Role Of Epithelial–To–Mesenchymal Transition In Acquired Drug Resistance In Non–Small Cell Lung Cancer

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Introduction

Non–small cell lung cancer (NSCLC) accounts for the majority of the cases of lung cancer. Although being a very heterogeneous disease, 20% of NSCLC tumours harbour activating mutations at the epidermal growth factor receptor (EGFR). Patients carrying such mutations are treated with EGFR tyrosine kinase inhibitors (TKIs), which have demonstrated to longer overall survival.

However, patients who initially respond to EGFR TKIs will eventually develop drug resistance and relapse.

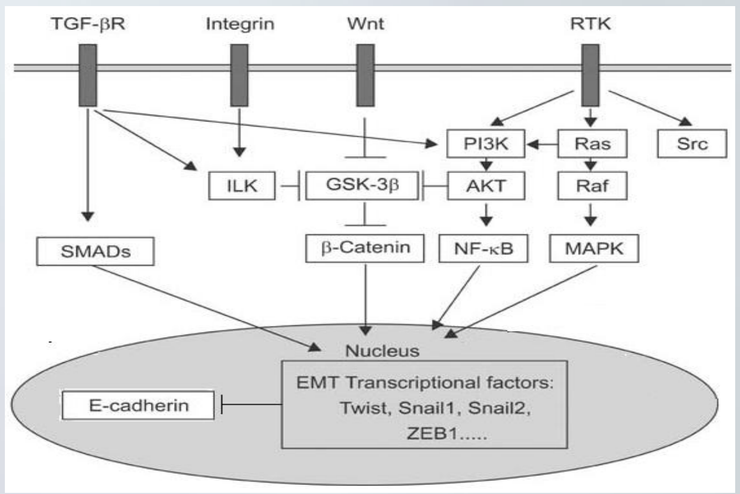
Epithelial to mesenchymal transition (EMT) is essential for acquiring drug resistance and promoting tumour metastasis in NSCLC, being both processes responsible for tumour progression and recurrence.

OBJECTIVES: to characterise EMT in NSCLC and its link with acquired drug resistance, especially focusing on the role of Met signalling pathway. Also, to review some of the therapies that are being currently developed to tackle with NSCLC.

EMT is characterised by:

- **Downregulation of E-cadherin**: it is responsible for epithelial cell–cell adhesion and the maintenance of cytoskeleton organisation.
- **Up-regulation of mesenchymal proteins** such as vimentin and N-cadherin.

These changes enable epithelial cells to acquire a more flexible and migratory phenotype, described as **EMT-like phenotype**, which promotes invasion and metastasis.



Adapted from: *Park SM, Kim SM, Han JH. The role of epithelial-mesenchymal transition in gastroenterology. Korean J Gastroenterol. 2010;56(2):69-77.*

There are various pathways that lead to an EMT-like phenotype, including tyrosine kinase receptors, integrins, Wnt or TGF-β. These signals activate transcriptional factors such as Snail 1, which repress the expression of E-cadherin and other cytokeratins → downregulation epithelial cell–cell adhesions and loss of cell polarity.

State Of The Art

EGFR In Non–Small Cell Lung Cancer

EGFR is part of the **HER family** of receptors, which consists of four members – EGFR, HER2, HER3 and HER4. Homo or heterodimerisation among them triggers proliferative and survival signals.

Activating mutations usually found on the tyrosine kinase domain of EGFR

↓

Constitutive activation and **oncogene addiction**

↓

Development of EGFR tyrosine kinase inhibitors – ***Erlotinib*** and ***Gefitinib***

(reversible competitive inhibitors of the ATP – binding site)

Acquired Resistance to TKIs

Resistance to TKIs can occur through:

- **Primary mechanisms:** K-Ras mutations present before treatment.
- **Secondary mechanisms** shortly acquired after the initiation of the therapy.

Acquired resistance to TKIs

- **T790M:** secondary point mutation in EGFR, located in the ATP –binding pocket
- **Kinase switch** and bypass signalling mechanisms: compensatory activation of other tyrosine kinase receptors to overcome EGFR addiction
- Acquisition of **EMT-like phenotype:** through paracrine and autocrine secretion of EMT – inducing signals
- **Cancer Stem Cells:** capable of self–renewing and differentiation into different cellular lineages

