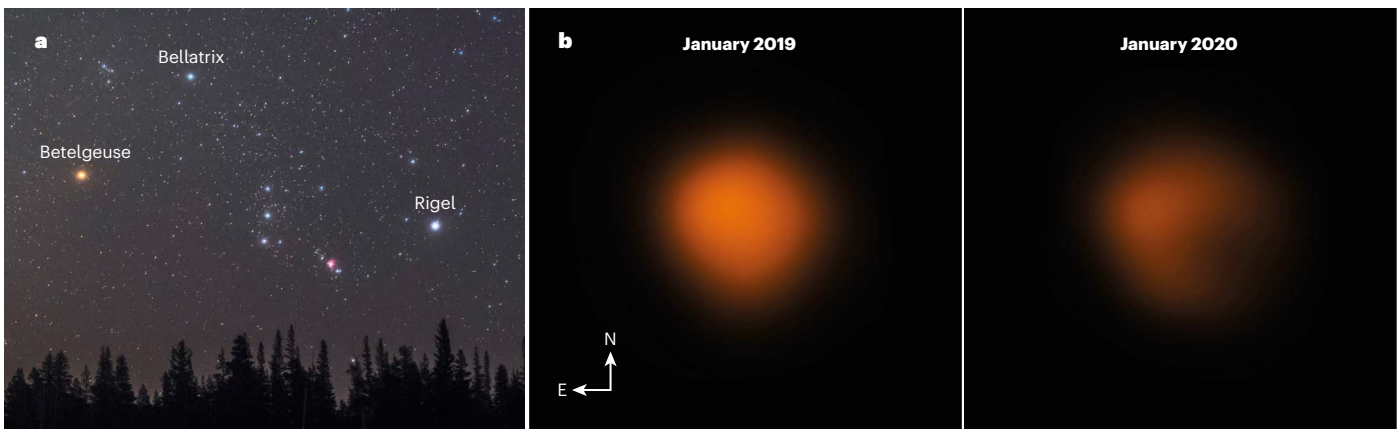
In December 2019, astronomers reported[1] a surprising change in the appearance of Betelgeuse. The bright red star in the shoulder of the Orion constellation had begun dimming dramatically during the preceding two months. In the following weeks, Betelgeuse's rapid and unprecedented dimming continued. By mid-February 2020, the star had plummeted to about 35% of its typical brightness[2] before swiftly recovering over the next few months. The event captivated professional and amateur stargazers alike because such rapid and visible changes in the night sky are rare. Now, a year after Betelgeuse's recovery from what has become known as its Great Dimming, Montargès *et al.*[3] (page 365) present a detailed picture of and compelling explanation for this strange behaviour.

Betelgeuse was born with about 20 times the mass of the Sun[4]. Such massive stars evolve much faster than their lower-mass counterparts, with lifetimes of mere millions rather than billions of years. Betelgeuse is a red supergiant — a stage in the evolution of massive stars that begins when these stars transition from fusing hydrogen in their cores to fusing helium; this leads to the cooling and expansion of their outer layers. The cores then spend several million years fusing progressively heavier elements before collapsing. These dying stars produce the spectacular fireworks show of a supernova, leaving behind neutron stars or black holes, and enriching their surroundings as they hurl the elements made in their interiors into interstellar space.

Red supergiants represent an extreme stage of stellar evolution. They are the largest stars in the Universe — for instance, Betelgeuse has a radius 900 times that of the Sun[4], and if it were placed at the centre of the Solar System, it would swallow all 4 inner planets and nearly reach the orbit of Jupiter. The huge cold outer layers of red supergiants pulsate, and host a handful of enormous convective cells (volumes of material that move as a result of convection). Furthermore, these outer layers shed mass that can eventually form dust in the star's surrounding environment.

Modelling the outer layers of red supergiants is extremely challenging, because the mechanisms driving mass loss and dust production are complex, and the effects of these various quirks on the star's brightness, evolution and eventual death are far from clear. Nevertheless, efforts to better understand red supergiants are worth the trouble because these stars are key players in the cycle of stellar birth and death and in the chemical evolution of the cosmos.

Betelgeuse's Great Dimming was evident with the naked eye, but the observations presented by Montargès *et al.* reveal the full details of the star's sudden change in appearance. Betelgeuse's large size and close proximity to Earth (about 220 parsecs, or 724 light years[5]) make it one of only a few stars that can be seen as a spatially resolved disk rather



A. BABAK TAFRESHI/SPL

Figure 1 | Location and observations of Betelgeuse. a, Normally, Betelgeuse is the brightest star in the Orion constellation; Rigel is the second brightest and Bellatrix the third brightest. **b**, Montargès *et al.*[3] observed Betelgeuse before (January 2019) and during (January 2020) a period known as the Great Dimming, in which the star was comparable in brightness to Bellatrix. The observations show that the light loss was concentrated in Betelgeuse's southern hemisphere. A detailed analysis by the authors suggests that a southern dust cloud temporarily blocked much of the star's light.