There are other unanswered questions. The mechanisms underlying signalling between cells were hotly debated: is signalling mediated by diffusion, or active transport, or by cells extending finger-like filopodia (S. Eaton, Max Planck Inst. Mol. Cell Biol. Genet., Dresden; T. Kornberg)? And, as several researchers pointed out, it is not known whether the long-range signals generated by boundaries can explain several important processes, such as growth control and regeneration (A. Garcia-Bellido, Univ. Autonoma Madrid; L. Wolpert, University College London). The concept of long-range signalling is at odds with older models, in which every cell was thought to have a molecular address that could be recognized by its neighbours. Developing cells are exceedingly clever, and it is possible that they are still hiding Something Big. ■

Seth S. Blair is in the Department of Zoology, University of Wisconsin, 250 North Mills Street, Madison, Wisconsin 53706, USA.
e-mail: ssblair@wisc.edu

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Neurobiology

A new way to network

Patrick Mehlen

Guidance molecules called semaphorins ensure that nerve cells grow in the correct direction during development. It now appears that one semaphorin interacts with integrin proteins to produce another effect.

During the development of the nervous system, nerve cells must extend projections called axons over considerable distances to construct a complex network of connections. How axons extend in the correct direction is conceptually simple: the extremity of the axon — the growth cone — explores its local environment for molecular cues, which guide it along the right trajectory. In practice, however, guidance of the growth cone is a complex, tightly regulated mechanism that involves several different families of guidance molecules. Some of these cues are soluble and can act at a considerable distance; others are bound to the cell membrane and act locally. Some cues attract the growth cone, others repel it and still others can act as both attractants and repellents[1]. One group of guidance molecules is the aptly named semaphorin family[2]. On page 398 of this issue, Pasterkamp *et al.*[3] reveal a new way in which one type of semaphorin acts on nerve-cell axons to ensure that the brain develops normally.

More than 20 semaphorins have been identified, but only a few have been shown to be involved in the development of the nervous system[2]. Others have been implicated in immune-cell function. It now appears that one member of the family — Sema7A — has a dual role, and functions during brain development as well as modulating the activity of immune cells. Pasterkamp and colleagues[3] observed that Sema7A is expressed during neural development in mice, and that the brains of mice genetically engineered to lack this protein fail to develop normally. The authors focused on the part of the brain that determines the sense of smell — the central olfactory system — and showed that Sema7A is normally present along the trajectory of a bundle of axons called the lateral olfactory tract. Strikingly, in the mice lacking Sema7A, this axon bundle had grown in the correct direction, but it was substantially smaller than normal. Semaphorins normally function as growth-cone repellents, but these results indicate that Sema7A functions in the olfactory system as neither a repellent nor an attractant. Instead, it seems to encourage axon outgrowth, in a direction that is probably dictated by other cues.

But how does Sema7A promote axon outgrowth? Other semaphorins are thought to guide developing axons by interacting with at least two families of receptors present on the growth-cone membrane: the neuropilins and the plexins[2]. The classical view is that binding of semaphorins to either type of receptor sets off a chain of intracellular signalling events within the growth cone, which in turn modulates its pathfinding (Fig. 1, overleaf). Could Sema7A be exerting its growth-promoting effects in the same way? Previous *in vitro* protein-binding studies had suggested that Sema7A interacts with PlexinC1; furthermore, both PlexinC1 and Sema7A are often present within the same regions of the brain[4]. To investigate further, Pasterkamp *et al.* engineered mice lacking functional PlexinC1. But these mutant mice did not show the same brain abnormalities as the Sema7A-mutant animals, suggesting that PlexinC1 is not, after all, used by Sema7A to promote axon outgrowth.

