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Cell biology

Uncoordinated protein coordinates cell migration

Alain Chédotal

Mounting evidence suggests that developing neurons and metastatic cancer cells migrate through similar mechanisms. Characterization of a previously unknown complex involved in cell migration confirms this idea.

During development, many cell types — including neurons — migrate in and across organs to reach the position they will occupy for the remainder of their lives. Similarly, in cancers, metastatic cells escape tumours and disperse around the body. Three decades of research have shown that cell migration is not random. Instead, the cell's motility, its orientation and whether it leaves or settles in a specific location are influenced and guided by molecular signals from neighbouring and, sometimes, distant cells[1]. Several families of cell-guidance molecules have been identified[2], but how they interact to coordinate cell movements is not well defined. Writing in *Cell*, Akkermans *et al.*[3] add to this picture through the characterization of a molecular complex that controls neuronal and metastatic cell migration.

In 1974, the biologist Sydney Brenner treated nematode worms (*Caenorhabditis elegans*) with a chemical that induces genetic mutations, and isolated more than 50 mutants that displayed uncoordinated body movements[4]. This included one mutant, carrying alterations in a gene dubbed *unc-5*, that had an abnormal nervous system. It was later found that *unc-5* encodes a membrane-spanning protein of the immunoglobulin family, expressed by both migrating cells and developing neurons. It is a receptor for the secreted protein unc-6 (ref. 5).

Parallel studies[6,7] identified four unc-5 proteins (Unc5A, Unc5B, Unc5C and Unc5D) in vertebrates, all of which bind to Netrin-1, the vertebrate unc-6. However, Unc5 receptors can also interact with other proteins either in the same cell (in *cis*) or in adjacent cells (in *trans*)[2,8]. In most settings, binding between Unc5 and Netrin-1 inhibits cell motility, but Unc5 receptors that are bound to either Netrin-1 or other partners can influence a large range of developmental processes, including brain wiring, blood-vessel growth and cancer[2,9].

Akkermans *et al.* used an array of methods to show that Unc5 receptors interact with a protein called Glypican 3 (GPC3) in humans and mice. GPC3 belongs to a small group of extracellular proteins that are covalently linked to the cell surface by a glycosylphosphatidylinositol anchor.

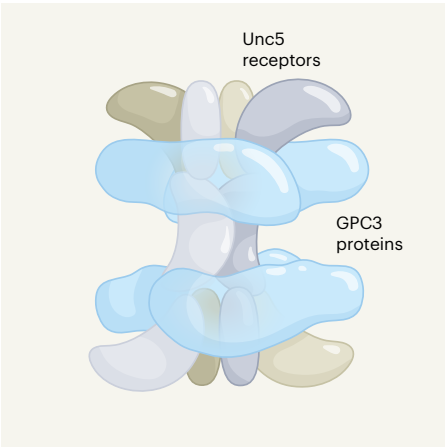

Figure 1 | The core of the GPC3–Unc5 protein complex. Akkermans *et al.*[3] resolved crystal structures for mouse and human GPC3–Unc5 protein complexes. They found that the core of each complex contains the extracellular domains of four Unc5 receptors, arranged in two antiparallel pairs. The receptors are enlaced by pairs of GPC3 proteins at either end.

The authors resolved the crystal structure of mouse and human GPC3–Unc5 complexes using X-ray crystallography. Surprisingly, rather than simple dimers, GPC3 and Unc5 proteins assemble into a large octameric complex that contains a core tetramer of four Unc5 proteins, bracketed at either end by pairs of GPC3 proteins (Fig. 1). The researchers found that GPC3 and Unc5 can interact both in *cis* and in *trans*; however, in *cis* interactions inhibit in *trans* interactions. All four members of the Unc5 receptor family seem to bind equally to GPC3, but previous work[10] suggests that the five other Glypican family members do not interact with any Unc5 protein.

