HER2-Positive Breast Cancer and its Treatments

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Abstract

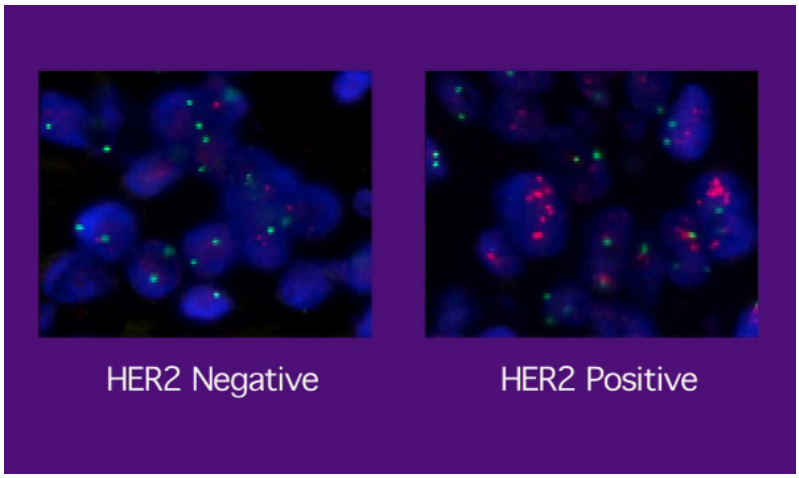
HER2-positive breast cancer is one of the worst iterations of the cancer, namely because the overexpression of this gene can make the cancer more painful and rigorous. This gene has been heavily studied, but the protein it produces, neu, and the drug that treats its overexpression, Trastumuzab, function in largely unknown ways. Scientists cannot reach a conclusion as to how exactly these peptides function, but they have been able to prove them effective, at least to some extent. The latest treatment that scientists are using is a vaccine, which works in more simple ways. This vaccine creates antibodies to another peptide produced by the gene, so when it becomes overexpressed again, there are proteins to keep it under control. While this vaccine can only be effective for women in remission, the drug Trastumuzab can be effective at all stages of the cancer. These treatments may also be effective for other HER2 positive cancers, which have been diagnosed using tumor biopsies and genetic and protein-based tests. Scientists have made many breakthroughs with HER2-positive breast cancer, but more study is required to be able to properly and comprehensively treat it.

Introduction

The majority of cancers are epithelial-derived, as epithelial tissues cover the whole body and most of the organs (Yoshino 2004). Breast cancer is no exception, as it starts in either the milk ducts or the lobules, both covered in epithelial tissues (cancer.gov). Breast cancer occurs in men and women, but more commonly in women, with over 200,000 women and only 2,000 men diagnosed in 2013 (cancer.gov). Breast cancer can be gene related, and a mutated BRCA gene makes its carrier more likely to have the cancer, making mastectomies more popular among women with the gene. Researchers are looking into more possible causes for breast cancer, from

working the night shift to smoking tobacco, and have found many external and cellular causes for breast cancer. One of the more common causes is a defect in the cell reproductive cycle, specifically in growth factor receptors.

There are several ways to diagnose a cancer as HER2-positive, and it's the first test that women with breast cancer undergo. A sample of the tumor is taken in order to test for overexpression of HER2/neu. The first test done is an immunohistochemistry test, which determines how much neu is present in the tumor (macmillan.org.uk). The results are measured from 1 to 3, with 1 meaning a normal amount of neu, 2 meaning that additional testing needs to be done in order to determine if HER2 is overexpressed, and 3 meaning the tumor is HER2-positive (macmillan.org.uk). The next test to determine if patients can benefit from Trastuzumab is fluorescence in-situ hybridization, which measures the number of HER2 genes in each cell, to see if there are too many copies (macmillan.org.uk). If this test is positive, the patient has about twice the normal amount of HER2, which happens about a quarter of the time (macmillan.org.uk). This test is used for patients with breast cancer and stomach cancer, but it is less routine with stomach cancer patients. As HER2 becomes associated with more and more cancers, the test will become even more essential to treatment than it already is.



