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Epidermal Growth Factor Receptor (EGFR) Activating Mutations

The Epidermal Growth Factor Receptor (EGFR) protein is part of the normal cell growth regulation system. It is located on the surface of cells where it acts as a receptor, or dock, for other proteins called growth factors.[1-5]

When a growth factor binds to the EGFR protein, EGFR is activated, which in turn sends signals into the cell. These signals tell the cell to grow and divide. Growth factor signaling through EGFR is critical for important processes such as wound healing and tissue repair.[1-5]

What is an EGFR activating mutation?
Although signaling through the EGFR protein is important for normal cell growth, it is essential that EGFR not be activated at inappropriate times. Research suggests that the uncontrolled cell growth of some cancers is due, at least in part, to abnormally activated EGFR signaling.

In some cases, abnormal EGFR signaling is due to specific activating mutations in the EGFR gene. These mutations keep the EGFR protein locked into an active state, irrespective of whether growth factors are present.[6-9]

Tumors with EGFR activating mutations may represent a specific type of cancer that uses EGFR signaling as its principal driver of growth.[7,9-11] Ongoing research is aimed at determining whether classifying tumors based on molecular characteristics like EGFR activating mutations will be useful in developing new strategies to address cancer.

Are all EGFR activating mutations the same?
EGFR activating mutations have mainly been studied in non-small lung cancer (NSCLC). Global estimates indicate that 10-30 percent of NSCLC tumors have EGFR activating mutations. Nearly all of the identified mutations (90 percent) fall into one of two categories. The first is a small deletion of DNA (exon 19 deletion). The second is a change in the DNA sequence referred to as "L858R."[7,9] Regardless of the type of EGFR activating mutation present in a tumor, the result is an EGFR protein that is locked into an active state.

How do researchers know if a NSCLC tumor has an EGFR activating mutation?
There are currently no FDA-approved EGFR activating mutation tests. However, EGFR activating mutations can be detected using real-time polymerase chain reaction (PCR), a sensitive technique able to detect small changes in the DNA sequence. Physicians can send

samples to laboratories certified under the Clinical Laboratory Improvements Amendments (CLIA) for analysis.

Is abnormal EGFR signaling always due to an EGFR activating mutation?
EGFR signaling can be abnormally activated in a variety of ways. For this reason, medicines designed to target the EGFR pathway are currently being studied in tumors with and without EGFR activating mutations.

Two common mechanisms for overactive EGFR signaling other than EGFR activating mutations are excess amounts of EGFR protein ("protein overexpression") and extra copies of the EGFR gene ("gene amplification"). These abnormalities are detected using immunohistochemistry (IHC) and fluorescent *in situ* hybridization (FISH), respectively.[12] Both of these techniques involve looking at tumor cells under a microscope.

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