EGFR in Non-Small Cell Lung Cancer and its role as a targeted therapy

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Introduction

Until recently, all types of Non-Small Cell Lung Cancer (NSCLC), which account for 85-90% of lung cancers, were treated with cytotoxic chemotherapy which produces great toxicities owing to the lack of selectivity for tumor cells. Further understanding of molecular alterations was vital to introduce a new approach: the targeted therapy. Some of these mutations occur in the Epidermal Growth Factor Receptor (EGFR). EGFR signalling pathway has become an encouraging targeted therapy to improve outcomes in NSCLC patients.
This review will provide a fresh insight into the major progress toward the understanding of EGFR so far.

Methodology

Literature research based on theses and reviews found in PubMed and ISI Web of Knowledge. Main areas of research: EGFR NSCLC, mutations EGFR, EGFR-TKIs, targeted-EGFR therapy, acquired resistance EGFR, T790M.

Results

EGFR in NSCLC

EGFR gene encodes a ~170kDa glycoprotein bearing ligand-inducible kinase activity.The activation of EGFR is highly regulated to provide a correct development of cells.

Figure 1

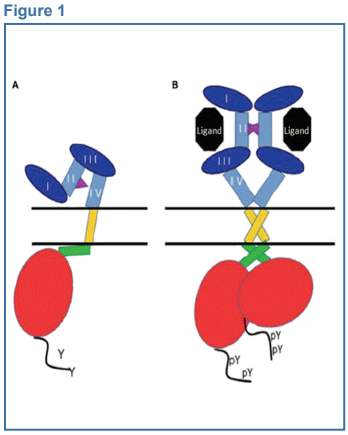

Figure 1: schematic view of the two conformations in the activation of EGFR. *A) Inactive conformation:* structure of the monomer prevents any interaction between ligand and receptor. *B) Active conformation:* ligand-bound receptor allows the dimerization with another monomer. Consequently, autophosphorylation of tyrosine kinase (TK) domain takes place and activation of the receptor occurs.

A wide range of biologic responses are mediated by the binding of different growth factors to EGFR receptors. However, an abnormal activation of the EGFR could be produced by: enhanced production of ligands, overexpression of the receptor and activating mutations. Those lead to downstream events stimulating five of the six hallmarks of cancer.

Figure 2

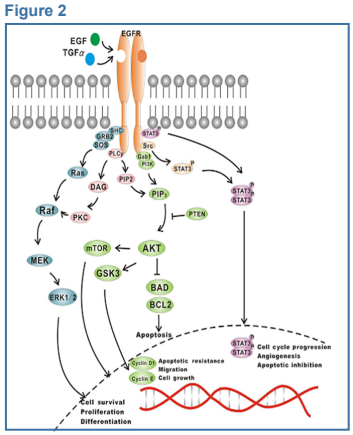

Figure 2: normal activation of EGFR and its downstream signalling pathways.

EGFR mutations

The discovery of somatic EGFR mutations was a very significant breakthrough in the understanding of NSCLC.

Clinical factors	• Women • Adenocarcinoma • Never-smokers • East Asia origin

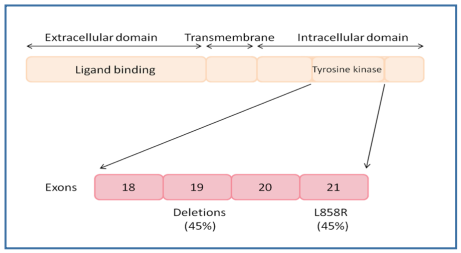

Figure 3: The most frequent mutations of EGFR which accounts for 90% of changes reported in this gene.

Oncogene addiction: EGFR-mutated cells require hyperactivated EGFR for its own survival → Key point for targeted therapy.

Total independence of ligand binding → Activation of downstream pathways → Promote cancer phenotype

TKIs: overcome EGFR mutations

Mutations on TK domain are the most reliable predictive biomarkers for the sensibility and the efficacy to Tyrosine Kinase Inhibitors (TKIs).

