Diminished repertoire cripples fungus

Long known to grow in several forms, the fungus *Candida albicans* may exploit this versatility to cause illness in mammals. Strains that can't switch between the different structures do not make mice sick, recent research shows.

Although *C. albicans* produces disease in humans more frequently than any other fungus does, it lives harmlessly in over 15 percent of people. Their healthy immune systems keep the microorganism in check. Yet *C. albicans* can induce a range of symptoms and even lead to death in people whose medical treatments or diseases interfere with the activities of immune cells or whose helpful bacteria have been killed by antibiotics.

The fungus alternates in shape between single ellipsoidal cells and long filaments made of many cells strung together. Scientists have suspected that this ability to change form contributes to *C. albicans'* virulence. Until recently, however, they have been unable to identify the genes involved in this process, so they could not test their hypothesis rigorously. Experiments with newly constructed strains defective in several such genes now indicate that the organism must switch back and forth in order to provoke disease.

A *C. albicans* mutant that exists only in the single-celled form can't induce a lethal infection in mice, report Gerald R. Fink of the Whitehead Institute for Biomedical Research in Cambridge, Mass., and his colleagues in the Sept. 5 CELL. Test-tube experiments suggest an explanation for this observation.

When mouse immune cells called macrophages engulf normal *C. albicans*, the fungus assumes its filamentous form and bores its way out of the cells. The mutant strain, in contrast, remains within the macrophages.

"We're trying to recreate some of the details under a microscope," says team member Julia R. Köhler. "When you inject *Candida* into animals' bloodstreams and count how many [mice] die, you can't really draw conclusions about exactly what happened in their bodies."

Although the researchers gauged virulence by the number of deaths, *C. albicans* can also induce more limited infections in an animal's mouth or vagina.

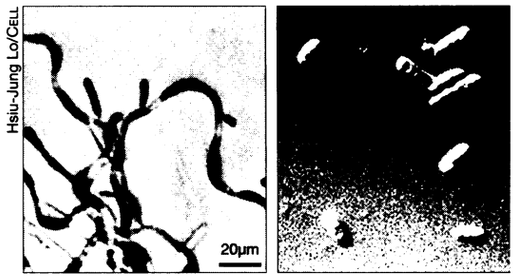
"It will be interesting to see whether the mutants are compromised in the localized infections as well," says William A. Fonzi of Georgetown University School of Medicine in Washington, D.C. "We can now start asking whether different aspects of *Candida* biology are important for different types of illness."

Researchers have already shown that a *C. albicans* mutant stuck in the filamentous form produces less vaginal and oral disease in mice than its normal counterparts, says Burkhard R. Braun of the University of California, San Francisco. He and Alexander D. Johnson described this mutant in the July 4 SCIENCE.

Combining the results from the two groups, "it looks like either form by itself is insufficient for *C. albicans* to infect," says Braun. Although highly suggestive, the data do not prove that *C. albicans* must change forms to provoke disease, warn the researchers. In addition to controlling changes in shape, the genes they have studied govern other—as yet unknown—cellular activities, some of which may play a role in virulence.

Despite this caveat, the scientists have begun speculating about how the different forms of the fungus contribute to disease. Perhaps they help *C. albicans* accomplish different feats within the body, says Fonzi.

"When disseminating through the blood vessels, the single-celled form would be less likely to get stuck in the capillaries. Then, after it arrives at tissues it wants to attack, it could turn into filaments and invade." —*E. Strauss*



C. albicans *can grow in a filamentous (left) as well as a single-celled (right) form.*

Drug sensitivity varies with ethnicity

For centuries, people of different cultures have used opiates to relieve pain. Now, it appears that sensitivity to the opiate codeine varies with ethnic background, according to a recent study. These findings could help doctors treat pain more effectively in different individuals.

Codeine's analgesic properties stem mainly from the body's ability to metabolize it into morphine, a much more potent opiate, says Alastair J.J. Wood of Vanderbilt University School of Medicine in Nashville. His research indicates that further reactions contribute to the pain-killing response.

Wood and his colleagues examined the effects of codeine in men of European extraction and in Asian men. Both groups transformed codeine into morphine similarly, but the Asian men experienced significantly weaker effects from the drug.

Wood presented the findings this week at a meeting of the American Chemical Society in Las Vegas.

"It's a nice piece of work," says Wendel L. Nelson of the University of Washington in Seattle. Researchers had suspected that morphine is responsible for the pain relief provided by codeine, but the current study "is the clinical piece that really nails it down."

Previous studies have shown that some people lack an enzyme called CYP2D6 that chemically alters codeine into morphine. The same enzyme metabolizes many drugs used to treat high blood pressure, heart arrhythmias, and depression. About 8 percent of whites, 6 percent of blacks, and 1 percent of Asians do not produce CYP2D6.

Currently, doctors tend to think that patients who don't respond to a pain-killing drug need higher doses. "Here's an example where a portion of the population will get no effect, and increasing their dose a lot more will still produce no effect," Wood says. "It's not that they're wimps or their pain is worse than [that of] other people."

All of the people in the current study, 10 white men from the United States and 8 men from China, possessed CYP2D6. Pain control is difficult to measure, so the researchers monitored how codeine affected breathing, blood pressure, and pupil dilation. Consistently, codeine affected the Chinese men less than the U.S. men. Their bodies cleared morphine faster and increased metabolism of codeine through enzymes other than CYP2D6.

No one knows whether the results shed any light on understanding addiction to opiates, Wood says. At first, he hypothesized that people who abuse codeine would possess CYP2D6, but his group realized that it would be difficult to find appropriate subjects.

Scientists once thought that ethnic differences in rates of alcoholism might have a biochemical basis. About half of Chinese and Japanese people flush uncomfortably after consuming alcohol because they lack the enzyme aldehyde dehydrogenase. Now, most scientists believe that social factors account for the alcoholism difference.

Not many researchers consider ethnicity when testing drugs, Wood says. Based on clinical studies of a "small, homogeneous population, we extrapolate dosage and toxicity with breathtaking confidence to worldwide use." In the case of codeine, the differences in metabolism aren't large enough to make toxicity a concern, says Nelson.

Knowledge of the important enzymes involved in metabolism, however, does spur drug companies to screen potential compounds very early, he says. "If the company is going to invest money in developing a drug, it wants to know if it won't work in a large percentage of the population." —*C. Wu*