## Abstractions

**LAST AUTHOR**

For years scientists have sought technological advances to allow them to study the neural pathways in the mammalian brain in more detail. Recently, it became possible to pinpoint specific neural circuits. Robert Malenka, of Stanford University in California, and his postdoc Anatol Kreitzer studied two related pathways, and their findings could contribute to the development of therapies for disorders such as Parkinson's disease. They focused on neurons in the striatum, a brain region involved in two circuits — one that promotes movement and one that inhibits unwanted movement. These processes are modulated by endocannabinoids, whose release from striatal neurons is promoted by dopamine. Dopamine is depleted in Parkinson's disease. Malenka and Kreitzer proposed that restoring normal function to the circuit that inhibits unwanted movement could improve motor control (see page 643). It is too early to tell whether an effective therapy for Parkinson's disease will emerge, but the authors show that two drugs — one that inhibits the normal breakdown of endocannabinoids and one that mimics dopamine — can drastically improve motor function in dopamine-depleted mice.

**How did you isolate specific brain pathways?**

Transgenic mice engineered with fluorescent markers for different subtypes of neurotransmitter receptor make it possible to distinguish between different circuits, such as the two pathways in the striatum. We couldn't have done this work without such mice.

**Are plant-derived cannabinoids, such as those in marijuana, a treatment option?**

Probably not. The drugs we used are very different from marijuana. We boosted the action of endogenous cannabinoids in specific pathways. But the primary cannabinoid receptor is found in nerve terminals all over the brain, and taking marijuana activates all of them indiscriminately.

**What new questions do your findings raise?**

The action of dopamine in the striatum has been the subject of intense interest and controversy for the past 30 years. We're just beginning to make significant progress in understanding its many different physiological effects. Our work looks at just one of dopamine's many actions in the brain.

**What is the future of neuropharmacology?**

With gene-expression maps and the ability to engineer transgenic mice encoding cell-specific activity markers, it is hoped that we'll be able to selectively study and manipulate specific circuits in the brain in a much more sophisticated way. This might, in turn, lead to the development of new pharmacotherapies. ■

# MAKING THE PAPER

Yan Zheng

### Finding the missing link between T lymphocytes and psoriasis.

The autoimmune disorder psoriasis inflicts itchy, red patches of thickened skin on more than 100 million people worldwide. Immune cells gone awry in some way direct skin cells to proliferate to form these lesions. Immunologist Yan Zheng and his colleagues at the biotechnology company Genentech in San Francisco, California, wanted to find which wires had got crossed between the immune system and the skin cells. They had several bits of key information, but like a frustrating jigsaw puzzle, it was impossible to fit them together to form a complete picture.

"Psoriasis is characterized by a lot of white blood cells infiltrating into the skin, and by thickening of the epidermis," Zheng explains. These white blood cells include T cells, which are known to be important in the disease. Patients also have raised levels of certain cytokines, proteins that act as communication signals between cells and which are produced by T cells, among others. One of these cytokines, interleukin 22 (IL-22), caught the group's attention, as its receptor is present on skin cells.

Were the infiltrating T cells the source of this IL-22? And if so, was it the cause of skin cell proliferation? "We wanted to ask 'what's the source of IL-22 and what's the target?'," says Zheng. The researchers knew that IL-22 could be produced by T cells, but they needed to find out which particular subset.

They started by testing $T_H1$ cells, the most likely candidates, but Zheng and group leader Wenjun Ouyang were not convinced by the small amounts of IL-22 these cells produced. Around this time, other researchers identified a new subset of T cells, called $T_H17$. The Genentech team immediately set up tests of these cells and showed that they could indeed pump out large quantities of IL-22 (see page 648).

This was only the start. "If we wanted to prove that IL-22 is truly a link between T cells and psoriasis, we had to try to pick an *in vivo* model to show it," says Zheng. There is no proper animal model of psoriasis, so Zheng and Ouyang scoured the literature looking for the best approximation.

They knew that psoriasis patients also had raised levels of the pro-inflammatory cytokine IL-23, and that some patients had responded well to an antibody treatment that blocks IL-23. What's more, Zheng had shown that adding IL-23 to the $T_H17$ cells in the lab dish made them produce IL-22.

The team found previous work in which injection of IL-23 into mouse ears caused the ear skin to thicken. This model brought all the parts together. Using it, Zheng and his colleagues could show that the IL-23 induced T cells in the ears, possibly $T_H17$ cells, to produce IL-22. And almost no skin thickening occurred in a mouse that lacked the gene for IL-22. This clearly marked IL-22 as the missing signal between the invading T cells and the skin cells' overgrowth.

"Once we picked the animal model, everything started to make sense," says Zheng. "It only took six months to finish the project." Ouyang's group was the first to the finish line in competition with several other labs to establish the nature of the link between T cells, cytokines and psoriasis. The next task is to find the trigger that causes the release of IL-23 in the first place. ■

# KEY COMPARISON

Geologists generally agree that about 33.5 million years ago Earth cooled significantly during a period known as the Eocene–Oligocene transition. How this cooling occurred and its prevalence throughout the globe is still a matter of debate.

Geologists investigating this transition typically gather data from marine environments, but two independent groups wanted to understand the changes on land.

Alessandro Zanazzi and his colleagues (see page 639) looked for clues in fossil bones and teeth from the Toadstool Geologic Park in northwestern Nebraska. They found that the fossils' composition of oxygen isotopes, which correlates with the temperature at the time the animals were living and during fossilization, revealed a temperature drop of 8 °C.

Guillaume Dupont-Nivet and his co-workers (see page 635) wanted to find the cause of the disappearance of lakes around this time in the region that is now the Tibetan plateau. Using known reversals of Earth's magnetic field to date rocks from the plateau, they found that the lakes' disappearance was recorded in sediments deposited in different parts of the region. This made it unlikely that tectonic-plate-induced mountain building caused the lakes to vanish. They surmise instead that the aridity during the Eocene–Oligocene transition dried up the lakes. ■