

Lung Cancer and RET Fusions

This material will help you understand:

- the basics of lung cancer
- the role of the RET gene[📄] in lung cancer
- if there are any drugs that might work better if you have certain changes in the RET 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.

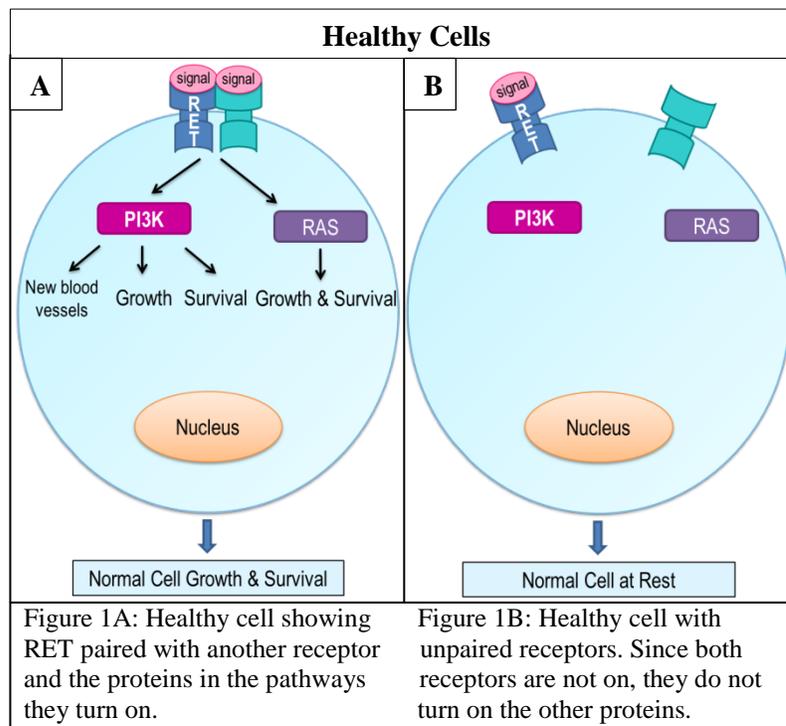
What is RET?

RET (pronounced “Rét”) is the name of both a gene and a protein. The RET gene contains the instructions for making the RET protein. RET is a receptor. Receptors are proteins that are often in cell membranes. The cell membrane is the outside surface of a cell. Receptors have three basic parts. One part is outside the cell, one part crosses the cell membrane, and one part is inside the cell. Receptors receive signals from outside the cell. These signals may tell the cell to grow, divide, or die. Each receptor usually receives one specific signal.

RET can work with or without a signal. In healthy cells, RET can turn on other proteins. These other proteins are usually in pathways. Proteins in pathways work together to do specific jobs within the cell.

Without a signal, RET can help a cell die. Dying is a normal function of cells.

When its signal binds, RET can turn on other proteins in pathways. When the outside part of RET receives the signal, it then pairs with a different receptor. The paired proteins can turn on pathways. Figure 1A shows some of the proteins and pathways turned on by RET when it pairs with another receptor. Paired RET can turn on at least two different cell growth and survival pathways. When the signal stops, the receptor proteins turn off and separate (Figure 1B).



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 RET mutations in lung cancer?

About 1 in 75 non-small cell lung cancers (NSCLCs) have a change in the RET gene that alters the RET protein. The most common change is a gene fusion. RET fusions are more common in adenocarcinomas, a type of NSCLC. RET fusions are found in smokers and never smokers.

What is a RET fusion?

A RET fusion is a protein made from a gene fusion. A fusion is when two different things are stuck together. In this case, part of the RET gene is fused to part of another gene. The protein made by the fusion contains parts from each gene. In RET fusion proteins, the part of the protein inside the cell is from RET. The outside part is from another protein.

What genes can be fused to RET?

CCDC6, TRIM33, and KIF5B are all genes that can be fused to RET.



What is the effect of a RET fusion?

Sometimes, a RET fusion gene can make a working protein. The part of the protein inside the cell is from RET. The outside part is from another protein. Figure 2 is an image of a KIF5B - RET fusion protein. Many of the proteins made from genes fused with RET can pair up, even without a signal. This results in the RET part always being on. This can cause cells to grow out of control and lead to cancer.

Are there targeted therapies for RET fusions?

At this time, it is unclear if any drugs target RET fusions. 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 RET 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.

