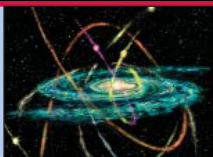


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proximately two times more likely in the paroxetine group than the placebo group.”

Spitzer's complaint alleges that GSK “repeatedly misrepresented the safety and efficacy outcomes” from these studies in internal memos to its sales force and in medical letters to physicians mailed between November 2001 and January 2003. In addition to holding back negative findings, GSK failed to point out that hints of efficacy in study 329

lacked statistical significance, Spitzer claims.

The apparent conflicts in GSK's data records came to light as GSK applied to drug authorities to win approval for pediatric use of paroxetine. As British, then Canadian, experts pored over the data, they challenged GSK's claims in 2003. The U.S. FDA held a review earlier this year and on 22 March issued a “talk paper” asking SSRI manufacturers to include new warnings that patients on

SSRIs should be closely monitored.

In its 2004 medical letter, GSK clarifies two points: Combined data on paroxetine “did not show a benefit for the treatment [of depression] in pediatric patients,” and “the incidence of adverse events possibly related to suicidal behavior” in pooled data on 1100 patients was 2.4% for those on paroxetine versus 1.2% on placebo. But, GSK adds, “no patients committed suicide.” —ELIOT MARSHALL

IMMUNOLOGY

Unexpectedly, Ancient Molecule Tied to Asthma

A surprise discovery in mice has linked a mysterious, largely unexplored class of molecules to asthma and may bolster the theory that the respiratory disease is a misplaced reaction to parasites. The molecules, called chitinases, were long considered a primordial response to certain parasites and insects; chitinase breaks down the compound chitin, which is produced in the shells and outer surfaces of these animals.

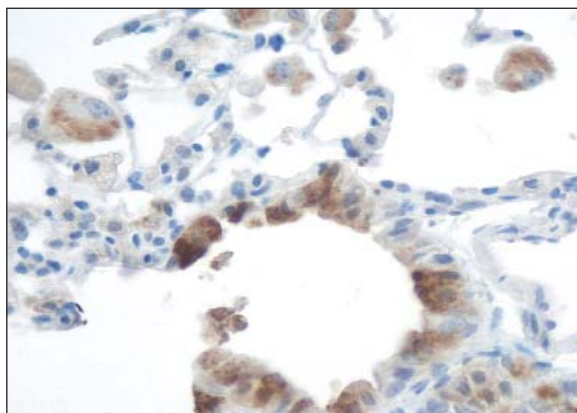
Because humans don't produce chitin, their half-dozen or so chitinase genes have often been dismissed as relics of evolution, although one has been linked to an inherited disease. Now, on page 1678, Yale University School of Medicine pulmonary specialist Jack Elias and his colleagues have tied a second chitinase, an enzyme called acidic mammalian chitinase, to a classic inflammatory response in asthma.

“I think it's going to open up a whole new area of exploration,” says William Busse, an asthma specialist at the University of Wisconsin Medical School in Madison. “A lot of people would have given up and said, ‘This [chitinase] has nothing to do with anything.’ They pursued it.”

The pursuit, however, came 2 years after the scientists mistook early evidence for something more mundane. Elias, pulmonary scientist Zhou Zhu, and others had noticed crystals in the lungs of mice bred to have an asthmalike disease. They assumed that the crystals were the same as those commonly seen in the sputum of asthma patients. Finally, “someone in my lab said, ‘Let's make sure,’ ” says Elias. After purifying the crystals, the researchers were astonished to learn that they'd hit on a chitinase.

Intrigued, they began tracing the chitinase path in asthma. First, they induced asthma attacks in their mice and then examined

their lung tissue. The scientists found far more of the chitinase there than in the lungs of healthy animals. Then they focused on a class of T cells, T helper type 2 (Th2) cells, that many consider critical to triggering asthma. Th2 cells, Elias's team found, prompted levels of the chitinase enzyme to soar. Interestingly, overproduction of the chitinase seemed to depend on a key Th2



Spotting chitinase. In mice with an asthmalike disease, chitinase (dark brown) shows up in lung tissue.

cell protein, interleukin-13 (IL-13). Extra IL-13, common in the lungs of asthmatics, is thought to help spark asthma attacks.

When Elias and his colleagues gave the sick mice a serum that blocked the chitinase, the animals' lung inflammation eased. The drug, however, didn't alter levels of IL-13 and other Th2 cell proteins. This suggests that the chitinase is a domino that falls later than IL-13 and other Th2 molecules when they precipitate asthma. It also suggests, says Elias, that the chitinase may be a new drug target for asthma; Yale has licensed patents on the discovery to MedImmune, a biotechnolo-

gy company in Gaithersburg, Maryland.

The scientists also studied lung tissue from humans with asthma and from healthy controls. Those with asthma had high levels of the chitinase in their lungs; the chitinase was undetectable in those without the disease.

That pattern reminds Rolf Boot, a biochemist at the University of Amsterdam, the Netherlands, of what he's seen of another chitinase in Gaucher disease, a rare enzyme disorder. Boot and his colleagues, who were also discoverers of the acidic mammalian chitinase that surfaced several years later in Elias's lab, have found that in Gaucher patients, a second human chitinase can reach levels 10,000 times higher than normal. Like acidic mammalian chitinase, the function of this other chitinase is a mystery.

Although the Elias work sheds light on acidic mammalian chitinase, it also “raises a lot of questions,” says Marsha Wills-Karp, who directs immunobiology at Cincinnati Children's Hospital Medical Center in Ohio. It's still uncertain whether the discovery that asthmatics overproduce a chitinase bolsters the popular theory that in asthma patients, the body senses parasites where there aren't any and sends the immune system into overdrive. But if that's the case, says Wills-Karp, chitinase should be among the first dominoes to fall in reaction to something in the environment, followed by overproduction of various Th2 molecules and then an asthma attack. “There may be more to the story, something we're missing,” she says, and she hopes that further study of the chitinase will fill in any gaps. —JENNIFER COUZIN