



Epidermal Growth Factor Receptor (EGFR) Fact Sheet

WHAT IS EGFR?

The Epidermal Growth Factor Receptor (EGFR) is one of four receptors in the HER (Human Epidermal Growth Factor Receptor) signalling pathway.

The pathway consists of at least four cellular receptors - EGFR (also known as HER-1 or ErbB1), HER-2 / ErbB2, HER-3 / ErbB3, and HER-4 / ErbB4. These proteins are found on the surface of different types of normal cells and some cancer cells and mediate cell survival, proliferation, invasion and angiogenesis.¹

THE EGFR MOLECULE CONSISTS OF:

- **Extracellular or ligand-binding domain:** The portion of the protein located outside the cell that contains the site where binding to growth factors such as Epidermal Growth Factor (EGF).
- **Transmembrane domain:** The portion of the receptor located inside the cell membrane that anchors the receptors in the cell membrane.
- **Intracellular (Tyrosine Kinase) domain:** The portion of the receptor that projects into the interior of the cell. The intracellular portion is responsible for transferring signals to other proteins inside the cell.

EGFR SIGNALLING CASCADE

The cells in our body constantly talk to each other using molecules, which tell them when to divide, when to die and what sort of specialised cell to become. These signals are passed from protein to protein within the cell in an elaborate game of Chinese whispers that scientists refer to as a 'signalling cascade'. The signals eventually reach the nucleus, where they switch genes on or off, telling the cell whether to multiply, die or specialise.

Specifically, EGFR is activated when the naturally occurring ligands, such as EGF, binds to the extracellular domain. This binding triggers internal cellular signals that stimulate cell growth. Normally, EGFR helps regulate the growth of many different cells in the body. However, it also can stimulate cancer cells to grow. Additionally, in some cancer cells, EGFR is either over-expressed or the EGFR biological processes that normally stimulate cell growth are constantly active, leading to the uncontrolled and excessive growth of cancer cells. EGFR overexpression is observed in several cancer types, including non-small cell lung cancer (NSCLC), colorectal cancer, squamous cell carcinoma of the head and neck and pancreatic cancer.

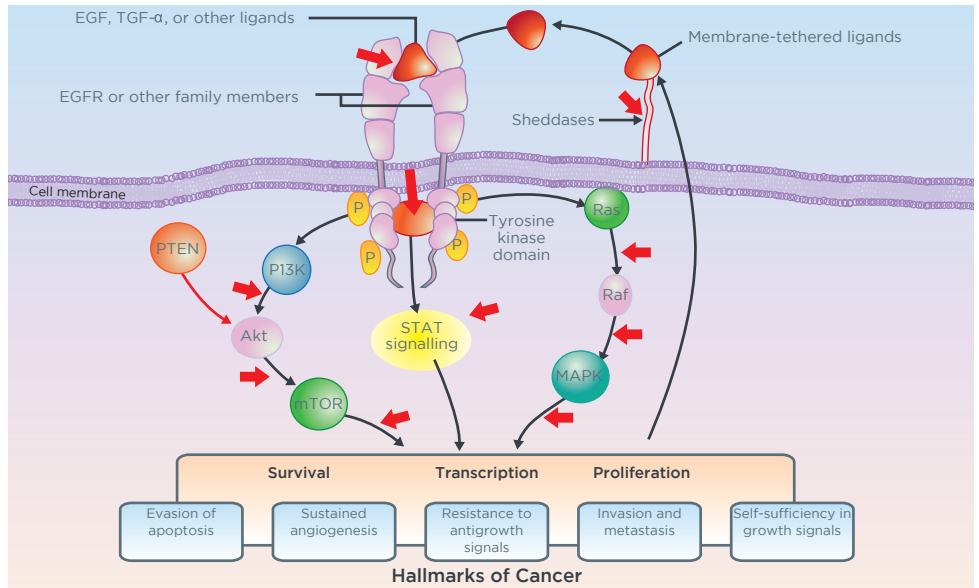


Figure 1: The Epidermal Growth Factor Receptor (EGFR) Signalling Pathway. Source: Gazdar AF (2009) NEJM 361: 1018-1020

EGFR MUTATIONS IN LUNG CANCER

EGFR overexpression is observed in tumours from more than 60% of patients with metastatic non-small cell lung cancer (NSCLC) and is correlated with poor prognosis.² EGFR mutations are the most prevalent and well characterised in NSCLC, owing to their relationship to clinical responses to EGFR Tyrosine Kinase Inhibitors (TKIs). The activating mutations of the EGFR gene are found in the first four exons (18 through 21) of the TK domain. EGFR mutations are not all created equal and do not all have the same significance.

TARGETED TREATMENTS

In recent years, targeted treatments, such as the EGFR Tyrosine Kinase Inhibitors Iressa® (Gefitinib) and Tarceva® (Erlotinib), are among the more encouraging advances to emerge in non-small cell lung cancer treatment. Targeted cancer therapies may be more effective than other types of treatment (including chemotherapy and radiotherapy which interfere with cancer cells as they divide into cancer cells) as the targeted therapies are designed to turn off a signal that tells cells to divide or delay cell growth. For patients whose tumours exhibit EGFR mutations, the response rate to Iressa® and Tarceva® is approximately 75%.³ Iressa® and Tarceva® inhibit downstream signalling by EGFR by crossing the cellular membrane and blocking the receptor's active site.