TKIs had superior outcomes in Overall Response Rates (ORR) and Progression Free Survival (PFS) compared with chemotherapy in NSCLC patients.

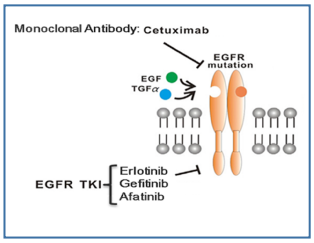

Figure 4: two major types of therapies against EGFR mutations.

Therapy	Drug	Target	Reversible or Irreversible	Stage of development	Toxicities
1st-generation TKI	Erlotinib	ATP cleft of TK domain	Reversible	FDA[1] approved EMA[2] approved	Nausea, rash, diarrhoea
	Gefitinib	ATP cleft of TK domain	Reversible	EMA approved	Nausea, rash, diarrhoea

Table 1: 1st-generation EGFR-TKIs. FDA[1]: Food and Drug Administration, EMA[2]: European Medicines Agency

Acquired resistance to TKIs

The overwhelming majority of patients bearing EGFR mutations inevitable become resistant to TKIs mostly within 6-12 months.

Main acquired resistances:

- Bypass signalling
- Histologic transformation
- T790M

- The most frequent resistance (50%)
- Aa substitution in exon 20
- Mechanism of action:
  - Modify ATP cleft of TK domain
  - Enhance ATP molecules affinity

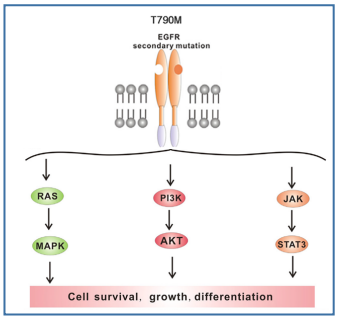

Figure 5: T790M leads to tumor progression.

TKIs: overcome T790M

Continuation of 1st-generation TKIs: to avoid a disease flare in select patients prior to initiation of a new therapy.

Table 2: 2nd and 3rd-generation EGFR-TKIs.

Therapy	Drug	Target	Reversible or Irreversible	Stage of development	Toxicities
2nd-generation TKI	Afatinib	EGFR, HER2, HER4	Irreversible	FDA approved EMA approved	Rash, diarrhoea, acne, nose bleed, dry skin
Block mutated and wild - type EGFR	Dacomitinib	EGFR, HER2, HER4	Irreversible	Phase III	Stomatitis, rash, diarrhoea, acne, fatigue
	Neratinib	EGFR, HER2	Irreversible	Phase II	Severe diarrhoea toxicity
3rd-generation TKI	AZD9291	Mutant EGFR	Irreversible	Phase I	Rash, nausea, diarrhoea, poor appetite
Target selectively T790M	CO-1686	Mutant EGFR	Irreversible	Phase II	Hyperglycemia, nausea, diarrhoea, fatigue

NEW APPROACH → *Dual inhibition:* TKI+ monoclonal Antibody
Afatinib+Cetuximab

Conclusion

Over the last decade, there have been significant advances in the identification of targeted-EGFR therapy to overcome EGFR mutations. However, the emergence of T790M is still one of the hindrances of NSCLC. The prevailing situation is focused on the establishment of the most suitable therapy to maximize efficacy and minimize toxicity with the hope that, in a not so distant future, we will be able to overcome NSCLC.

References

Fig 1: edited from Appert-Collin A, Hubert P, Crémel G, Bennasroune A. Front Pharmacol. 2015;6. **Fig 2,4,5:** edited from Huang L, Fu L. Acta Pharm Sin B. 2015;5(5):390-401. **Fig 3:** Carla Serra Pascual. **Table 1,2:** Data collection from 5 articles (information in detail provided in the assignment).