many brain regions[4]. To investigate whether activity-dependent changes in synaptic CD47 might determine which synapses are removed, Lehrman *et al.* set up an artificial competition assay, in which they used the neurotoxin tetrodotoxin (TTX) to suppress neuronal activity in one eye in mice. They found that CD47 levels were higher in synaptic inputs from RGCs that originated in the more-active control eye than in the inputs from the TTX-treated eye, suggesting that CD47 is either degraded or moves away from synapses in RGCs of the less-active eye.

Finally, Lehrman and colleagues showed that, in wild-type mice, CD47 levels were higher in more-active than in less-active synapses, and that, in CD47-deficient animals, microglia showed no preference for less-active inputs. Together, the authors' data indicate that protective 'don't eat me' signals prevent aberrant microglial engulfment in the dLGN.

As Lehrman *et al.* point out, a major challenge for the immune system is to remove dying cells, disease-causing organisms and toxic molecules without removing or damaging healthy cells. This study is particularly interesting in that regard, because the 'eat me' and 'don't eat me' signals from synapses both act on microglia. Whether the complement system and CD47–SIRP-α act separately or interact to ensure that the correct synapses are removed or protected remains an open question. This aspect is also not clear for macrophages in the immune system.

The mechanisms by which synapses that are either unwanted or to be retained send these signals to microglia remain to be demonstrated — in particular, the interaction between CD47 and SIRP-α in microglia as a leading factor in constraining synaptic pruning has not been shown directly and has been validated using *in vitro* models. The physiological relevance of this signalling pathway also needs to be examined, because CD47-deficient mice do not seem to have major defects in brain development[5].

Another question is whether these events modulate other innate immune responses in the brain, such as those involved in disease. For instance, in multiple sclerosis, a sheath of a fatty substance called myelin that insulates neurons becomes damaged. Microglia have a key role in removing damaged sheaths to enable remyelination[6]; perhaps 'eat me' and 'don't eat me' signals help the microglia to determine whether myelin should be removed.

Synaptic protection is essential for normal brain development. The identification of a 'don't eat me' signal in microglia reveals a new aspect of this crucial developmental phenomenon. ■

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ASTRONOMY

Evidence of ancient Milky Way merger

An analysis of data from the Gaia space observatory suggests that stars in the inner halo of the Milky Way originated in another galaxy. This galaxy is thought to have collided with the Milky Way about ten billion years ago. SEE LETTER P.85

KIM VENN

From studying the exquisite images collected by ground- and space-based telescopes over the past century, astronomers have learnt that galaxies can collide. On page 85, Helmi *et al.*[1] use data from the Gaia space observatory to determine that the Milky Way was hit by a satellite galaxy roughly ten billion years ago. Stars from this galaxy are still around us today to tell the story.

Gaia was launched in 2013 by the European Space Agency as the successor to Hipparcos — a satellite that in 1997 produced the first high-precision catalogue of nearby stars[2]. Gaia was designed to conduct ongoing observations of the visual characteristics and positions of more than one billion objects in the sky[3] (Fig. 1). Such map-making might seem like tedious work, but repeated measurements made by Gaia can also be used to determine precise distances and velocities across the sky for about 1% of all the stars in our Galaxy[3].

The information from Gaia can be combined with spectroscopic measurements of velocities along the observer's line of sight to make videos that show the precise motions of the stars (see, for example, go.nature.com/2atris8). Playing these videos backwards allows astronomers to study how our Galaxy was assembled and how it has evolved.

Helmi and colleagues used the Gaia mission's second data release, which was published earlier this year[4], to analyse the motion of stars near the Sun (within a distance of about 10 kiloparsecs). The authors compared these observations with predictions from simulations in which the Milky Way and a satellite galaxy with 20% of the mass of our Galaxy merged in the past[5]. The similarities are striking, particularly the detailed motions of some high-velocity stars that orbit the Galactic Centre in the opposite direction to the Sun.

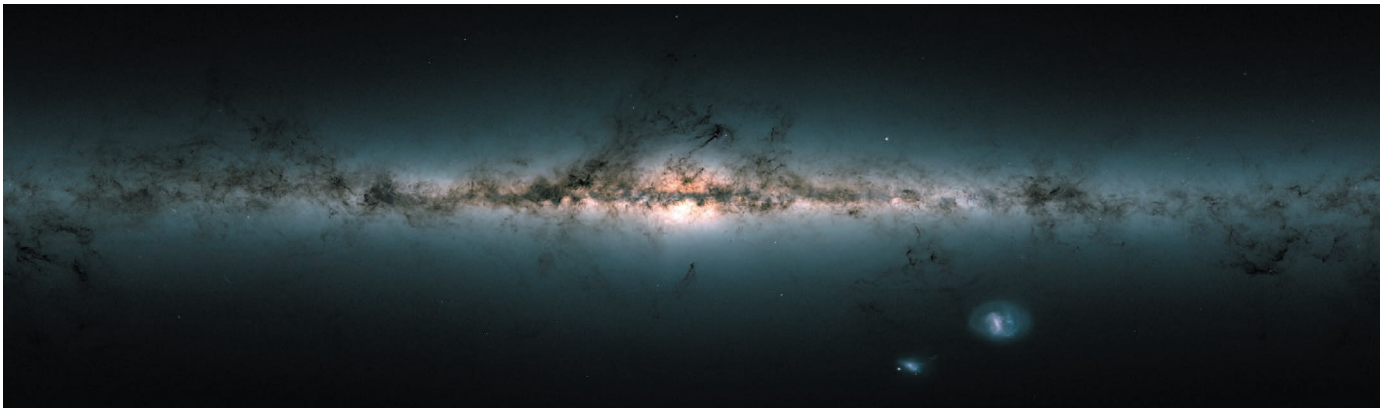
Using astronomical-data catalogues that provide the ages and chemical compositions of stars[6], Helmi *et al.* determined that the Milky Way's inner halo — a region that surrounds the thick stellar disk — is made up mainly of stars from the satellite galaxy. These stars provide a record of the galactic collision, which the authors estimate took place approximately ten billion years ago.