EGFR IN CLINICAL TRIALS

Three recent representative studies (INTEREST [Iressa NSCLC Trial Evaluating Response and Survival Versus Taxotere], IPASS [Iressa Pan-Asia Study], and SATURN) underscore the fact that the presence of EGFR mutation best identifies those who would derive the most benefit, as measured by progression free survival. The most suitable candidates to be tested for the mutation are females who are never-smokers or those with a remote smoking history with an adenocarcinoma. EGFR positive mutations are present in approximately 30-50% of East Asian and 10% of North American and Western European patients with NSCLC.²

IMPORTANCE OF TESTING FOR EGFR

- By testing for EGFR, clinicians can select the most appropriate treatment from the beginning for their patients and thus improve their overall long-term outcomes.
- Clinical trials have shown that patients with certain EGFR mutations derive significant benefit from TKIs while patients without these mutations gain more benefit from standard chemotherapy.⁴

REFERENCES

1. Rowinsky EK. (2004) The erbB Family: Targets for Therapeutic Development Against Cancer and Therapeutic Strategies Using Monoclonal Antibodies and Tyrosine Kinase Inhibitors. *Annu Rev Med.* 55:433-57.
2. Sharma SV et al. (2007) Epidermal Growth Factor Receptor Mutations in Lung Cancer. *Nature* 7: 169-181
3. Reilly GJ et al. (2006) Clinical Course of Patients with Non-Small Cell Lung Cancer and Epidermal Growth Factor Receptor Exon 19 and Exon 21 Mutations Treated with Gefitinib and Erlotinib. *Clin Cancer Res* 12: 839-844
4. Mok TK et al. (2009) Gefitinib or Carboplatin-Paclitaxel in Pulmonary Adenocarcinoma. *NEJM* 361: 947-957

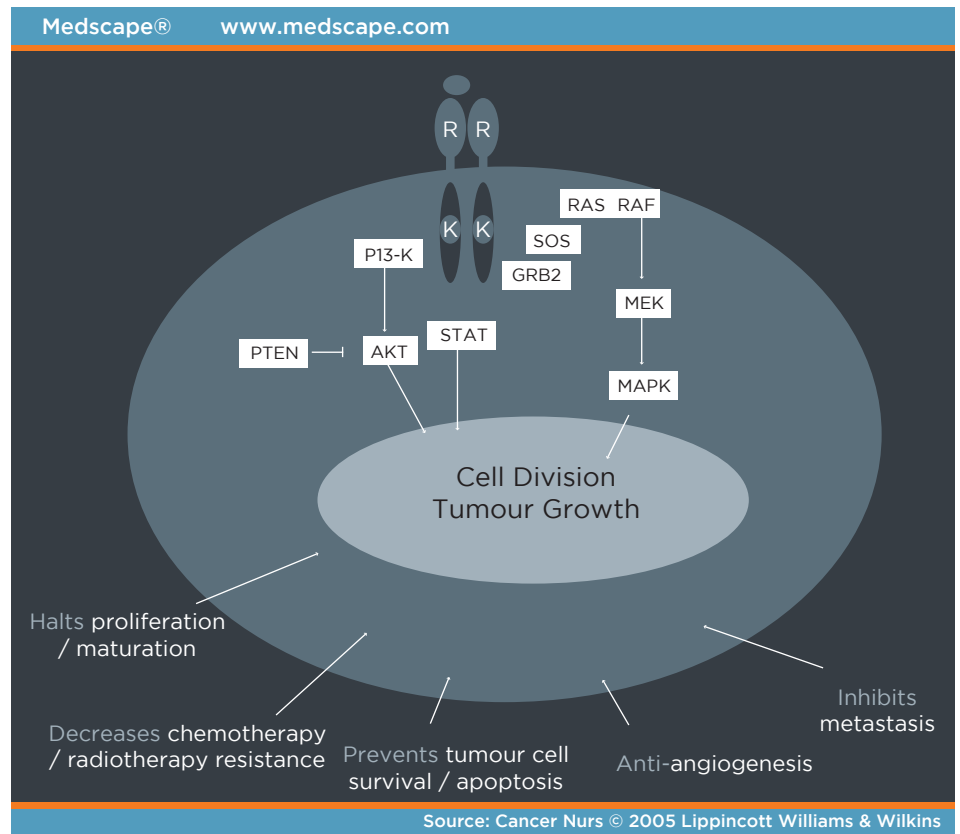


Figure 2: The role of TKIs. An overabundance of EGFRs (R) is located on various tumour cell types. EGFRs are the first step along a detailed signal transduction pathway that leads to cell division and tumour growth. Tyrosine Kinase Inhibitors block Tyrosine Kinase (K), thereby preventing further progression through the transduction pathway. As a result, cell division and tumour growth are stopped.

EGFR TESTING AT HEALTHSCOPE ADVANCED PATHOLOGY

- Formalin-fixed paraffin embedded tumour sample or seven unstained slides and one H & E stained section are required for mutation analysis.
- All the logistics in getting the tumour block to our laboratory for analysis is handled by our staff.
- Each sample undergoes a pathologist review to ensure that tumour cells are present and a macrodissection so to enrich tumour cells for analysis.
- To detect EGFR mutations, a highly sensitive nested PCR for exons 18-21 is performed. This is followed by DNA sequencing to analyse exons 18-21 of the EGFR gene. The advantage of using this technique is that all mutations may be detected.
- Results are available within 5-7 working days from sample receipt in the laboratory.
- Currently this test is not Medicare rebated but we are optimistic about reimbursement as the market becomes more aware of the value of such testing.