Lung Cancer and the BRAF Y472C Mutation

This material will help you understand:

- the basics of lung cancer
- the role of the BRAF gene in lung cancer
- if there are any drugs that might work better if you have certain changes in the BRAF gene

What is lung cancer?

Lung cancer is a type of cancer that starts in the lungs. It is the number one cause of cancer deaths in the world. Doctors name lung cancers based on how lung cells look under a microscope. There are two main groups of lung cancer: small cell lung cancer (SCLC) and non-small cell lung cancer (NSCLC). Most people with lung cancer have NSCLC. Adenocarcinoma, squamous cell carcinoma, and large cell carcinoma are types of NSCLC.

What causes lung cancer?

Cancer is a result of changes in our genes. Genes contain the instructions for making proteins. Changes in genes, called mutations, may result in changes in proteins. These changes may cause cells to grow out of control which could lead to cancer.

The biggest risk factor for lung cancer is exposure to cigarette smoke. But, not all lung cancers are due to smoking. Other risk factors include exposure to radon gas, asbestos and pollution.

What are the most common current treatments for lung cancer?

Doctors may treat lung cancer using one or more of these options:

- **Surgery** – operation that removes as much of a cancer tumor as possible.
- **Radiation** – treatment that uses high-energy beams to kill cells in the area where the cancer is growing.
- **Traditional chemotherapy** – drugs that kill growing cells. All cells grow. Cancer cells usually grow faster than most healthy cells. So, these drugs kill more cancer cells. But because these drugs kill healthy cells too, this can cause unwanted side effects.
- **Precision medicine therapy** – treatments that target proteins involved in cancer. These therapies mainly kill cancer cells and not healthy cells. This also means you may have fewer side effects. Two types of precision medicine therapies are:
    - **Small molecule therapy** – mainly acts on cells with specific protein changes. Small molecule therapy uses drugs to target those proteins. Genetic testing can tell if your cancer cells have protein changes that can be targeted. Small molecule therapy is a type of targeted therapy.
    - **Immune-based therapy** – works with your body's defense system to fight cancer. These can mark cancer cells so they are easier for your immune system to find.

Can I pass on mutations found in my cancer cells to my children?

You cannot pass on mutations found only in your cancer cells to your children.

How well does cancer drug treatment work?
After a while, your cancer cells may stop responding to the drug(s). This means your cancer may start to grow again. Your doctor will do regular checkups to watch for this. If the cancer starts to come back, your doctor can try another drug or treatment.

What is BRAF?
BRAF (pronounced "B-răf") is the name of both a gene and a protein. The BRAF gene contains the instructions for making the BRAF protein. BRAF is a member of the RAF family of proteins. Their main job is to help control cell growth. RAF proteins are part of a pathway. Proteins in pathways work together to do specific jobs within the cell. Some of the other proteins in this pathway include RAS, MEK and ERK. This is shown in the healthy cell image below (Figure 1). This pathway is a signaling pathway. It passes signals from outside the cell to the cell's nucleus. The nucleus is the control center of the cell. These signals may tell the cell to grow, divide, or die. These are all normal cell functions. The body turns the signals on and off as needed.

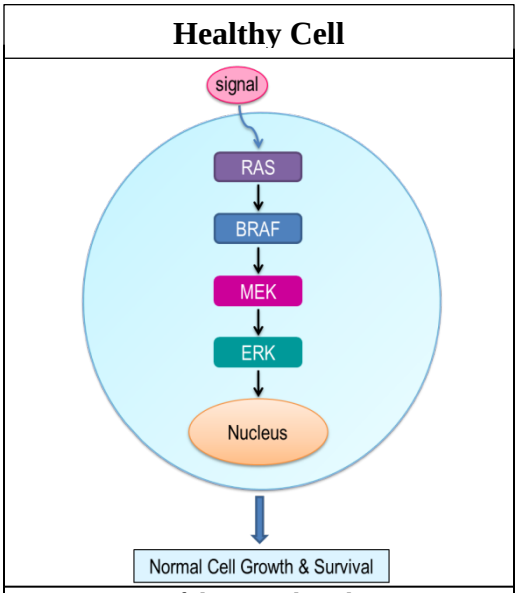


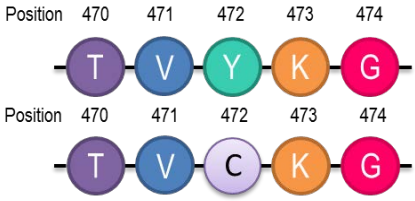
Figure 1: Part of the growth pathway in a healthy cell. The proteins pass the signal to the nucleus, which leads to normal cell growth.

