BEN SADD

Bumblebees (*Bombus terrestris*) can pass on immunity to their offspring.

Generation game

Many vertebrates pass short-term immunity to their offspring, but plants and invertebrates take the process to greater extremes. **By Brian Owens**

An organism's immune response to attack is usually considered to be a personal battle. A pathogen or parasite attacks, the organism mounts a defence, and one of them wins. But sometimes, the target's relatives get involved. Many species have the ability to prepare their offspring to meet immune challenges that they themselves have faced. "Parents can somehow transfer the immunological memory of what they experienced during their lives to their offspring," says Olivia Roth, an evolutionary ecologist at the GEOMAR Helmholtz Centre for Ocean Research in Kiel, Germany.

One way in which intergenerational protection can manifest is by parents directly providing active immune components such as antibodies to their offspring. In mammals, including humans, mothers transfer antibodies through the placenta or in their breast milk to help protect their offspring from disease early in life. Many other vertebrates, such as birds and fish, transfer antibodies to their offspring by depositing them in their eggs. And it's not just mothers – in syngnathid fishes, such as pipefish and seahorses, the males that incubate the eggs can also pass on immune components.

"It's there to protect the offspring until their immune system gets up and running," says Ben Sadd, an infectious-disease ecologist at Illinois State University in Normal. The vertebrate adaptive immune system – which can recognize and remember specific threats – needs a lot of time to mature. By providing antibodies that can spot invaders, parents can protect their offspring during the early stages of life.

The antibody-producing adaptive immune system is unique to vertebrates. Some insects pass on antimicrobial peptides in their eggs, but invertebrates and plants have found another way to give their descendants a leg-up against the pathogens and parasites they might encounter: they boost the non-specific physical, chemical and cellular defences that make up their offspring's innate immune system.

In contrast to the short-lived protection afforded by transferring antibodies, enhancement of the innate immune system can provide lifelong protection – not only to immediate offspring but also to subsequent generations. It isn't clear how this is mediated (heritable alterations to gene expression have been proposed), but researchers are trying to find new examples, work out how they function and determine whether the mechanisms can be harnessed to improve our lives, by boosting agriculture or fighting insect-borne disease.

Seeding immunity

Because they cannot get away from attackers or infections, it is especially important for plants to put up a fight. "Plants have a sophisticated system to detect pathogens and insects that triggers a suite of defences," says Mike Roberts, a plant biologist at Lancaster University, UK. Receptors on the wall of a plant cell can recognize molecules associated with attackers. The plant can mobilize two types of defence mechanism in response to attack. They can adapt physically, for example by creating thicker cuticles or denser thickets of hairs called trichomes to reduce the amount of tissue that herbivores can eat. And they can respond chemically, by producing molecules that poison pathogens and herbivores.

As the attack goes on, it triggers a response throughout the plant. Both physical and chemical defences can spread to unaffected parts of the plant to defend against repeat infection – a process known as systemic acquired resistance. And there are dozens of examples of this resistance being passed down to offspring, enabling them to mount a faster defence to the same attacker.

In many species, the seeds of plants attacked by a pathogen or herbivore contain higher concentrations of chemical defence compounds. In tobacco plants (*Nicotiana tabacum*), exposure to tobacco mosaic virus makes a plant's progeny more resistant not only to the virus but also to some bacteria and moulds[1]. Physical defences can also be passed on – in the yellow monkeyflower (*Mimulus guttata*), the offspring of plants that have been damaged by insect herbivores have an increased density of protective trichomes[2].

Like plants, invertebrates lack an adaptive immune system. The innate immune system on which they rely was long thought to provide a fast but non-specific response to pathogens, and considered unable to use experience of previous attacks to improve protection in the future. But Roth says there is growing evidence that the invertebrate innate immune system is more complicated than that. "The classification of innate versus adaptive immunity is getting confused," she says.

Sadd, for example, found that the innate immune system of bumblebees (*Bombus terrestris*) could provide specific protection[3]. He showed that bees exposed to a non-lethal dose of a bacterial pathogen had an enhanced ability to survive a potentially lethal dose of the same bacteria later. He and his colleague also found that specific protection could be passed on. Antimicrobial activity in bumblebee offspring reflects their mother's immune experience, and it comes from factors transferred through the egg[4]. The genes responsible for producing peptides to defend against particular pathogens are turned up in bees with mothers that had been challenged by the pathogens, even if the bees themselves had not encountered the threat. "Not only is the immune system primed, it is up and running," Sadd says.

