Blocking Breast Cancer

Do faulty estrogen receptors make a meaner, tougher tumor?

By KATHY A. FACKELMANN

Hidden within every breast tumor lies a clue to its character: the presence or absence of receptors that bind with the hormone estrogen.

Receptor-rich tumors depend on estrogen for their growth, and some scientists believe they represent a milder form of breast cancer than tumors without estrogen receptors. Furthermore, women with estrogen-dependent tumors are considered candidates for a relatively nontoxic drug called tamoxifen, which can halt tumor growth by blocking estrogen binding. Tamoxifen's discovery in the 1970s was hailed as both a lifesaver and a deliverance from the terrible side effects of cell-killing chemotherapy.

Yet the presence of estrogen receptors in a breast tumor may, in fact, offer a false and perhaps fatal promise. New research suggests that the estrogen receptors in some breast tumors are defective, allowing the cancer to proliferate and spread aggressively.

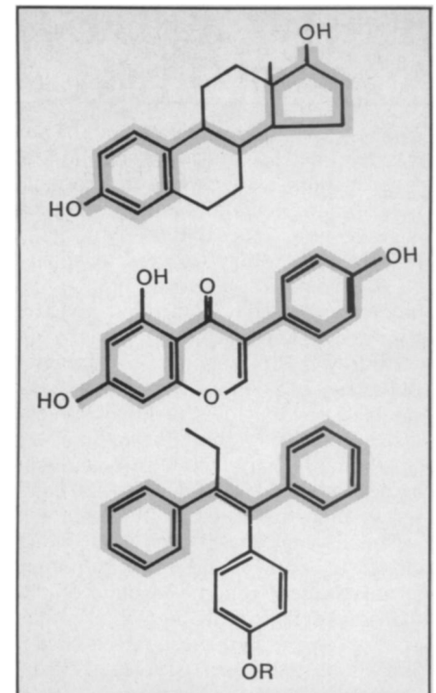
Estrogen receptors work by snaring estrogen molecules entering a tumor cell from the bloodstream. The hormone spurs the tumor cell to proliferate at a steady but relatively slow pace. If an active receptor instead encounters tamoxifen—estrogen's chemical lookalike—it binds the drug rather than the hormone, and thus has no impetus for growth.

But the new findings suggest that tumors with flawed receptors have lost their ability to respond to estrogen or to tamoxifen, and that their "growth switch" stays on at all times. These tumors no longer need estrogen to grow, the researchers speculate. The result: a rapidly proliferating malignancy requiring harsh chemotherapy.

In separate work, other scientists report finding tamoxifen-like substances in soybeans that may block tiny "seeds" of estrogen-dependent breast cancer early in the disease process, before estrogen receptors have a chance to go bad.

The two studies fit into a hypothetical scenario in which functioning estrogen receptors, while allowing breast tumors to grow, also restrain the pace of proliferation. But these receptors may gradually lose their binding ability – a process that leads to rapid, out-of-control cell growth. If this theory is confirmed, physicians will need to distinguish between functional and flawed receptors in order to select the best treatment for women with receptor-containing breast tumors. In addition, potential preventive measures such as the soybean compound could become especially important for women at high risk of developing breast cancer, which ranks as the second leading cause of cancer deaths in U.S. women.

Samuel Broder, director of the National Cancer Institute, calls this concept of receptor malfunction "exciting" because it may explain why some receptor-containing breast cancers do not respond to tamoxifen and instead spread to distant body parts. Still, Broder cautions that evidence supporting the theory remains preliminary. "A lot of interesting studies don't pan out. We should get some answers on this in a couple of years," he says.



Mammalian estrogen molecule (top) chemically resembles the soy compound genistein (middle) and the anticancer drug tamoxifen (bottom).

Barnes

Since May 1988, the National Cancer Institute has recommended that all women with breast cancer receive some form of drug therapy after surgery, even if their lymph nodes show no evidence of cancer spread (SN: 3/4/89, p.135). The goal of such treatment is to kill any cancer cells missed during surgery. But the individual physician must decide whether to recommend toxic chemotherapy, which can cause vomiting, hair loss, blood abnormalities and other harsh side effects; or tamoxifen, which tends to have milder side effects such as hot flashes and vaginal discharge.

Physicians currently base that decision on a number of factors, including a laboratory test to detect estrogen receptors in tumor cells. Women with a positive test result are candidates for tamoxifen, while women whose tumors lack the receptors usually get standard chemotherapy.