What is the function of the GPC3–Unc5 complex? Akkermans *et al.* first focused on the brain's cerebral cortex, where GPC3 is expressed by apical progenitor cells. These cells have long processes that act as a scaffold along which neurons expressing Unc5 migrate. To avoid the fact that the large palette of Unc5 and GPC3 binding partners could complicate their analysis, the authors developed an approach to selectively modify the GPC3–Unc5 complex. They identified small antibodies called llama nanobodies that could enhance (in the case of a nanobody called Nano^{glue}) or inhibit (in the case of Nano^{break}) GPC3–Unc5 interactions.

The researchers placed Unc5-expressing neurons on a surface that contained stripes of GPC3 *in vitro*. The found that the neurons were repelled from the GPC3 stripes, and showed that adding Nano^{break} can overcome this repulsion. Interfering with GPC3–Unc5 interaction *in vivo* — by using nanobodies, by blocking GPC3 production or by overexpressing the extracellular portion of Unc5 — significantly delayed cortical neuron migration (Fig. 2a). Thus, interactions between these binding partners promote or facilitate migration, perhaps to ensure that Unc5-expressing neurons reach the correct final position in the brain at the correct time. Given that Unc5 proteins are involved in neuronal migration in many brain regions outside the cortex, the GPC3–Unc5 complex could have other neurodevelopmental functions, too.

Unc5 proteins and GPC3 have been linked to the development of various types of cancer, and are expressed in some cultured tumour cells[9]. This prompted Akkermans and colleagues to investigate the role of GPC3–Unc5 complexes in tumour-cell migration. They found that, when very aggressive cancer cells that expressed both Unc5 and GPC3 were transplanted into a chick embryo, they migrated extensively along nerves and settled in neuronal masses called peripheral ganglia. Reducing the levels of Unc5 or GPC3 in these transplanted cells, or unbalancing GPC3–Unc5 interactions using nanobodies or mutated receptors, impeded

