sideways motion. Pattern and movement, in other words, act together.

But this association could still be coincidental because butterfly wing patterns are shaped by many forces. The authors therefore let artificial wing patterns evolve in a computer system, selecting for motion confusion. The resulting patterns were more similar to the natural ones of European butterflies than to randomly generated patterns or those evolved by chance.

So far, the evidence is indirect. The key question is whether motion confusion translates into altered attacks on a moving butterfly. Because experiments with wild predators would be extremely difficult, the authors used human participants as a stand-in. In 3,000 trials, participants attempted to catch virtual butterflies with realistic flight paths and wing movements. Butterflies with more backwards-pointing apparent motion drew attacks that landed farther back relative to their direction of flight: the difference in attack location between the forms with the most and least motion confusion amounted to about 38% of the average body length. The attacks, in other words, were misdirected, but there was no evidence that the butterflies were harder to catch overall. Nevertheless, such misdirection might still have consequences. For example, in swallowtail butterflies, it could help to explain how wing patterns divert attacks towards their long hindwing tails during flight[8].

The chain of evidence is compelling, but not every link is equally strong. The study rests on assumptions about how a predator sees a flying butterfly. The modelling assumes specific viewing distances, visual limits, backgrounds, wingbeat frequencies and viewing angles. These assumptions are reasonable given how little is known about butterfly flight and predator vision, but real attacks will vary. Unlike most previous experiments, which have used simplified targets[4], this study uses filmed butterflies and natural patterns, bringing the evidence closer to the conditions under which natural selection actually operates. The simulated evolution, meanwhile, shows the patterns that selection for motion confusion can produce, but not whether this selection has happened in the real world.

Even so, the larger unknown is whether natural predators respond to these cues as the participants did, tending to strike farther back as motion confusion increases. The decisive test is still wild predators attacking live butterflies.

Taken together, the evidence puts a century-old intuition on a measurable footing. The study gives fresh weight to the idea that some animal patterns have evolved for how they look in motion, rather than at rest. For butterflies, it could help to explain how such striking wings could be advantageous in flight, despite making the animals easy to spot. More broadly, with a way to quantify how natural patterns alter perceived motion during realistic movement, it is now possible to look beyond butterflies and ask whether the demands of moving prey have helped to shape animal colouration[9]. As Thayer described in 1909, the bold pattern of a butterfly flickering through light and shade "must strongly tend to baffle a pursuer"[3]. More than a century later, Thayer's idea has acquired a plausible biological mechanism.

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Neuroimmunology

Pipework issues as cancer spreads to brain boundary

Jang Hyun Park & Jonathan Kipnis

Analysis of cancer growing adjacent to the brain reveals that bone-eroding cells interfere with lymphatic drainage vessels and hinder anti-tumour immune responses. **See p.1025**

Tumours called dural metastases — those that spread to the outermost membrane surrounding the brain — do not just sit passively at the brain border. A picture is emerging of how extensively they restructure the surrounding area. On page 1025, Zeng *et al.*[1] show that these tumours recruit cells called osteoclasts, which naturally degrade bone. Moreover, the osteoclasts disrupt fluid 'pipes' adjacent to the brain called meningeal lymphatic vessels and blunt local anti-tumour immune responses. This evidence reveals several possible targets in efforts to develop therapies.

For decades, the central nervous system (CNS), which comprises the brain and spinal cord, was considered to be immunologically isolated — cut off from the rest of the immune system by several barriers and not connected to the lymphatic system (the body's fluid-drainage mechanism). This view no longer holds. Cerebrospinal fluid (CSF) circulates continuously around and through the brain, carrying molecular waste into the brain's 'drainage pipes', the meningeal lymphatic system[2].

The brain sits inside three nested membranes — the innermost pia mater, the arachnoid mater and the outermost dura mater — collectively known as the meninges (Fig. 1). CSF moves between the pia and arachnoid, eventually reaching the dura through dedicated exit routes called arachnoid cuff exit points[3]. Unlike the brain itself, the dura is open to circulating molecules and immune cells. It is a border tissue that reflects what is happening immunologically inside the brain[4].

The dura itself has lymphatic vessels[5], which drain brain-derived waste to immune-system structures outside the brain called cervical lymph nodes. If this drainage system fails, it results in waste accumulation, which has been linked to various neurological diseases. These vessels also carry protein fragments called antigens, which help immune cells to target defence responses, from the CNS to the periphery, aiding immune responses under both normal and disease conditions, including when brain tumours arise[6]. The dura is also connected directly to the skull's bone marrow above it through tiny channels in the bone[7,8]. Brain-derived molecules and CSF can travel through these channels into the marrow, enabling the tissue to sense what is happening in the brain and take part in CNS immune surveillance. This traffic runs the other way, too, with the bone marrow acting as a local supply of immune cells for the CNS and its borders[2].

But evidence suggests that the marrow does more than just provide cells — it can mount CNS-specific immune responses of its own (probably responding before immune cells in cervical lymph nodes can be primed by antigens draining from the CNS)[9]. The brain borders, including the dura and the bone marrow, are therefore in constant communication.

