

Lung Cancer and the KRAS G12D Mutation

This material will help you understand:

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

KRAS (pronounced “K-rās”) is the name of both a gene and a protein. The KRAS gene contains the instructions for making the KRAS protein. KRAS is a member of the RAS family of proteins. RAS proteins are part of at least six pathways. Proteins in pathways work together to do specific jobs within the cell. Many pathways relay 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. The body turns the signals on and off as needed.

In healthy cells, one of the pathways KRAS turns on is a growth pathway (Figure 1). As the growth signal reaches each protein in the pathway, it turns on the protein. When the KRAS protein receives the signal, it passes it on to a RAF protein. RAF 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.

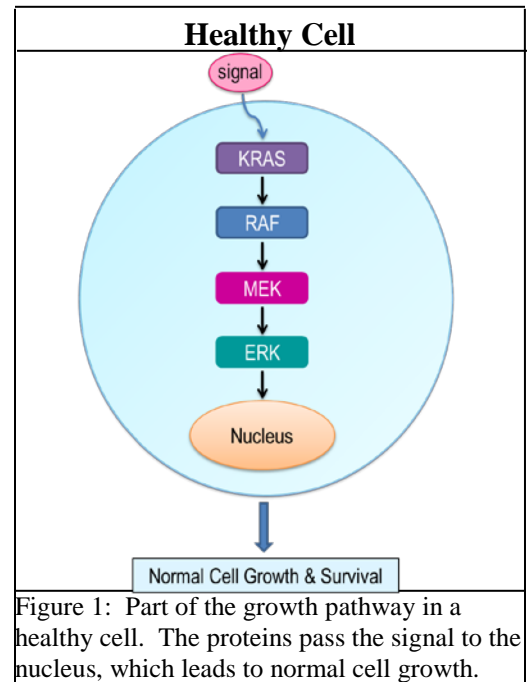


Figure 1: Part of the growth pathway in a healthy cell. The proteins pass the signal to the nucleus, which leads to normal cell growth.

How do mutations in proteins affect pathways?

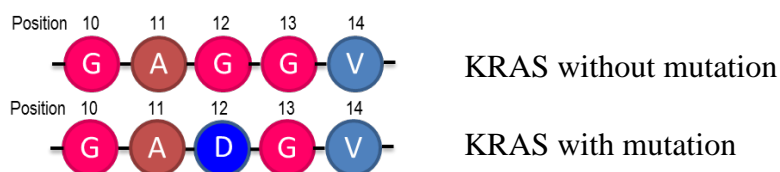
If a mutation affects one or more proteins in a pathway, the proteins may not be able to be turned on or off as expected. This can cause cells to grow out of control and lead to cancer.

How common are KRAS mutations in lung cancer?

About 1 in 5 non-small cell lung cancers (NSCLCs) have a mutation in the KRAS gene that changes the KRAS protein. KRAS mutations are most common in adenocarcinoma, a type of NSCLC. But, KRAS mutations can happen in all types of NSCLC, regardless of smoking status.

What is the KRAS G12D mutation?

KRAS G12D is a specific variation in the KRAS protein. Proteins are long chains of amino acids. The KRAS protein has 189 amino acids. KRAS with no mutation at amino acid position 12 has a glycine, or G for short. The amino acid at position 12 in KRAS with the G12D mutation is an aspartic acid, or D for short.



What is the effect of this mutation?

The most common mutations in KRAS occur at positions 12, 13, and 61. All three of these amino acid positions are important in turning on the protein. When a mutation occurs at any one of these positions, the growth pathway cannot be turned off. This can cause cells to grow out of control and lead to cancer (Figure 2).

Are there targeted therapies for KRAS G12D?

At this time, it is unclear if any drugs target KRAS with this specific mutation. But, scientists are working on new potential therapies all the time. So, you should talk to your doctor about your treatment options.

What if I have a different mutation in KRAS or “no mutation”?

Your cancer cells might still have other 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.

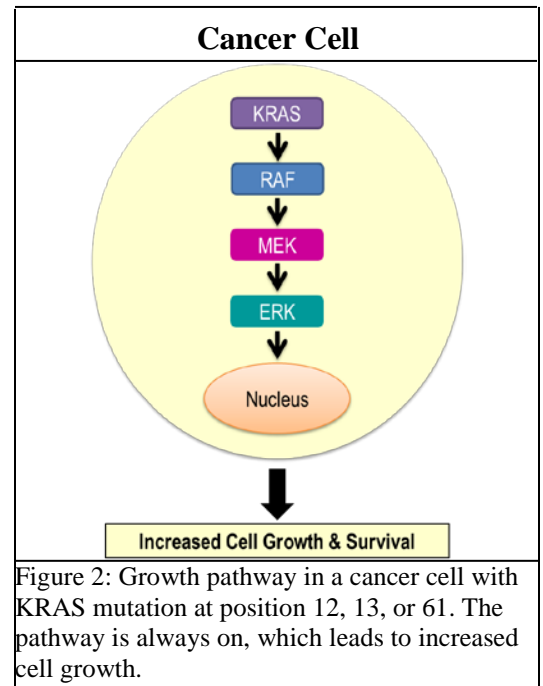


Figure 2: Growth pathway in a cancer cell with KRAS mutation at position 12, 13, or 61. The pathway is always on, which leads to increased cell growth.