100 YEARS AGO

It is known that salt (NaCl) at a temperature of 200° C is phosphorescent; during a course of experiments in June last I found that radium bromide induces phosphorescence at ordinary temperatures. The following is a convenient way of observing the phenomenon. Fill a wooden match-box with table salt removed from the inner portion of a block; press the radium bromide tube into the yielding mass and just barely cover it with the substance. If it be now put on one side for a few hours, say into one of the compartments of a chest of drawers, on opening the box in the dark all round the tube will be found to phosphoresce with a white light, but, unlike zinc blende and barium platinocyanide, the salt continues visibly to phosphoresce after removal of the radium bromide… The image of the visible portion round and where the radium bromide tube has lain is impressed on a photographic plate in thirty minutes, but only very faintly in two or three minutes.

From *Nature* 23 July 1903.

50 YEARS AGO

Evidence for 2-chain helix in crystalline structure of sodium deoxyribonucleate. **Watson and Crick [*Nature* 171, 737, 1953] have proposed a structure for sodium deoxyribonucleate consisting of two co-axial helical chains related by a diad axis. We have shown [page 740 of the same issue] that the main features of their structure are consistent with certain important features of our X-ray diagrams of structure *B* (the high-humidity less-ordered form of the salt). A subsequent closer investigation of density and water content in relation to the prominent equatorial spacing, and also of equatorial intensities calculated from a projection of the proposed structure (kindly provided by Watson and Crick), makes it clear that in detail the structure is not consistent with the observed equatorial reflexions. Both density and intensity considerations lead us to favour a more compact helical structure in which the phosphorus atoms lie on a helix of radius about 8.5 A. rather than 10 A. This value also lies within the range of spread of the more diffuse layer-line peaks. We are more concerned here, however, with evidence which confirms in principle the type of structure suggested by Watson and Crick, than with criticism on points of detail.** **Rosalind E. Franklin and R. G. Gosling**

From *Nature* 25 July 1953.

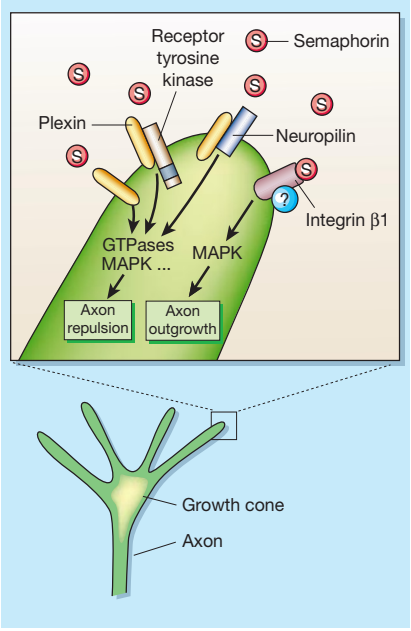

Figure 1 **Effects of semaphorins on the development of the nervous system. Several receptor complexes have been proposed to interact with semaphorins present in the environment of developing nerve cells. For instance, semaphorins can interact with a plexin receptor, a complex formed by a plexin and a receptor tyrosine kinase, or a complex formed by a plexin and a neuropilin to steer the growing axon (see ref. 2 for a review). Pasterkamp *et al.*[3] have now found that one semaphorin, Sema7A, interacts with integrins, thereby stimulating the growth of the axon. The semaphorin–receptor interactions produce these effects through cascades of intracellular signals that include small GTPases or mitogen-activated protein kinases (MAPKs).**

In search of alternative receptors, the authors scanned the amino-acid sequences of different semaphorin proteins for clues. They observed that several semaphorins, including Sema7A, contain the arginine–glycine–aspartate (RGD) sequence, which is frequently associated with binding to integrin proteins. Integrins are a large family of membrane-spanning receptors that are involved in cell adhesion[5]. They usually function as dimers of an α-subunit and a β-subunit, of which there are many different types. Using a panel of inhibitors to block specific integrin subunits, together with mutant Sema7A proteins lacking the RGD sequence, Pasterkamp *et al.* determined that a β1-type integrin subunit is required for the growth-promoting activity of Sema7A (Fig. 1). Moreover, addition of Sema7A to cultured neurons led to intracellular signalling events that included the activation of the key enzymes focal adhesion kinase and mitogen-activated protein kinases — enzymes known to be activated by integrins and to be required during axonal guidance[6,7].