Now, a team led by Christopher C. Benz of the University of California, San Francisco, contends that current estrogen receptor tests offer an incomplete picture by failing to reveal whether the receptors work properly. Their findings indicate that a positive test result may falsely imply a mild, tamoxifen-responsive form of cancer when in fact the receptors may be flawed, making tamoxifen treatment useless. The researchers have developed a novel assay for defective estrogen receptors, which they say could help identify women who need cell-killing chemotherapy after surgery to avoid cancer recurrence.

The team examined cancerous breast tissue taken from 40 women, finding estrogen receptors in the tumors of 34 of the women. Traditional thinking would assign these 34 women to the most favorable prognostic category, with a low risk of cancer recurrence and a good chance of responding to tamoxifen. Yet when the researchers analyzed the tumors with the new assay, they discovered that about one-third of this subgroup had abnormal estrogen receptors.

Says Benz, "They would have been told, with a high degree of certainty, that they would respond to tamoxifen" – a prospect that would leave them vulnerable to a potentially deadly recurrence, if Benz is correct in his belief that flawed receptors cannot bind tamoxifen.

To find defective estrogen receptors, he and his colleagues grind up tumor samples and add the DNA sequence normally bound by the receptor in the tumor cell. In the samples taken from the 34 women, they discovered that some estrogen receptors attached to the DNA normally, others attached in an irregular manner, and still others couldn't bind with the DNA at all. Benz reported the results in March at the American Cancer Society science writers' seminar in Daytona Beach, Fla.

He speculates that the abnormal estrogen receptors identified by his test may signal a tumor-in-transition – one that is losing its ability to respond to estrogen's

controlled-growth message and is now starting to proliferate wildly. Benz believes further studies will show that women whose tumors lack functional estrogen receptors do not respond to tamoxifen therapy. He plans a larger study in which researchers at several U.S. medical centers will compare cancer recurrence rates among tamoxifen-treated women with working and defective estrogen receptors.

Another research team approached receptor responsiveness from a different angle in an animal study described at the same meeting. Stephen Barnes of the University of Alabama at Birmingham and his colleagues presented results suggesting that a tamoxifen lookalike found in soybeans may block cancer at an early stage, presumably when the estrogen receptors still function. They say their findings may help explain why Japanese and Chinese women, who eat lots of soy-rich foods, have a much lower incidence of breast cancer than women in the United States.

The researchers devised six test diets containing varying amounts of powdered soybean chips, and one control diet with no soy. For 25 days, they fed the soy diets to the 30 rats in each of the six test groups and fed regular chow to a group of 30 control rats. The team then injected all rats with N-methylnitrosourea, a chemical known to cause multiple mammary tumors in rodents.

After a 140-day observation period, Barnes and his co-workers found that rats eating the soy diets had 40 to 70 percent fewer breast tumors than the control rats. The protective effect showed a dose-response relationship: Rats eating the most soy had the fewest breast tumors, Barnes says.

Barnes tentatively attributes these results to a compound called genistein, which is found in soybean and red clover and which resembles estrogen and tamoxifen in structure. Like tamoxifen, genistein may discourage tumor growth by blocking off estrogen receptors, he speculates.

Its potential value as a preventive would hinge on a lifelong dietary regimen, the researchers suggest. Scientists trace the genesis of breast cancer to genetic damage to normal breast cells between the ages of 15 and 25. The immune system kills most of the damaged cells before cancer takes root, but in some cases a few of the cells survive. By blocking a wayward cell's growth at this preclinical stage, genistein might give the immune system a better shot at destroying the cell, Barnes proposes.

While there's generally no harm in adding soybean products to a balanced diet, other scientists say the study's conclusions can't be taken too far. "This is a carefully done study in rats," comments F. Andrew Dorr, a senior investigator at the National Cancer Institute. Dorr says it would be difficult, however, to prove that a soy-rich diet can prevent breast cancer in humans. Other factors, such as the fat-laden Western diet, may contribute to the high incidence of this and other diseases in the United States compared with Japan or China, he notes.

Dorr advises similar caution in interpreting the results of the California study. "If it were my wife, I might send her tumor sample to California for analysis," he speculates. However, he says he would still recommend tamoxifen even if the test showed flawed receptors. Dorr notes that Benz has yet to prove that women with defective receptors are likely to fail tamoxifen treatment and develop cancer recurrence.

Benz acknowledges the advantages of tamoxifen treatment and agrees that the recurrence link remains speculative. But until further studies settle the issue — perhaps leading to routine use of the new receptor assay — he emphasizes the need to monitor patients closely during tamoxifen treatment and to switch them to standard chemotherapy at the first hint of cancer spread. □