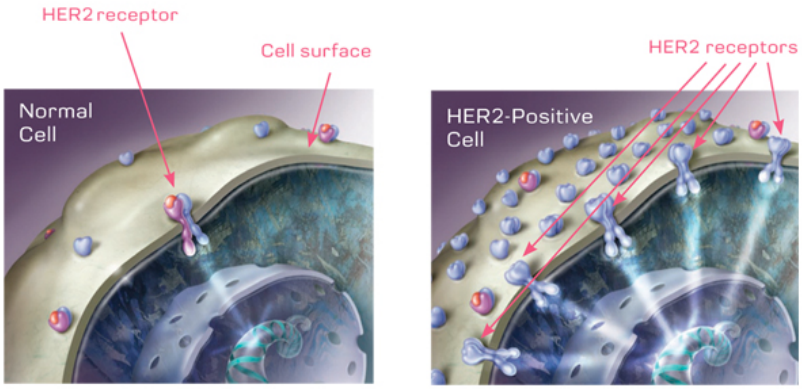
"Photos Related to HER2 Positive Breast Cancer"

HER2, or the human epidermal growth factor receptor, is a proto-oncogene located on

chromosome 17 that produces neu, a protein that regulates pathways for cell growth (Mitri 2012). The neu protein's exact function is not completely understood, but it is believed to be a surface growth factor receptor and acts as a ligand (Singer 1997). A ligand is a signal that triggers a molecule and binds to it, altering the function of the receptor. This protein is linked to the EGF receptor and is expressed in the majority of cells (Singer 1997). The normal form of neu is almost identical to its oncogenic form, except for a single amino acid, valine (Singer 1997). At position 664, this valine is replaced by glutamic acid, which makes the activity of oncogenic neu increase five to ten times, or is overexpressed (Singer, 1997). This mutation helps the protein form a ligand independent dimer (2 like proteins bound together), which increases its activity (Singer 1997). Scientists believe that glutamic acid found at position 664 is able to form a hydrogen bond with another glutamic acid found at the same position on a different oncogenic protein (Singer 1997). This neu dimer increases the activity of the receptor and causes cancerous cells to grow rapidly (Singer 1997). However, this research about neu is not definite, and scientists are still trying to understand its mechanism. One of the most recent studies was completed in 1997, and little new information has been acquired since then. This theory does explain neu's contribution to cancer fairly well, and would make sense based on the effects of HER2-positive breast cancer.

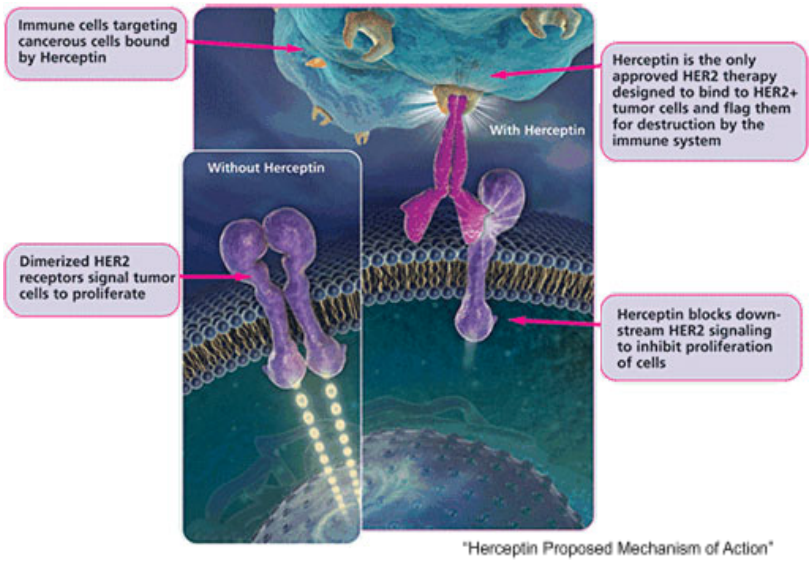
In a fourth of breast cancer cases, HER2/neu is overexpressed and can make the cancer more aggressive and deadly (Mitri 2012). In addition to breast cancer, the overexpression of HER2/neu can contribute to ovarian cancer, non-small cell lung cancer, and epithelial cancers (Yoshino 1994). While it is called HER2-positive cancer, often it is the neu protein that is mutated, not the HER2 gene itself. Sometimes, a cell will have too many copies of HER2, or too

