YAP- and TAZ-mediated gene expression.

Might other mutations beyond those in the Hippo pathway also regulate ferroptosis in mesothelioma? The most commonly mutated gene in this cancer[11] encodes the tumour-suppressor protein BAP1. This enzyme affects gene expression, and can cause a reduction in the expression of SLC7A11, which, in turn, leads to ferroptosis[12]. If the gene that encodes BAP1 is mutated, ferroptosis does not occur[12]. Therefore, the presence of wild-type BAP1 might help to enhance ferroptosis, along with any boost to ferroptosis provided by the use of SLC7A11 inhibitors. It is not known whether drugs that induce ferroptosis, such as sorafenib, would be effective in cells in which mutations inactivate BAP1.

Other approaches to targeting mesothelioma in which the Hippo pathway is inactivated are being explored. For example, in animal studies, loss of merlin expression is associated with cancer-cell vulnerability to inhibition of a protein called focal adhesion kinase[13]. However, no clinical benefit was found with this approach in a clinical trial[14]. Direct targeting of the interaction between YAP and TEAD, a protein to which YAP binds when it drives gene expression, is another strategy being pursued to block cancer-promoting gene expression[15]. Finally, YAP and TAZ recruit the protein BRD4 to drive the expression of specific genes, and use of a small-molecule inhibitor to target BRD4 can disrupt YAP- and TAZ-mediated gene expression[16]. This class of small-molecule inhibitor is entering early clinical trials. All of these approaches aim to block YAP- and TAZ-mediated gene expression. However, if the anticancer strategy being used aimed to trigger ferroptosis in mesothelioma cells, then YAP- and TAZ-mediated gene expression would be required.

Identifying a tumour that has an inactivated Hippo signalling pathway as a means of a developing personalized cancer therapy — the ultimate goal — poses some challenges for mesothelioma. Focusing only on tumours that have lost merlin function would probably miss mesotheliomas in which Hippo signalling is inhibited by inactivation of other proteins, such as LATS1 and LATS2. A previous study[17] of the Hippo pathway in various cancers has revealed that 22 genes are commonly transcribed by YAP and TAZ, and this transcriptional profile might offer a way to identify ferroptosis-sensitive tumours. Furthermore, because this profile was found[17] in several types of tumour, triggering ferroptosis might be worth exploring for cancers other than mesothelioma.

Wu and colleagues' report highlights a strategy that could offer a way of developing a personally tailored anticancer therapy. However, therapies targeted to mutations in an individual's mesothelioma are still in their infancy. Clinical trials that take this approach, for example the mesothelioma stratified therapy trial in which I am involved (see go.nature.com/2o19lah), might help to make progress in such endeavours, and provide improved treatments at a time of unmet clinical need. ■

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PLANETARY SCIENCE

Signs that Jupiter was mixed by a giant impact

Simulations suggest that Jupiter's dilute core might be the result of a collision between the planet and a Uranus-mass planetary embryo. This finding indicates that giant impacts could be common during planet formation. SEE LETTER P.355

TRISTAN GUILLOT

In the past couple of years, NASA's Juno spacecraft has measured Jupiter's gravitational field with exquisite accuracy[1,2]. The results have revealed that the planet's fluid hydrogen–helium envelope does not have a uniform composition: the inner part contains more heavy elements than the outer part[3,4]. On page 355, Liu *et al.*[5] propose that this asymmetry resulted from a head-on collision between the young Jupiter and a planetary embryo that had a mass about ten times that of Earth. The authors suggest that the primordial cores of the planet and of the embryo would have merged and then partially mixed with Jupiter's envelope, explaining the structure of the planet seen today.