The proposal that integrins are receptors for semaphorins opens up a new vista on their role during brain development. Integrins have already been implicated in axon guidance, but until now it was thought that they simply allowed nerve cells to attach firmly within an environment that had already been deemed 'permissive' by other guidance signals[8]. Pasterkamp *et al.* have shown, however, that integrins have a more direct part to play. Specifically, they are receptors, or part of a receptor complex, for a cue that stimulates axonal outgrowth.

As usual, this discovery prompts yet more questions. Other semaphorins, and proteins belonging to other families of guidance cues, also contain RGD motifs. Do they also interact with integrins? As integrins usually function as dimers, what is the nature of the other half of the integrin receptor used in Sema7A signalling? Is it an α-integrin, or does an alternative receptor substitute for the α-subunit? Is the growth-cone-repelling activity of semaphorins also transmitted through integrins? Finally, Sema7A is also a potent modulator of immune responses. Does this activity require interaction with integrins?

Elsewhere in this issue, Serini *et al.*[9] propose that Sema3A proteins, although they do not have an RGD motif, control blood-vessel development by altering integrin activity. So a deeper understanding of the intracellular signalling pathways that are activated by semaphorins through integrins will provide insight into a variety of physiological processes, from vascular and neural development to immunity. The semaphorin–integrin interaction may also have implications for disease, shedding light on events such as the formation of new blood vessels in cancers, harmful immune responses, and how nerves regenerate after injury. ■

Patrick Mehlen is in the Apoptosis/Differentiation Laboratory, Molecular and Cellular Genetic Center, CNRS UMR 5534, University of Lyon, 69622 Villeurbanne, France.
e-mail: mehlen@univ-lyon1.fr

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Astronomy

An early stellar nursery

Philip Solomon

Searching for distant objects in our Universe is equivalent to looking back in time, to the early origins of stars and galaxies. The most distant object known shows the earliest evidence of star formation.

In the astronomical hunt for ever more distant objects, and hence a window on the early Universe, the current leader[1] is J1148 + 5251 at a redshift of 6.4. The light we now see from this particularly luminous object was emitted only 800 million years after the Big Bang, making it the youngest object known. J1148 + 5251 is a quasar (from 'quasi-stellar' object). Whereas stars are powered by nuclear fusion, a quasar's power is derived from gravitation: quasars are powered by matter from rotating accretion disks spiralling into massive black holes at the centres of galaxies.

Observations of an object as young as J1148 + 5251 could reveal much about the evolution of galaxies early in the history of the Universe, and about the relation between the formation of stars and massive black holes. New data are now reported, by Walter *et al.*[2] on page 406 of this issue, and by Bertoldi *et al.*[3] in a complementary article in *Astronomy and Astrophysics*. These authors have detected radiation at millimetre wavelengths from molecules of carbon monoxide, indicating the presence of a large mass of interstellar molecular gas, and from which the presence of molecular hydrogen (the dominant component in molecular clouds) can be inferred. This is the raw material from which stars form. These measurements, combined with the observation of strong emission at far-infrared wavelengths from interstellar dust[4] in this very young galaxy, point to an ongoing burst of star formation that began only a short time after the Big Bang.

The combination of high luminosity at far-infrared wavelengths and a large mass of molecular gas and dust is an accepted signature of star formation in galaxies. Young stars embedded in the molecular clouds heat the interstellar dust, which then radiates at infrared wavelengths. In the local Universe, many spiral galaxies show significant infrared luminosity from star formation, and the most powerful galaxies — ultraluminous infrared galaxies[5] — all have large masses of molecular gas[6] and CO emission similar to that seen in the distant J1148 + 5251. Most ultraluminous galaxies seem to have formed from collisions between separate galaxies[5], and their molecular gas is