Transcript Details
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HER2 (ERBB2) Mutations in NSCLC: Mechanism of Disease

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Welcome to ReachMD. This medical industry feature titled, "*HER2 (ERBB2)* Mutations in NSCLC: Mechanism of Disease", is sponsored by Daiichi Sankyo and AstraZeneca.

Host
HER2 (ERBB2) Mutations in Non-Small Cell Lung Cancer: Mechanism of Disease.

The HER Receptor Family and *HER2 (ERBB2)* Mutations in Non-Small Cell Lung Cancer.

HER2, or human epidermal growth factor receptor 2, is 1 of 4 receptor tyrosine kinases in the HER family. These receptors can be activated to transmit intracellular signals through homodimerization or heterodimerization, resulting in cell growth, differentiation, movement, and survival.

During activation, the tyrosine kinase domain of EGFR, *HER2*, and HER4 becomes phosphorylated, but this activity is impaired in HER3. And while EGFR, HER3, and HER4 can initiate intracellular signaling by binding to a ligand, *HER2* cannot.

Although *HER2* has no known ligand, it is the preferred binding partner of the other HER receptors, and it provides the strongest activation across all possible heterodimers.

Alterations of EGFR and *HER2* play a critical role in the pathogenesis of several cancers.

In lung adenocarcinoma, three subsets of *HER2* alterations—*HER2* gene amplification, *HER2* receptor overexpression, and *HER2* genetic mutations—have been investigated with anti-*HER2* agents in clinical trials but with disappointing results.

Activating *HER2* mutations, often called *ERBB2* mutations, account for 2-4% of all lung adenocarcinomas, but they also play a role in other forms of cancer, including bladder, stomach, and cervical cancer.

HER2 is a membrane receptor. When mutated, it may lead to the development of non-small cell lung cancer and other cancers.

The Effect of *HER2 (ERBB2)* Mutations on Intracellular Signaling.

In lung adenocarcinoma, *HER2* gene mutations, also called *ERBB2* mutations, change the shape of the *HER2* receptor and trigger hyperactive signaling.

Mutations rarely occur in the extracellular and transmembrane domains of *HER2*. But 80 to 90 percent of *HER2* mutations in non-small cell lung cancer are in the kinase domain and are intrinsically resistant to many currently approved targeted therapies due to changes in the shape of the receptor.

Normally, *HER2* signals through the PI3K and MAPK pathways, which stimulate cell growth, differentiation, movement, and survival. However, mutations in *HER2* make the receptor hyperactive and increase its rate of heterodimerization, even in the absence of a true ligand. This promotes uncontrolled cell growth and tumorigenesis. Mutations in *HER2* can also affect the rate of receptor internalization.

HER2 gene mutations in non-small cell lung cancer may trigger hyperactive signaling that promotes uncontrolled cell growth and tumorigenesis.

The Effect of *HER2 (ERBB2)* Mutations on Receptor Internalization.

Receptor internalization is a process that transports large molecules such as proteins and transmembrane receptors into a cell. It is

controlled by the action of receptors binding to their ligands. During internalization, the plasma membrane encloses a portion of the external environment to form an endosome.

Once inside an endosome, receptors and their ligands may either be recycled and return to the cell surface or be degraded inside a lysosome, allowing the release of nutrients back into the cell.

Therapeutic agents such as antibody-drug conjugates, which are investigational in non-small cell lung cancer, may rely on this natural mechanism of receptor internalization to release their cytotoxic payload inside the cell.

Like other receptors, *HER2* receptors are internalized. However, the rate of *HER2* internalization is faster when certain mutations exist in the extracellular or kinase domains.

HER2 mutations found in non-small cell lung cancer may increase the rate of *HER2* receptor internalization. Antibody-drug conjugates, which are investigational in non-small cell lung cancer, may rely upon receptor internalization.

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