in a real-life example of how a genetic disease can inform understanding of human physiology, the authors showed that women with an inherited blood disorder called β-thalassaemia, who typically have high levels of GDF15, rarely report nausea and vomiting in pregnancy.

The picture emerging from the genetic data is that the risk of experiencing nausea and vomiting in pregnancy is greater if maternal levels of GDF15 before pregnancy are low, rather than high. By contrast, high levels of GDF15 during pregnancy (mostly originating from the fetus) are associated with increased nausea and vomiting. How can these seemingly contradictory findings both be true?

The authors hypothesized that people who have naturally low levels of GDF15 might be more sensitive to the rise in fetal GDF15 during pregnancy — and therefore more susceptible to its sickness-inducing effects — than are those with naturally high levels of GDF15. They tested this hypothesis in mice, using suppression of appetite as an indirect measure of nausea because mice do not vomit. They showed that mice that had been treated with a long-acting version of GDF15 were less likely to show suppressed appetite when given an acute dose of GDF15 than were mice that had not been pre-exposed in this way. Similarly, mice that had been genetically engineered to lack GDF15 were more sensitive to its effects than were mice that expressed GDF15 normally. Overall, the results support a mechanism in which the sensitivity of some mothers to fetally derived GDF15, as a result of their relatively low previous exposure to this hormone, is responsible for nausea and vomiting during pregnancy.

The authors' findings provide a scientific basis for HG that could be used to develop treatments for and preventive measures against severe nausea and vomiting during pregnancy. Blocking the action of GDF15 could relieve the symptoms of HG, and therapeutically increasing the levels of GDF15 in susceptible people before they become pregnant might even prevent the onset of symptoms. However, before any treatments can reach the clinic, experiments are needed to verify that humans who are exposed to GDF15 become desensitized to its nauseating effects, in the same way that appetite is affected in mice.

Interactions between the mother and the fetus are relevant to many other poorly understood health conditions in pregnancy, and the study by Fejzo *et al*. is of broad interest to researchers who are attempting to understand such interactions. The authors analysed data from 17 pregnancies of 6 mothers with a rare genetic variant that is associated with an increased risk of developing HG. They observed that the prevalence of HG was lower if the fetus had the same variant as the mother. This finding would need to be replicated in a study with a larger sample size, but it suggests that the risk of HG is lower when the fetus is genetically predisposed to producing less circulating GDF15. Because the risk of HG might be moderated by the genetics of the fetus, future studies that account for maternal, fetal and paternal genotypes would be a valuable addition to this work.

Besides the precise contribution of the fetus to pregnancy sickness, some interesting questions remain. Do factors other than GDF15 contribute to nausea and vomiting? Variation in a gene expressed in the placenta called *IGFBP7* has also been shown to be associated with HG[6], so the role of this gene is an avenue for future research. Finally, pregnancy sickness seems to be unique to humans[12]. Why did a physiological system that causes such extreme vomiting evolve? One theory is that this mechanism protects the developing fetus from poisoning[13].

The identification of a possible link between maternal sensitivity to GDF15 and HG reflects real progress in the understanding of a disease that causes misery for many. The work by Fejzo *et al*. is likely to prompt further investigations and an appetite for clinical trials in the field of pregnancy-related diseases.

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Cell biology

How plants iron out competing interests

Shanice S. Webster & Mary Lou Guerinot

Once a plant recognizes a pathogen, part of its defence strategy is to withhold iron. The mechanism involves suppression of root acquisition of iron by degrading a molecule that activates the iron-uptake pathway. **See p.750**

How do plants strike a balance between regulating iron uptake to promote their own growth and nourish their associated non-harmful microbes (commensal microbiome), while inhibiting pathogenic microorganisms? On page 750, Cao *et al*.[1] provide insights into a molecular mechanism of crosstalk between iron and immunity during iron deficiency, and highlight the complex interplay between plants and their commensal and pathogenic bacteria.