many receptors for human growth factor (Ménard 2000), which facilitates neu mutation. Often, the neu protein is responsible for the rapid growth, as opposed to the HER2 gene. However, most of this is speculation, as scientists are not sure if their understanding of the mutation process is correct. Whatever the case is, scientists are sure of one thing, and that is the extra receptors make it easier to employ drugs targeting HER2/neu to inhibit its effects (Ménard 2000).



"About HER2 and Breast Cancer"

While scientists may not be exactly sure about how Trastuzumab works, it has proven very effective in treating HER2 positive breast cancer. It is thought to act in two phases, by inhibiting cell growth (and marking the cells for antibodies) and stimulating T-cells to release antibodies that kill cancerous cells (Mitri 2012). Antibody therapy has been used to treat HER2 positive breast cancer for years, and can increase the lifespan of people with the disease to longer than people with HER2 negative breast cancer (Dawood 2009). However, these treatments are generally effective only for the first 24



"Herceptin Proposed Mechanism of Action"

months, but they do reduce the risk of death by 44% (Dawood 2009). Since this treatment is antibody dependent it relies on antibodies, who can always be present, to function (Petricevic 2013). This makes it effective at all stages of the cancer, whether localized or metastatic (Petricevic 2013).

E75 is a peptide from the HER2/neu protein, and vaccines are incorporating it in order to reduce the effects of overexpressed HER2 (Peoples 2008). E75 creates an immune response in the body that stimulates cells to produce antibodies against this peptide, but more importantly the HER2/neu that creates it and causes cancer (Peoples 2008). These antibodies are created by B lymphocytes, who recognize the protein as an antigen and make molecules to find and destroy it. After they take care of the E75 introduced by the vaccination, there will be B cells to produce more antibodies to attack neu proteins and cancerous cells. As a result, the patient's own immune system is able to fight the tumor. Another peptide derived from HER2/neu is GP2, and although it is studied far less, it is theorized that it has potential to serve as a vaccine as well (Mittendorf 2010). More recent studies concerning both of these peptides have been conducted, but they are more geared toward improving the efficacy and safety of the vaccines as opposed to discovering new ways in which they work (Mittendorf 2010). For women in remission from HER2 positive breast cancer, these peptide vaccines decrease the rate of cancer recurrence (Peoples 2008).

Conclusion

HER2-positive breast cancer can be very deadly, but antibody-dependent treatments seem to be the most successful. By building immunity to peptides created by HER2, patients are able to control its overexpression and control the cancer to some extent. Trastuzumab operates

this way and has been a leading drug for many years, but new vaccines are proving to be effective in treating the cancer as well. However, scientists need to devote more time to learning the mechanisms, especially when it comes to the specific function of neu, whose most recent study was conducted in 1997. Expanding on neu, researchers should study it in other epithelial cancers as well, because while a link is suspected, it is not confirmed. Better procedures should used when testing for it in stomach cancer, as well as non-small cell lung cancer. Another possibility is for the vaccine to be implemented sooner, maybe even to women before they are diagnosed with breast cancer. If the vaccine built up antibodies to a certain protein that is mainly created when HER2 is overexpressed, then it should not hurt women to have it sooner, and alleviate some of the pains of HER2 positive breast cancer. Other peptides should be examined in accordance with HER2 to create a more effective and long-lasting vaccine, with an effectiveness period longer than 24 months. Needless to say, there is much more research waiting to be done to treat HER2-positive breast cancer, and other cancers like it. However, this is one of the best methods of treating cancer because if does not involve chemotherapy, which is a very long and harsh treatment, especially in addition to the added pain that HER2 causes. This treatment is pain free, generally, and patients can still function normally while undergoing current treatments, so they are an overall success.

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