Scars of impacts abound on rocky planetary bodies. For example, the Moon is covered in craters, and was formed by a collision that occurred 4.5 billion years ago between Earth and a massive body[6]. Although impacts leave no direct imprint on the surfaces of fluid planets, the tilts of the rotational axes of Saturn (27°), Uranus (98°) and Neptune (30°) might indicate that violent collisions occurred in the past[7]. After all, it is known that massive planetary embryos on the order of ten Earth masses must have been present in the early Solar System[8], in addition to the planets that are still here. Jupiter, with its small tilt (3°), seems to have escaped unscathed[7]. But according to Liu and colleagues, this was not the case.

Jupiter is mostly made of hydrogen and helium. However, observations of its atmospheric composition[9] and gravitational field show that it contains a non-negligible proportion of heavier elements in the form of a central core and in the hydrogen–helium envelope. This envelope is fluid and is expected to be largely convective[10], so it was surprising when Juno revealed that the envelope's composition is not uniform. Instead, the core seems to be partially diluted in the envelope, extending to almost half of the planet's radius[3,4] (Fig. 1).

Producing this internal structure directly would require the delivery (accretion) of 10–20 Earth masses[3,4] of heavy elements to the young Jupiter after the core had formed and during the first half of the growth of the envelope. The accretion of this material would need to have stopped after the planet had grown to about half of its present mass.

Formation models indicate that this hypothesis is unlikely. In these models, when Jupiter reaches about 30 Earth masses, the growth of the envelope by accretion is fast[11], and the planet efficiently pushes away any dust particle that is millimetre-sized or larger[12]. As a result, the envelope should be poor in heavy elements. Any subsequent delivery of heavy elements by planetesimals (the asteroid-sized precursors of planets) or small planets is inefficient and cannot explain a heavy-element abundance that would increase with depth, as is observed. Erosion of the core into the envelope is possible[10,13], but simulations show that this process tends to remove any small composition gradients that exist in the

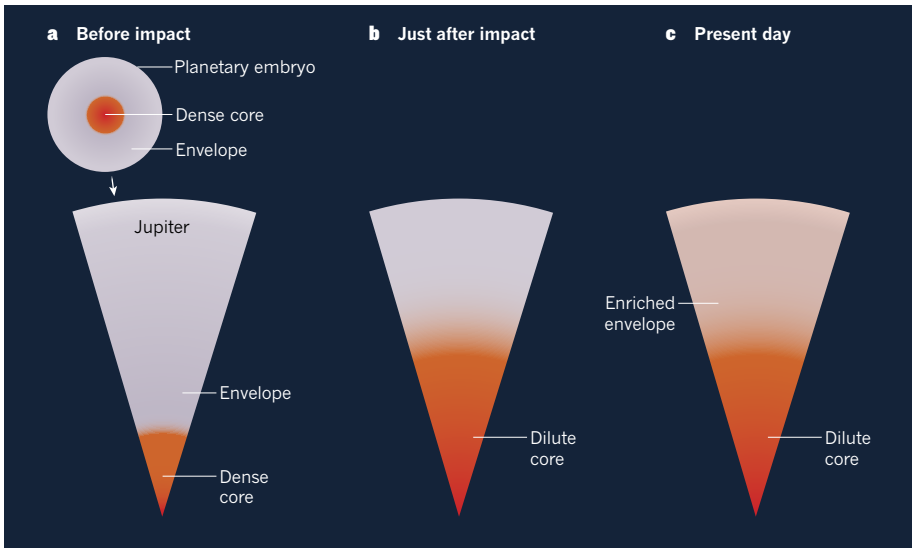

Figure 1 | Three phases of Jupiter. Liu *et al.*[5] propose that the present-day internal structure of Jupiter is the result of a giant impact between the young planet and a planetary embryo that had roughly the mass of Uranus. **a**, In the authors' model, before the impact, both Jupiter and the embryo contained a dense central core of heavy elements and a hydrogen–helium envelope. The colours represent the density of material, ranging from low (white) to high (dark orange). **b**, Just after the impact, the two cores merged and partially mixed with the planet's envelope to produce a dilute core. **c**, After subsequent evolution, the dilute core remained, but was partially eroded into the envelope, causing the envelope to be enriched in heavy elements.

envelope, rather than increase them[14].