Transgenerational innate immunity is mostly seen in invertebrates and plants, but there are some tantalizing hints in vertebrates. Roth and her colleagues have reported differences in the expression of immune-related genes in the offspring and even grand-offspring of immune-challenged pipefish[5]. And glass frogs (*Hyalinobatrachium colymbiphyllum*) can transfer innate immune defences such as antimicrobial skin peptides and mutualistic microbes to their embryos[6].

Roll of the dice

Transgenerational immune priming is widespread among plants and invertebrates, but it is not universal. Diverse species show no signs of it, and publication bias against negative results means there are likely to have been many more unreported failures to find it[5].

Even in those species that have the ability, it is not always used. In many plants, the response is proportional to the amount of stress a parent plant experiences, says Roberts. If the plant is hit by the same pathogen once or twice, that plant will be resistant. If it faces the same challenge more than four times, then its offspring will also show resistance.

This kind of threshold probably exists because building a robust immune system can take resources away from other physiological needs, such as growth and reproduction. Plants that are primed against insect attackers have a reduced yield in the absence of insect pressure, says Georg Jander, a plant biologist at Cornell University in Ithaca, New York.

Preparing defences against one attacker can also leave organisms vulnerable to another. In plants, chemical defences involve two hormone pathways: the salicylic acid pathway, which defends against organisms such as fungi that feed on living tissue; and the jasmonic acid pathway, which defends against those that kill the plant, and against insect herbivores. "These are antagonistic pathways – you can only activate one or the other," says Roberts. "If your offspring are primed against one, they are more susceptible to the other."

Bumblebees are another case in point. Sadd found that the offspring of bumblebee mothers that had been exposed to a bacterial pathogen were more susceptible to a trypanosome parasite than were bees that had not been primed against the parasite[7].

Transgenerational immunity, therefore, mainly benefits organisms that have offspring that are likely to face similar threats to their parents. That's true, for example, of species with lengthy parental care or those that do not disperse far. This pattern has been observed in many laboratory experiments, but there are some exceptions – scallops, for example, inherit some immunity, but disperse their eggs into the ocean[5]. More work is needed to determine whether the pattern holds up in natural systems. "Field studies are lagging behind," says Liza Holeski, an evolutionary geneticist at Northern Arizona University in Flagstaff.

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Uncovering mechanisms

The biggest question, however, is how innate immune memory is passed on, because there are no changes to the underlying genome.

The leading candidate theory is that some kind of epigenetic mechanism adds chemical modifications to the genome that turn gene expression up or down, changing the offspring's phenotype more quickly than could be achieved by changing their genes, says Holeski. "If the selection pressure is sudden, it provides a way to ramp up defences."

In plants, all three main epigenetic mechanisms have been implicated: DNA methylation to silence particular genes; histone modification to change how accessible DNA is for transcription; and small RNAs that intercept and degrade messenger RNA. And Roth found that the offspring of immune-challenged parent and grandparent pipefish express 15 genes linked to epigenetic regulation differently[5].

There are several unanswered questions, however. "We still don't know which genes are targeted, or how they are targeted, or even whether it is specific genes or a broader genome-wide effect that just happens to have an effect on immunity," says Roberts.

Despite the lack of a clear understanding of how transgenerational immunity works, there are already efforts to see how the phenomenon could be used in areas such as agriculture and pest control. The simplest application might be to create a vaccine that can be sprayed on plants to produce seeds that are inherently more resistant to insects, says Jander. "It would be a way to shorten breeding times, so you don't have to painstakingly breed for that particular trait," he says. Some evidence suggests that treating plants with jasmonic acid induces resistance to herbivores in the next generation, but there are no products on the market yet. And there are signs that treatment with the compound β-amino-butyric acid can induce pathogen resistance in plant progeny[8].

Joachim Kurtz, an evolutionary ecologist at the University of Münster, Germany, says transgenerational immunity in insects will have clear value for pest control, and for insect farmers. "Lots of insects are vectors for disease," he says. "This could potentially be exploited for a control strategy." It might be possible, for example, to prime multiple generations of mosquitoes to resist the malaria parasite.

But to anyone harbouring the idea that transgenerational immunity renders vaccines for people less necessary, Roth is quick to set the record straight. Babies who are breast fed are less likely to become unwell with minor ailments such as coughs and colds than are formula-fed babies, because they are protected by their mother's antibodies, but that only holds for a limited time. Once they start to eat solid food, their immune system has to fend for itself. "Not everything we experience can be transferred," she says. How to defend against pathogens is something that we must learn on our own.

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