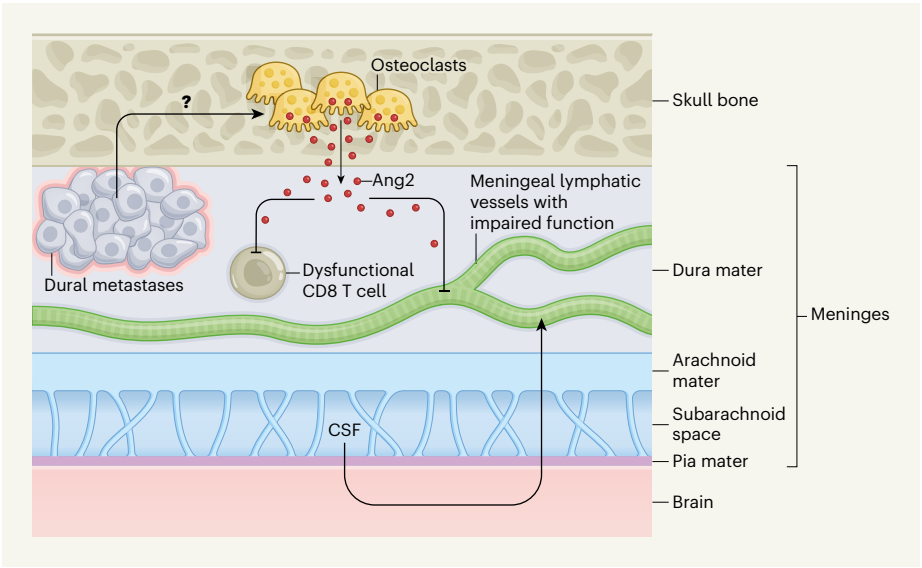


Figure 1 | The consequences of a tumour spreading to an area bordering the brain. Zeng *et al.*[1] studied tumours called dural metastases, which have spread to a membrane called the dura mater. The dura and two other membranes, the arachnoid mater and the pia mater, surround the brain. The arachnoid is separated from the pia by a region called the subarachnoid space. Cerebrospinal fluid (CSF) moves around the brain and reaches the dura, where waste molecules from the brain are placed into a system of 'drainage pipes' called meningeal lymphatic vessels. The authors report that, through an unknown mechanism, dural metastases activate bone-destroying cells called osteoclasts. These cells thin the skull bone and release the molecule Ang2, which impairs the function of meningeal lymphatic vessels and causes tumour-killing immune cells called CD8 T cells to enter a dysfunctional state called exhaustion. Ang2 can be targeted by the clinically approved drug zoledronic acid (not shown), raising the possibility of testing this as a therapy for dural metastases.

So, what happens when a tumour moves into the neighbourhood? Zeng and colleagues decided to investigate this.

Estimates vary, but dural metastases arise in around 9% of people who have cancer, most often from tumours that began in the breast, prostate or lungs[10]. Cancer cells colonize other regions of the CNS, too, including the brain parenchyma and the leptomeninges — both of which have received more attention than dural metastases.

The authors started with a clinical observation. They found that people who have dural metastases have thinner skulls than do people with other patterns of cancer spread, hinting at an active process of bone erosion. They then generated a mouse model that reproduced dural metastases and skull thinning. Bone remodelling comes down to two cell types working against each other: osteoblasts building bone and osteoclasts breaking bone down. In the studied mice, osteoclasts piled up around the tumour. Furthermore, osteoclast-lineage cells extended out of the skull and into the tumour itself, which points to an active, continuing interaction between osteoclasts and cancer cells, rather than a passive bystander effect.

Further analysis revealed that meningeal lymphatic vessels were enlarged and abnormally shaped and that CSF drainage to the cervical lymph nodes was lower than usual. CD8 T cells, a type of immune cell that can kill tumour cells, were also less active than normal and showed signs of being in a dysfunctional state termed exhaustion. These defects could all be traced back to the osteoclasts, with the osteoclast-derived protein Ang2 found to be the common thread tying together the lymphatic and immune dysfunction.

Treating the mice with zoledronic acid, a clinically approved drug that shuts down osteoclast-mediated bone destruction, reversed the microenvironmental remodelling and its functional consequences. This change was also achieved by engineering mice to reduce their expression of Ang2, highlighting the osteoclast–Ang2 axis as a potential target for treatment of dural metastases, and opening the door to the repurposing of an existing drug.

Zeng and colleagues have shown that the cancer cells do not just adapt to this environment but actively reshape it in their favour. And the consequences are probably not limited to the tumour itself. Meningeal lymphatics and local immunity both matter for broader brain function, so disrupting them might result in neurological dysfunction beyond tumour growth.

Previous mouse studies[11] have indicated that a condition called craniosynostosis is linked to impaired meningeal lymphatic function and, with it, cognitive and neurological problems. It is therefore not a stretch to propose that some of the neurological and cognitive changes seen with dural metastases can be traced back to the same impaired drainage. It is possible that complications such as raised cranial pressure, swelling and seizures could be shaped by this phenomenon, too. If so, targeting meningeal lymphatic function might do more than slow tumour growth; it might also ease some of these related complications directly.

The study answers many important questions, but it raises even more. What signal does the tumour send out to trigger osteoclasts in the first place? And is this circuit specific to dural metastases, or does the same mechanism operate in other brain tumours, such as glioblastoma, which also erodes the skull[12], and in other meningeal tumours such as meningioma?

It is also possible that some of the remodelling is in fact the result of the body trying to adapt to the presence of the tumour, rather than being purely a consequence of the disease. Thinning the skull might relieve some of the pressure caused by the mass of dural metastases pressing on the brain. Moreover, the remodelling of lymphatic vessels might limit further tumour spread through the body's drainage routes. As these functional consequences are being investigated, therapies targeting this axis will need to be checked for any potential harm that they might do alongside any that they might prevent.

Zeng and colleagues have provided a mechanistic link between cell biology and a possible therapeutic strategy, and there is also a broader lesson to learn. If one part of the skull–meningeal interface is disturbed, the damage does not stay local, but instead spreads across bone, lymphatic systems and immune responses. And this principle is unlikely to be limited to cancer spread alone. The skull is not just the brain's armour; it is a listening post and tumours have found a way to jam the signal.

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