The solution proposed by Liu *et al.* is simple. In their model, a planetary embryo that has a dense core of heavy elements collides with the forming Jupiter. The cores of the two bodies then merge and become partially mixed with Jupiter's envelope. This explanation requires a massive embryo (of about ten Earth masses) and an impact that is somewhat head-on, but these two requirements seem reasonably likely. The authors show that cooling and subsequent convective mixing of the outer part of the envelope mixes only some of the heavy elements, leaving the planet's dilute core relatively unaffected (Fig. 1). In one fell swoop, this picture might therefore explain the dilute core detected by Juno[3,4] and the global abundance of heavy elements in Jupiter's atmosphere[9].

Liu and colleagues' model should now be refined. In particular, it needs to be coupled to realistic scenarios for the formation of the Solar System[8]. Moreover, the mixing of heavy elements in the model should take into account heat and element diffusion — a process known as diffusive convection[13]. The results should also be compared quantitatively with constraints on Jupiter's gravitational field from Juno[1,2] and on the planet's atmospheric composition obtained from spectroscopy[10].

The authors' model indicates that giant impacts might frequently occur during planet formation. This possibility could account for the tilts of the planets in the Solar System. It might also explain how some giant exoplanets, known as hot Jupiters, have accreted more than 100 Earth masses of heavy elements[15,16] — a feature that is extremely difficult to obtain from conventional formation models. Hot Jupiters are situated close to their host stars, in regions in which the gravitational pull of the star is extremely strong. As a result, these exoplanets might be able to collect planetary embryos efficiently through a series of giant impacts, rather than ejecting them, and thus increase their heavy-element content.

Although giant planets have a fluid surface that cannot record traces of impact events, such planets hold clues to a violent past that led to the planetary systems observed today. The model proposed by Liu *et al.* enables present-day observations to be linked to the early days of the formation of the Solar System. Progress will come from an extension of studies such as this one to giant planets around the Sun and other stars. A continued exploration of the Solar System is crucial, particularly of Uranus and Neptune, which might be thought of as leftovers from a large population of massive planetary embryos in the early Solar System. ■

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MICROBIOLOGY

No bacteria found in healthy placentas

Analysis of hundreds of placentas provides convincing evidence that this organ does not harbour microorganisms that can enter the fetal gut — a key finding for research into how the human microbiota is established. SEE ARTICLE P.329

NICOLA SEGATA

The early human embryo is free of microorganisms, whereas the post-weaning infant hosts a community of microbes — a microbiota — comparable in complexity to that in adults. How and when the symbiosis between a human and their microbiota is established are subjects of active research. On page 329, de Goffau *et al.*[1] provide evidence that the placenta, which acts as the interface between the maternal body and the fetus, is not colonized by microorganisms in healthy pregnancies and is thus unlikely to be the main gateway for the development of the infant microbiota *in utero*.

If the microbial colonization of humans occurs in the womb, then this would have key implications for the shaping of the early immune system. An infant's first stool is already populated with microorganisms, but it is unclear whether this is solely the result of microbial acquisition during[2] and after[3] delivery, or if microbes also reach and colonize the fetus before birth. Because sampling fetal gut content is much more difficult than collecting the placenta and amniotic fluid during (elective) caesarean delivery, scientists have focused on the latter two at the interface between the maternal and fetal bodies. The conclusive identification of microbial communities in and on the placenta would indeed suggest that microbes colonize the fetus, but, in the past few years, evidence has been presented both that supports[4–7] and that refutes[8–11] the long-standing dogma that the placenta and amniotic fluid are sterile in physiological conditions — that is, during healthy pregnancy. The debate about this issue therefore remains open[12,13] (Fig. 1).