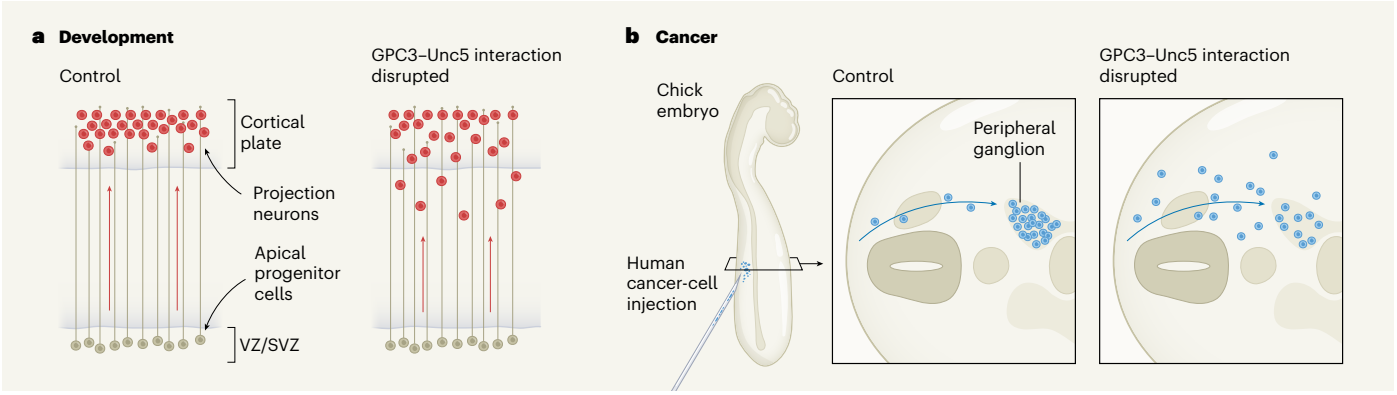

Figure 2 | GPC3–Unc5 controls neuronal and cancer-cell migration. **a**, In the cerebral cortex of the developing mouse brain, cells called projection neurons that express Unc5 migrate from a region called the ventricular/subventricular zone (VZ/SVZ) to the cortical plate, moving along processes from apical progenitor cells that express GPC3. Akkermans *et al.* demonstrated that disrupting GPC3–Unc5 interactions prevents normal migration. **b**, Similarly, when human cancer cells that express both Unc5 and GPC3 are injected into the back of chick embryos, they migrate along nerves to colonize structures called peripheral ganglia — but interfering with GPC3–Unc5 interactions prevents this directed migration, with tumour cells instead dispersing and invading other organs.

tumour-cell migration, cohesion and homing to peripheral ganglia (Fig. 2b).

In sum, these results define the GPC3–Unc5 complex as a key regulator of both normal neuron migration and aberrant tumour-cell migration. Although Akkermans and colleagues' study focused on cell migration, Unc5 receptors are also involved in cancer-cell survival, triggering cell death in the absence of Netrin-1 (ref. 9). It is tempting to speculate, then, that enhancing GPC3–Unc5 interactions might prevent Unc5 from binding to Netrin-1, killing tumour cells.

Akkermans *et al.* have added to the already impressive diversity of Unc5 binding partners. Going forward, much remains to be learnt about the potential influence of other Unc5 partners on the stability and function of the GPC3–Unc5 complex. For instance, Unc5-binding proteins called fibronectin leucine-rich transmembrane proteins (FLRTs) can also modulate cortical-cell migration in an Unc5-dependent manner[11]. Is there a hierarchy involving Unc5, GPC3 and FLRTs or other partners? Moreover, because Akkermans and colleagues' structures each contained only one type of Unc5 receptor, owing to difficulties in controlling the stoichiometry of multiple receptors, an open question is whether GPC3 can bind to different combinations of Unc5. It will also be interesting to analyse how Unc5 receptors integrate the choir of upstream signals, and whether the downstream pathways elicited by them are shared or different. Discerning how Unc5 interprets these converging signals is key to understanding how neurons or cancer cells choose to stop or go.

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Structural biology

Folate transporter offers clues for anticancer drugs

Larry H. Matherly & Zhanjun Hou

Structural insights into a long-studied folate-transport protein provide evidence that might lead to entirely new targeted anticancer treatments, or boost the success of immunotherapy approaches to tackling tumours. **See p.170**

The transport protein SLC19A1, better known as the reduced folate carrier, resides in the cell membrane. It has been studied for decades because it is the main tissue transporter of the B9 vitamins (called folates), which are required for reactions needed to make certain types of nucleotide and to make the amino-acid residues serine and methionine[1]. SLC19A1 also happens to be the main transporter of the drugs methotrexate and pemetrexed — which are called antifolates, because they block the action of folates. These drugs are used in the treatment of cancer, rheumatoid arthritis and psoriasis[1]. In 2019, a new role for SLC19A1 was identified, as a transporter of signalling molecules called cyclic dinucleotides (CDNs), which stimulate a wide range of immune-system cellular responses[2,3].

Although extensive biochemical and molecular studies have implicated structural and functional determinants of folate transport by SLC19A1, the detailed molecular basis for the binding of various SLC19A1 substrates and their movement through the transporter, from outside the cell into the cytoplasm, is largely unexplored. Zhang *et al.*[4] (page 170) and Wright *et al.*[5] (in a study published in September) shed some light on this.

These studies used cryo-electron microscopy (cryo-EM) to determine the molecular structures of human SLC19A1 without a binding partner (in what is known as the protein's apo form) and with bound folates, antifolates or CDNs (Fig. 1). In both reports, SLC19A1 assumed a structure with 12 membrane-spanning segments in an 'inward'-facing orientation opening onto the cytoplasm — with membrane-spanning segments surrounding a positively charged substrate-binding pocket that is lined