Iron is an essential micronutrient for plants and their associated microorganisms. Its ability to facilitate electron transfer makes it invaluable for key cellular processes such as photosynthesis and respiration, but excessive amounts of iron can be detrimental[2]. Plants must therefore control iron uptake and maintain a suitable level — this iron homeostasis allows plants to maximize benefits while minimizing adverse effects. Furthermore, because iron can aid the proliferation of microbes that cause disease, plants, in a similar way to animals, have evolved mechanisms to restrict iron availability as a defence strategy — a phenomenon called nutritional immunity.

Iron homeostasis is linked to plant immunity defences[3]; however, little is known about the mechanisms of crosstalk between iron deficiency and plant immunity defence signalling. Cao *et al*. demonstrate that flg22, a peptide fragment derived from the flagellin protein of a bacterial surface component called a flagellum, suppresses iron uptake through a process during which the peptide IMA1 is degraded. IMA1 is one member of the IMA family of mobile signalling peptides. These are evolutionarily conserved across flowering plants, and are expressed during iron deficiency to regulate iron uptake by preventing the turnover of transcription factor proteins needed to activate the iron-deficiency response[4]. The

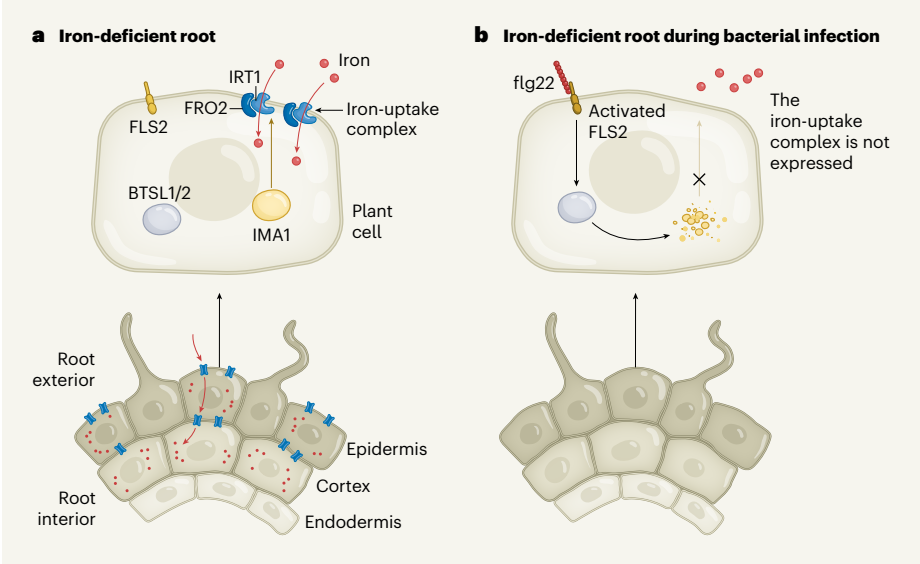

Figure 1 | How plants regulate iron uptake during iron deficiency and bacterial attack. **a**, When plants need iron, uptake of this nutrient from the soil is mediated by the protein IMA1, which drives production of the proteins IRT1 and FRO2 that form the iron-uptake complex (blue). IMA1 is in the root's outer cell layers (the epidermis and the cortex), but not in an inner layer called the endodermis. In the absence of the bacterial peptide flg22 binding to the FLS2 receptor, the proteins BTSL1 and BTSL2 do not target IMA1. **b**, Iron can aid the growth of harmful bacteria, and Cao *et al.*[1] shed light on how plants restrict iron uptake during bacterial infection. When flg22 binds to and activates FLS2, IMA1 is degraded through the action of BTSL1 and BTSL2, resulting in loss of the iron-uptake complex.

authors show that in plants starved of iron, two key proteins for iron uptake — an enzyme called FRO2 and the iron-transporter protein IRT1 — are not induced in the presence of flg22 (Fig. 1).