Several other research groups working with the Gaia data have reached a similar conclusion to that of Helmi and colleagues, using other analytical methods or data catalogues[7–9]. However, there are small differences between the results of Helmi *et al.* and those of the other groups, such as the mass of the satellite galaxy, when the collision occurred and whether the event involved a single satellite galaxy or a few smaller galaxies.

One conclusion on which all of the groups agree is that the event might have contributed to the formation of the Milky Way's thick stellar disk. If a thin disk of stars encircled the Galactic Centre at the time of the merger, the orbits of the stars would have been disrupted. Originally, the stars would have had a specific chemical composition that reflected the young age of the Milky Way. But today, they would be old and relatively poor in metals (elements heavier than helium), and on orbits in a thickened disk. All the research groups reported the possible identification of these old stars in the Gaia data.

Astronomers have speculated for several decades that an ancient satellite galaxy merged with the Milky Way in the past, because such an event could explain differences in the motions and chemical compositions of stars in the neighbourhood of the Sun. For example, one of the most unusual objects in our Galaxy is Omega Centauri — a cluster of stars so distinctive that it is thought to be the core of a satellite galaxy that was disrupted and absorbed by the Milky Way. Researchers have suggested that some of the stars found in the Gaia data might be debris from this event[10,11].

Obtaining proof that some stars are associated with a merger required the high precision and large survey area of Gaia, in combination



ESA/GAIA/DPAC

Figure 1 | View of the Milky Way based on data from the Gaia space observatory.

with large databases of the spectral and chemical properties of stars. Over the next decade, several international observatories will carry out massive surveys of the spectra of stars throughout the Milky Way. These surveys will provide new data to identify the characteristics of more stars from the satellite galaxy.

The Gaia mission will continue for another few years, sharpening our vision of the Milky Way. With Gaia's detection of even more stars that originated in the satellite galaxy, astronomers will be better able to determine the mass of this galaxy, and when the merger occurred. It might even be possible to learn about the star-formation history of the satellite galaxy before it collided with the Milky Way.

Helmi and colleagues named the satellite galaxy Gaia–Enceladus, in honour of the space observatory that provided the crucial data and after one of the Giants of Greek mythology. Enceladus was the offspring of Gaia (Earth) and Uranus (the sky). He was said to be buried under Mount Etna in Italy and responsible for earthquakes in the region. The authors suggest that this is an appropriate name because Gaia–Enceladus was a giant compared with other past and present satellite galaxies of the Milky Way. Furthermore, it shook our Galaxy, leading to the formation of the thick stellar disk. Regardless of the name, it is clear that the history of the merging event is written in the stars. ■

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BIOLOGICAL TECHNIQUES

Complementing the forebrain

A new technique, in which forebrain-precursor cells are ablated from early-stage mouse embryos and replaced with embryonic stem cells, promises to facilitate our ability to study the central nervous system. SEE LETTER P.126

JIMENA ANDERSEN & SERGIU P. PAŞCA

For the past few decades, it has been possible to directly manipulate an organism's genes early in development, to generate, for example, mice that harbour genetic modifications. Such transgenic mice have been powerful model systems in which to study human disease[1], but conventional approaches for generating these animals can be costly and time-consuming. On page 126, Chang *et al.*[2] describe an alternative approach to building complex mouse models with which to interrogate the function and diseases of the forebrain. The authors' approach could also be used to produce models focused on other regions of the central nervous system (CNS).

In conventional transgenic approaches, genes are modified in mouse embryonic stem (ES) cells, which are pluripotent — they can give rise to all cell types of the animal's body. The genetically engineered cells are then injected into a mouse embryo at an early stage of development called the blastocyst stage. The result is a chimaeric mouse, in which some cells are genetically modified and some are not. If the animal's eggs or sperm contain the genetic modification, it can be bred to produce offspring in which all the cells are modified (Fig. 1a). This approach, although recently accelerated by gene-editing technologies such as CRISPR–Cas9, remains expensive and labour-intensive. Moreover, unless the genetic modification is engineered to be expressed in only certain cell types, this approach is limited to genes that are not essential for early embryonic development.

More than two decades ago, the laboratory that performed the current study devised a technique called blastocyst complementation, to circumvent these limitations in the immune system[3]. The approach is based on the fact that, if the development of a particular organ in the host is disabled, a vacant niche is created that can be filled by tissue derived from newly introduced ES cells. In that paper, the authors used RAG2-deficient mice, which do not have mature immune cells called T and B cells. They showed that embryos of this strain could give rise to mice that generated T and B cells normally if blastocysts were injected with wild-type mouse ES cells. Moreover, these immune cells were exclusively of donor origin.

Blastocyst complementation has since been used to generate the lens of the eye[4], the kidney[5] and the heart[6]. The technique has also been used to generate pancreases made mainly of cells from another species, by injecting mouse cells into pancreas-disabled rat blastocysts and vice versa[7]. This type of animal, called an interspecies chimaera, offers great potential both for understanding fundamental principles