

Lung Cancer and the EGFR L858R Mutation

This material will help you understand:

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

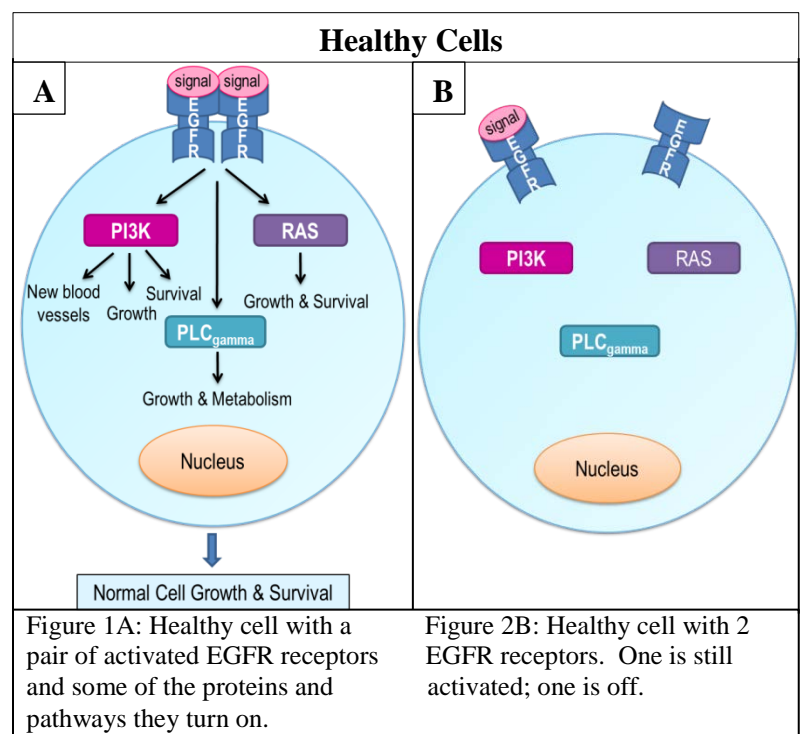
After a while, your cancer cells may stop responding to the drug(s). This means your cancer may start to grow again. Your doctor will do regular checkups to watch for this. If the cancer starts to come back, your doctor can try another drug or treatment.

What is EGFR?

EGFR is the name of both a gene[📄] and a protein[📄]. The EGFR gene contains the instructions for making the EGFR protein. It is a member of the ERBB family of proteins, and is sometimes called ERBB1. EGFR is short for epidermal growth factor 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. These signals are turned on and off as needed. Unlike most receptors, EGFR can receive several different signals.

In healthy cells, a signal binds to EGFR. When the outside part of EGFR receives a signal, it activates, or turns on, the EGFR protein. It then pairs with another activated EGFR. This pairing turns on the part of EGFR inside the cell.

When the inside part is on, EGFR can turn on other proteins. These other proteins are usually in pathways. Proteins in pathways work together to do specific jobs within the cell. EGFR can turn on at least three different cell growth and survival pathways. The healthy cell image shows a few of the proteins and pathways turned on by EGFR (Figure 1A). PI3K, RAS, and PLC-gamma are proteins EGFR turns on. When the signal stops, the EGFR proteins turn off and separate (Figure 1B).



How do mutations in proteins affect pathways?

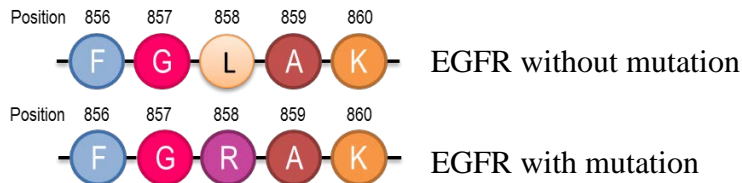
If a mutation[📄] affects one or more proteins[📄] in a pathway, the proteins may not be able to be turned on or off as expected. This can cause cells to grow out of control and lead to cancer.

How common are EGFR mutations in lung cancer?