Cao *et al.* confirmed these findings using the technique of transcriptomic analysis to monitor gene expression. This revealed a cluster of genes that were both strongly induced by iron deficiency and repressed by cellular exposure to flg22. Notably, among those genes were members of the IMA family (*IMA1*, *IMA2* and *IMA3*). The authors therefore reasoned that IMAs probably function downstream of the flg22 signalling cascade. Using a plant mutant that has higher than normal levels of IMA1, the authors found that flg22 suppression of iron uptake was abolished, providing further support for IMA1 involvement, and hinting at direct interference of IMA1 function by flg22.

To investigate how flg22 regulates IMA1 function, the authors examined where IMA1 is expressed. Cao and colleagues found that it localizes to a region of the root known as the differentiation zone, in cell types called the epidermis and cortex, where FRO2 and IRT1 are normally expressed. IMA1 expression decreases in these locations on flg22 treatment. The authors propose that IMA1 needs to be locally expressed in the cortex and the epidermis to induce expression of FRO2 and IRT1.

Cao and colleagues set out to determine the mechanism of flg22-triggered IMA1 depletion. IMA peptides are known to be modified by BTS proteins through addition of the protein ubiquitin, and these modified IMA peptides are subsequently broken down by the degradation machinery called the proteasome[4]. BTS proteins are mainly expressed in the shoot and in the inner core of the plant root in a structure called the stele. However, the two other members of the BTS family, BTSL1 and BTSL2, are expressed in the root and regulate iron levels[5]. Cao *et al.* show that, compared with wild-type plants, plants with mutations in the genes *btsl1* and *btsl2* (encoding BTSL1 and BTSL2) had fewer signs of iron deficiency and were less sensitive to flg22 immune-activation defence responses. Furthermore, the level of IMA1 protein increased under iron deficiency in the *btsl1*/*btsl2* mutant plants, suggesting that flg22-induced suppression of IMA1 occurs in a BTSL1/2-dependent manner.

How exactly does recognition of flg22 lead to IMA1 degradation? This remains unanswered, and so the quest is on to find what mediates the BTSL1/2-dependent destruction of IMA1.

Plant roots provide an attractive niche for microbes because of the iron available. Given IMA1's dual role in immunity and iron uptake, regulation of this protein could have a notable effect on microbial colonization. Interestingly, Cao *et al.* demonstrate that plants with higher expression of IMA1 have increased colonization by the commensal bacterium *Pseudomonas protegens* (formerly known as *Pseudomonas fluorescens*), but reduced colonization by the pathogenic bacterium *Pseudomonas syringae*. However, the presence of a flagellum in both species calls into question why plants respond differently to flagellin in commensals and pathogens.

Research from several laboratories has tackled this question. Commensal bacteria encode many diverse flg22 sequences and most are unrecognized by the immune system[6,7]. It also seems that roots require both microbial-specific proteins and damage to plant tissue to mount localized antibacterial immune responses, revealing an effective strategy to respond to pathogens while sparing commensals[8]. Future work will need to explore the role of IMA1 in the context of the microbiome community.

Cao and colleagues' results go a long way towards explaining how a plant, on detecting a pathogen, can implement a program to withhold iron using some of the same components that it uses to restrict iron uptake under iron-sufficient conditions. Because BTS proteins are gatekeepers of the iron-uptake pathway, it is perhaps unsurprising that pathogens, in turn, have targeted BTS. The bacterial protein AvrRps4, produced by some strains of *P. syringae*, can sequester BTS, enabling uptake of iron that the pathogen can exploit[9].

Echoing the situation for iron, there is also crosstalk between the phosphate-starvation response and plant immunity[10]. These mechanisms highlight a fundamental and probably general connection between nutrient acquisition and the immune response. We need to use our understanding of the competition for nutrients between microbes and hosts to develop sustainable solutions that boost the nutrient content of food without inadvertently increasing plant susceptibility to pathogens. Stay tuned as scientists learn more about how plants have managed to strike a balance between regulating nutrient uptake while suppressing pathogen growth.

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