It is not disputed that, during a healthy pregnancy, the placenta and amniotic fluid cannot host a concentration of bacteria as high as that observed in the adult mouth or gut. The technical challenge in studies of placenta samples is therefore to distinguish any microorganisms that are truly present in small quantities on these tissues from those found on laboratory tools and from contamination of the samples during collection. Small amounts of microbial contamination can be pervasive, and sources range from the air to supposedly sterile DNA-extraction kits[14] and other items associated with DNA processing and sequencing[15]. There was thus a need for studies to rigorously account for potential contamination; these studies would also need a sufficiently large sample size to ensure statistical robustness. De Goffau and colleagues now report on such a study.

The authors analysed placenta samples from 537 women — by far the largest number of samples used in a study of this kind — using a thorough DNA-sequencing approach to search for microbial content. They used the same DNA-extraction toolkit and sequencing procedures on negative controls — 'blank' samples that were supposedly free from biological material. They also used positive controls, produced by spiking placental samples with a known amount of the bacterium *Salmonella bongori*, to calibrate the abundance of other microbes that might be in the sample. The sequencing was performed using two complementary techniques, known as shotgun metagenomics[16] and 16S rRNA gene amplicon sequencing[17], to account for technique-specific potential biases. The results were clear: the placenta does not harbour microbes during healthy pregnancy, and contamination issues were a convincing explanation for the presence of any detected bacteria.

Some of the details reported in the paper reveal how pervasive contaminating microbes can be when concentrations of bacteria in the samples are very low. For example, two potential

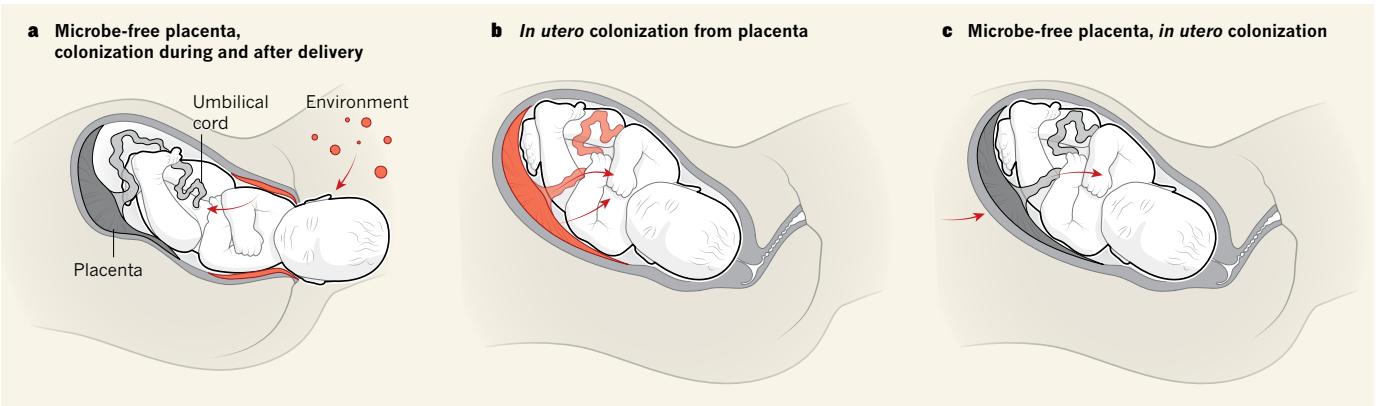

Figure 1 | Scenarios for bacterial colonization of the infant gut. a, It has long been thought that the human placenta and the fetus are free of microorganisms. Newborns were therefore expected to acquire gut bacteria from the mother during delivery and from the environment (red regions indicate sources of bacteria), with further influences associated with the mode of delivery and feeding regime (breastfeeding or formula milk). **b**, However, in the past few years, evidence has been published[8–11] suggesting that the placenta contains bacteria and that bacterial colonization of the fetal gut therefore occurs in the womb. **c**, *In utero* colonization of the fetal gut from the mother might also occur under certain circumstances, even if the placenta is microbe-free. De Goffau *et al.*[1] now report convincing evidence that the placenta is free of bacteria during healthy pregnancies, thus ruling out the scenario in **b**.