Abstractions

FIRST AUTHOR

In the birth defect phocomelia, the long bones of the limbs are shorter than normal or, in the worst cases, do not develop at all, meaning that the hand or foot is attached directly to the shoulder or hip. Scientists studying the disorder — also seen in the 1950s and 1960s in the children of women who were prescribed the sedative thalidomide while pregnant — can mimic its characteristics by exposing the limb buds of developing chick embryos to irradiation.

Researchers had thought that the effects of both X-irradiation and thalidomide resulted in a defect in patterning — the correct laying-out of cells during development. In this model, a cell's identity is determined by the length of time it spends in a region near the tip of the developing limb bud. The thinking was that X-rays or thalidomide forced cells to stay too long in this region, called the progress zone, blocking their ability to form the bone cells of the limb regions closest to the shoulder and hip. But postdoc Jenna Galloway at Harvard Medical School in Boston, Massachusetts, and her colleagues have discovered that X-irradiation leads to problems with differentiation, the process by which progenitor cells assume specialized characteristics and functions (see page 400). She tells *Nature* more.

How does irradiation affect limb-bud cells?

During normal development the limb bud grows out and skeletal progenitor cells differentiate into bone cells. After we irradiated chick embryos, their limb buds lost some of the progenitor cells that become bone cells in the upper and middle parts of a limb, or proximal segments. These proximal segments still form, based on the presence of segment-specific, or patterning, markers. But when we looked for a differentiation marker for skeletal progenitors, we could not find it in the proximal segments. The marker was left only in the distal segments, the cells that would develop into hands or feet.

Were any results unexpected?

We were surprised that a major signal for limb growth and for telling cells to become distal cells was not disrupted by X-rays. This signal remained intact, which is why that part of the limb develops even after irradiation.

Did you encounter challenges?

When I started irradiating chick embryos, I put whole eggs into the X-ray machine. The embryos were fine, but did not get irradiated because of the shell. Then I tried cutting out a section of eggshell, leaving the embryo exposed, but it died. Finally, I cut a hole in the egg and placed shell pieces over part of the embryo to shield it, and that worked. ■

MAKING THE PAPER

Susan Alberts and Greg Wray

Baboon susceptibility to a parasite reveals parallels with humans.

Susan Alberts (left) and Greg Wray.

During the past four decades, US and Kenyan scientists have been monitoring a population of yellow baboons (*Papio cynocephalus*) in the Amboseli National Park in Kenya. The animals' detailed life histories are now being combined with genetic analyses to gain a glimpse into their evolutionary past.

As a first step, Susan Alberts and Greg Wray of Duke University in Durham, North Carolina, and their colleagues have identified a variation in a baboon gene that is associated with susceptibility to a malaria-like pathogen — the first report of a link between a gene and a complex trait in a wild population of non-human primates (see page 388). The fact that a similar association exists in humans suggests that both species endured comparable pressures from pathogens during their evolution.

"Like early humans, baboons are savannah foragers that adapted to a wide range of habitats and opportunities. They can be put in almost any environment and will thrive," says Alberts. "We think they share a parallel evolutionary history with humans."

Because of such parallels, the Amboseli Baboon Research Project was established in 1971 by Jeanne and Stuart Altmann of Princeton University, New Jersey, to study a population of about 300 baboons organized into 5 social groups, or extended families. "Literally every day someone is observing them," says Alberts, who co-directs the project with Jeanne Altmann.

In addition to careful monitoring of baboon behaviour, such as eating and sleeping habits, researchers have gathered physical measurements, as well as hormone and DNA samples from the animals' faeces. A few years ago, Alberts and Wray, a geneticist, started discussing the idea of applying genetic methods to gain further insight into these animals.

Both researchers credit first author Jenny Tung with getting that idea off the ground. She wanted to find connections between variations in certain genes, or genotypes, and particular traits (phenotypes) in the Amboseli baboons.

As a first phenotype, they chose to examine the susceptibility of baboons to infection with the blood parasite *Hepatocystis kochi*, which is related to the *Plasmodium* parasite that causes human malaria. Human susceptibility to pathogens is a trait that is often linked to single genes, and is thus amenable to genetic analyses. The main challenge for doing this type of study in wild animals is obtaining enough high-quality DNA and RNA samples for analysis.

Tung and Alberts spent two months during three consecutive summers living in tents at the Amboseli research site, collecting blood samples from baboons to extract DNA and RNA. Working with Kenyan researchers, they first had to put the animals to sleep by darting them, while being careful to minimize disruption to the group. "We would only dart animals who were alone, away from the rest of their social group, and no more than two animals each day and no more than six each week," says Alberts. "As a result the animals never lost habituation to us."

Back in the lab at Duke, the group analysed DNA samples from 190 baboons for the presence of *Hepatocystis* DNA. They discovered that infection rates varied substantially between individuals. They then looked at the DNA sequences of several candidate genes to identify changes that were associated with the observed variations in *Hepatocystis* susceptibility. In the end, they found that a change of one nucleotide in a gene called *FY* confers protection from the parasite. A different variation in the human *FY* gene is known to confer protection against malaria.

The fact that a genotype is associated with similar traits in baboons and humans shows that "given the same evolutionary pressures, the same type of thing can happen in parallel in different organisms", says Wray. "One lesson from this is the precision with which natural selection acts." Another important conclusion, notes Wray, "is that field studies such as this one can be done despite all the challenges".

Alberts and Wray next plan to tackle an even more ambitious project: finding genotypes associated with behavioural traits. In a 2003 paper in *Science* on baboon social integration, Alberts and her colleagues examined the observation that, although female baboons spend their whole lives in the same social group, some are well integrated — having lots of other baboons to groom with, for example — whereas others are more isolated. "We found that the degree of social integration predicts how well the offspring will do," says Alberts. "So there is an evolutionary pressure on females to be social."

The team will now look for the genetic determinants of social isolation. "It is a risky project. But this is the kind of population you need to do it in," says Wray. "And if we can't do it here, then it probably can't be done." ■

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