What is BRAF's role in the growth pathway?
In healthy cells, the growth signal turns proteins "on." As the signal reaches each protein in the pathway, it turns on the protein. BRAF receives the signal via RAS. BRAF passes it on to MEK, and MEK passes it on to ERK. ERK is the last protein in the pathway. When ERK is on, it turns on genes in the nucleus that help cells grow. When the signal stops, the proteins turn off.

How do mutations in proteins affect pathways?
If a mutation affects one or more proteins in a pathway, the proteins may not be able to be turned on or off as expected. This can cause cells to grow out of control and lead to cancer.

How common are BRAF mutations in lung cancer?
About 1 in 50 lung cancers have a mutation in the BRAF gene that changes the BRAF protein. BRAF mutations are more common in current or former smokers.

What is the BRAF Y472C mutation?
BRAF Y472C is a specific variation in the BRAF protein. Proteins are long chains of amino acids. The BRAF protein has 766 amino acids. BRAF with no mutation at amino acid position 472 has a tyrosine, or Y for short. The amino acid at position 472 in BRAF with the Y472C mutation is a cysteine, or C for short.



BRAF without mutation

BRAF with mutation

What is the effect of this mutation?
The Y472C mutation is in the part of BRAF that passes along the cell growth signal. In cells with this mutation, BRAF can no longer pass along the signal. So, the cell tries to find another way to turn this pathway back on. BRAF Y472C does not cause cancer by itself. It requires that RAS be activated, or turned on. The growth signal can activate RAS. Mutations in the RAS gene can also keep it activated. Since BRAF cannot pass along the growth signal, the activated RAS protein works with CRAF, another RAF protein (Figure 2). Cancer may develop in cells that have both the BRAF Y472C mutation and another mutation that keep the pathway on.

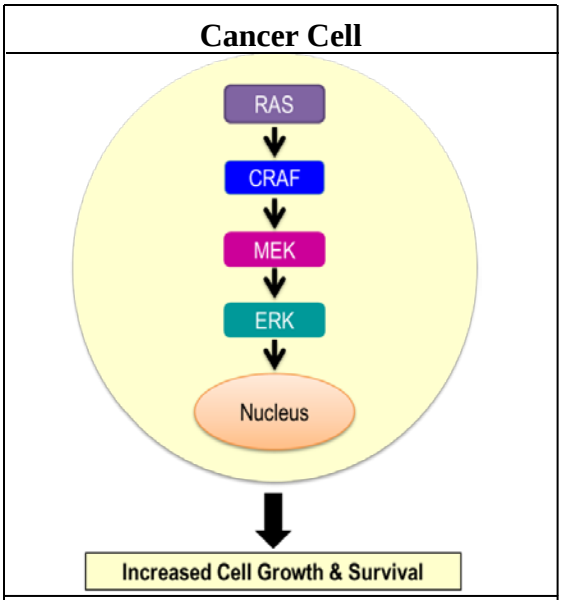


Figure 2: The cancer-causing mutated RAS protein works with CRAF to increase cell growth. BRAF with Y472C mutation is not shown, since it cannot pass the signal.

Are there targeted therapies for BRAF Y472C?
At this time, it is unclear if any drugs target the BRAF Y472C mutation. But, there are targeted therapies that inhibit MEK. MEK is another protein in this cell growth pathway. Cells with this BRAF mutation can still turn on MEK. If we block MEK, we can stop this pathway. Trametinib and selumetinib are two common MEK inhibitors. These drugs inhibit the growth of cells and may lead to cell death (Figure 3). But, you should talk to your doctor about your treatment options.

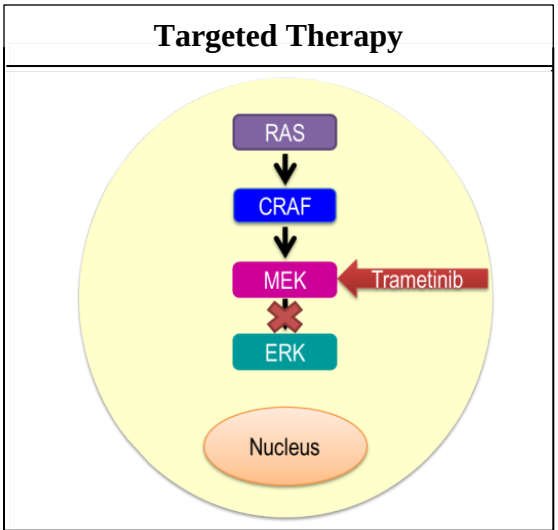


Figure 3: Results of MEK inhibitor drugs. These stop the MEK protein from turning on the rest of the cell growth pathway.

What if I have a different mutation in BRAF or "no mutation"?
Your cancer cells might have mutations in this gene or in other genes that were not tested. Your genetic test results will still help your doctor determine the best treatment for you.