About 1 in 3 non-small cell lung cancers (NSCLCs) have a change in the EGFR gene[📄] that changes the EGFR protein[📄]. EGFR mutations[📄] are most common in female nonsmokers with adenocarcinoma, a type of NSCLC. But, EGFR mutations are found in all types of NSCLC. They are most common in nonsmokers.

What is the EGFR L858R mutation?

EGFR L858R is a specific variation in the EGFR protein. Proteins are long chains of amino acids. The EGFR protein has 1,210 amino acids. The inside part of the protein starts at amino acid 669 and goes to the end of the protein chain. EGFR with no mutation at amino acid position 858 has a leucine, or L for short. The amino acid at position 858 in EGFR with the L858R mutation is an arginine, or R for short.



What is the effect of this mutation?

This mutation is in the part of EGFR that is inside the cell. When the inside part is on, EGFR can turn on other proteins. In cells with this mutation, the signal is not needed. The inside part of EGFR is always on. This means cells with this mutation could grow out of control, which can lead to cancer (Figure 2).

Are there targeted therapies for EGFR L858R?

EGFR L858R is a target for inhibitor drugs. Erlotinib and gefitinib are examples of drugs that target the inside part of EGFR (Figure 3). These drugs inhibit, or stop, the inside part of EGFR from turning on other proteins. There are other similar targeted therapy drugs that might also work.

EGFR inhibitors work well. But, after a while, your cancer cells may stop responding to these drugs. So, your doctor may prescribe another drug. You should talk to your doctor about your treatment options.

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

About 1 in 5 NSCLCs tested for mutations in EGFR do not find any. But, 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.

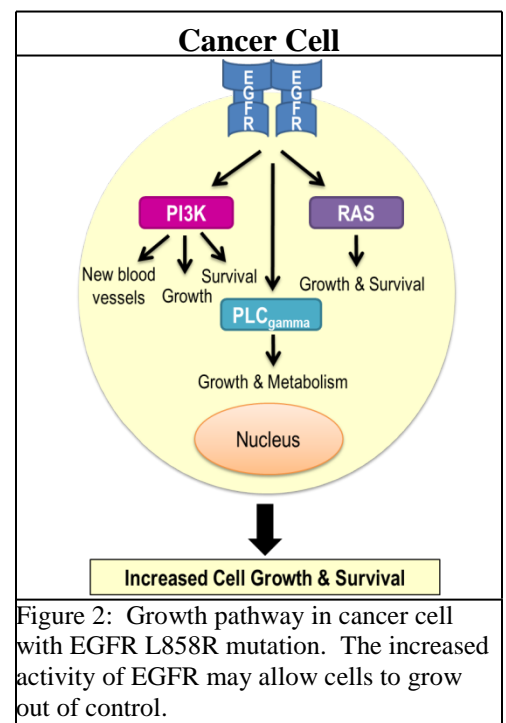


Figure 2: Growth pathway in cancer cell with EGFR L858R mutation. The increased activity of EGFR may allow cells to grow out of control.

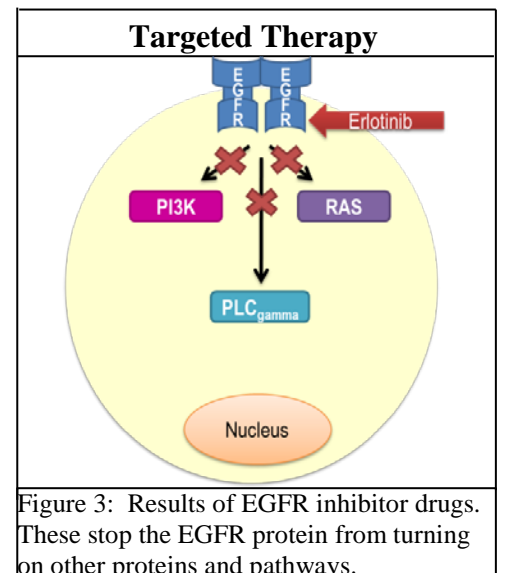


Figure 3: Results of EGFR inhibitor drugs. These stop the EGFR protein from turning on other proteins and pathways.