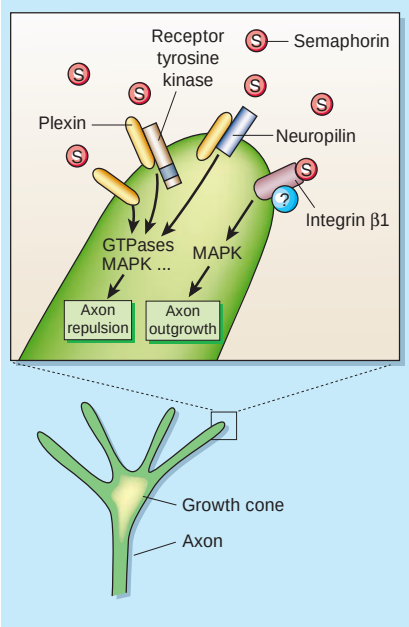

Figure 1 **Effects of semaphorins on the development of the nervous system. Several receptor complexes have been proposed to interact with semaphorins present in the environment of developing nerve cells. For instance, semaphorins can interact with a plexin receptor, a complex formed by a plexin and 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. ■

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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

found concentrated in rotating disks or rings a few thousand light years across[7] — a central region much smaller than the galaxies but much larger than a quasar accretion disk. An analysis of the CO emission from a quasar at lower redshift than J1148 + 5251 showed that the molecular gas is also distributed in a star-forming ring with a size of about 6,000 light years[8].

From the observed infrared luminosity of J1148 + 5251, Walter *et al.*[2] and Bertoldi *et al.*[3] have calculated the rate of star formation in its galaxy. It is equivalent to the creation of about 3,000 Sun-like stars each year — a thousand times greater than the star formation rate in the entire Milky Way, and a few times greater even than that of ultraluminous galaxies. Star formation on this scale is a major event in the evolution of a galaxy.

It is possible that some of the far-infrared radiation originates from dust heated by the quasar itself. However, there is another very strong line of evidence in favour of a major episode of star formation in this galaxy. The very existence of a large mass of interstellar molecules and dust is proof that substantial star formation is taking place, or occurred at an even earlier time. In addition to carbon monoxide gas, the small dust particles are composed of what astronomers refer to as heavy elements or 'metals', such as carbon, oxygen, silicon and magnesium. All of these elements were produced after the Big Bang, inside stars, by a process known as nucleosynthesis[9], and then ejected into the interstellar medium. This interstellar matter provides the raw material for a new generation of stars and planets. There are already indications from the spectrum of the optical-wavelength emission[1] that high-redshift quasars show strong emission from metals, but this does not by itself indicate the amount or extent of star formation. The molecular gas and dust around J1148 + 5251 clearly show that the process of chemical enrichment was well advanced only 800 million years after the Big Bang. For this to occur in such a short time implies that the enrichment is due to the formation and evolution of high-mass stars, the same type of star responsible for the heating of the dust.

J1148 + 5251 is not the first high-redshift quasar found to have strong far-infrared radiation from warm dust. More than 20 quasars at redshift, z, higher than 3.8 have been identified[10] whose high far-infrared luminosity is associated with star formation. CO emission has been detected in more than 13 quasar host galaxies with z larger than 2, including the previous high-redshift record-holder[11] at $z = 4.7$. In addition, a large number of far-infrared sources have been found from 'blank field' surveys[12,13], most of which are also very luminous and have redshifts in the range 1 to 3.5 (ref. 14). For only two of these have CO spectral lines been reported[15], but it is likely that CO emission will be found in most of them now that their redshifts are known. These dust-enshrouded molecular-gas-rich galaxies account for about half of all star formation in the Universe.

K. GATLIN/P. SMILEY/NRAO/AUI

A. RAMBAUD/IRAM

Figure 1 **East meets west. The Very Large Array (left), on the plains of New Mexico, USA, is a Y-shaped configuration of 27 radio telescopes. In the Hautes Alpes of France, an array of five (now six) antennas forms the Plateau de Bure Interferometer (right). Arrays of telescopes such as these, operating synchronously, are equivalent to a single antenna dish up to many kilometres in diameter, and hence offer more power for resolving distant objects. Walter *et al.*[2] and Bertoldi *et al.*[3] have used data from both arrays in their study of the most distant astronomical object known, a quasar called J1148 + 5251, and have uncovered evidence for star formation at an early stage in the history of the Universe.**

Among all of these, the galaxy hosting J1148 + 5251 is the most distant and the earliest example of a star-forming region. That also makes it the only example so far of star formation occurring at a time before the hydrogen between galaxies (the intergalactic medium) was completely ionized by ultraviolet radiation from other galaxies and quasars, a time in the evolution of the Universe known as the epoch of reionization. The presence of even a few per cent of unionized intergalactic hydrogen atoms is a clear indicator that the Universe was in the early stages of lighting up, following the cooling off of the intergalactic medium a few hundred thousand years after the Big Bang.

The ability to observe molecular emission from such distant objects is due to the remarkable sensitivity of the instruments used by Walter *et al.*[2] and Bertoldi *et al.*[3] — the National Radio Astronomy Observatory's Very Large Array and the Plateau de Bure Interferometer of the Institut de Radio Astronomie Millimétrique (Fig. 1). In some cases there is also help from magnification of the signal by gravitational lensing along the line of site, although this is probably a small effect[1] in J1148 + 5251. In addition, there is what astronomers refer to as a 'negative K correction' for the highly redshifted radiation from thermally excited rotational energy levels[16] of molecules. For a given telescope operating at an approximately fixed frequency, it is possible to observe CO emission from redshifted galaxies simply by observing a spectral line from a higher rotational energy level and higher rest frequency, instead of lowering the frequency to match the redshift. This switching of spectral lines means that it is no harder to detect CO when the source is at a redshift of 6 than when it is at a redshift of 1 (provided that the source redshift is well known and the gas is not extremely cold).

Nonetheless, these measurements are right at the limit of existing telescopes. The constraints will be lifted by the new generation of instruments, particularly the Atacama Large Millimeter Array of telescopes being built by an international collaboration in Chile. With increased resolution, sensitivity and bandwidth, this array will produce images of interstellar molecules and dust with the clarity that the Hubble Space Telescope has brought to optical astronomy. A fuller understanding of the formation of galaxies and stars in the early Universe awaits us. ■

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