MET Signalling Pathway

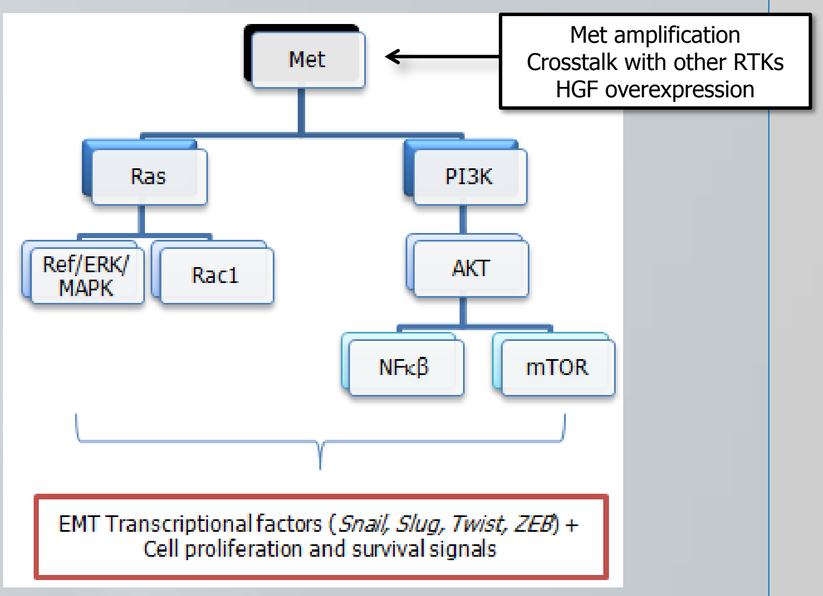
Met is a tyrosine–kinase receptor located at the surface of epithelial cells, which is activated by the binding of its natural ligand (HGF). In adult life, Met plays a role in tissue repair and organ regeneration, but also in human cancers – both in primary tumours and in cancer progression, as a secondary event that exacerbates malignant properties

Possible mechanisms leading to constitutive Met activation:

- **Transcriptional upregulation**: due to hypoxic conditions, Met transcription is activated and causes Met protein overexpression.
- **HGF overexpression**: HGF is a motility factor that can activate Met by autocrine or paracrine signalling.
- **Crosstalk with other RTKs:** in NSCLS, HER3 forms heterodimers with Met for the synergic activation of downstream modulators.
- **Met gene amplification**: it is more frequently amplified in metastatic tumours and as a secondary event in TKIs resistant tumours (5 – 25% of NSCLC with acquired TKIs resistance)

Activation of multiple signalling pathways associated to cell proliferation, survival, migration and invasion through various effectors, including mTOR, NFκβ, Rac1 and MAPK

In NSCLC, Met constitutive activation is likely to promote the acquisition of an EMT-like phenotype through these intracellular transducers:



Met aberrant activation attenuates NSCLC addiction to EGFR signalling, eliminating the anti- tumour potency of EGFR TKIs. However, alternative mechanisms of cell survival and proliferation may appear after acquiring the mesenchymal phenotype (Axl, FGFR...).

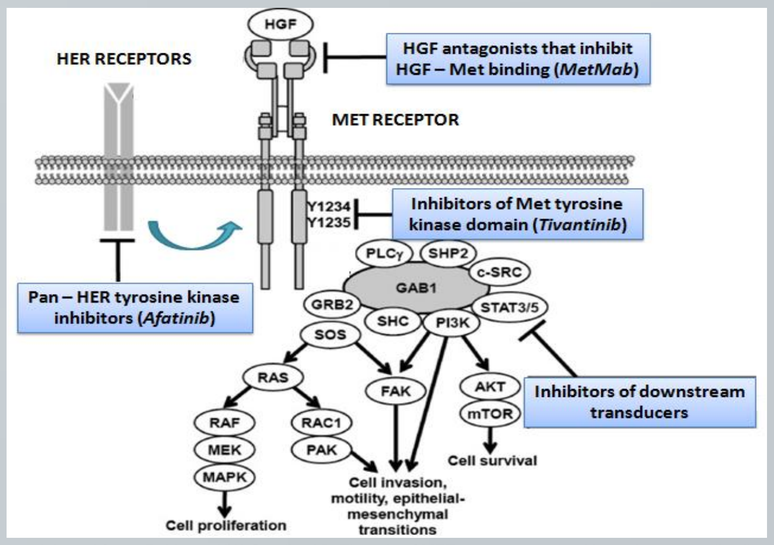
Prospective Therapies

Met is one of the major contributors to the EMT-like phenotype, which is in turn essential for tumour invasion, metastasis and drug resistance. Therefore, **Met signalling is a potential target** to block tumour growth and drug resistance.

Therapeutic approaches that are being currently tested:

- ***MetMab***: Anti–Met monoclonal antibody that acts as an antagonist of HGF.
- ***Tivantinib***: Met tyrosin kinase inhibitor selective for the closed conformation of the kinase domain.
- ***Afatinib***: Pan–HER inhibitor that covalently binds to the tyrosin kinase domain of EGFR, HER2, HER3 and HER4.

Although the initial phases of the studies demonstrated promising clinical activity, phase III results don't show any benefit on the overall survival of NSCLC patients.



Adapted from: *Robinson KW, Sandler AB. The role of MET receptor tyrosine kinase in non-small cell lung cancer and clinical development of targeted anti-MET agents.Oncologist. 2013;18(2):115-122.*

Combining treatments that target several molecules, or targeting downstream signalling transducers, could address the common problem of crosstalk between signalling pathways.

The most promising strategy in preclinical models is the dual use of Met inhibitors and EGFR TKIs in tumours displaying Met gene amplification

Conclusions

- Failure of phase III trials of the most promising Met inhibitors have put into doubt the potential anti – cancer effect of this therapy → It is essential to develop good biomarkers to stratify NSCLC patients into subgroups that could benefit from each therapy
- Combination of EGFR tyrosine–kinase inhibitors and anti – Met therapies is emerging as a promising approach to improve overall survival of NSCLC patients
- Anti–cancer therapies should focus on targeting cancer stem cells to eradicate any chance of relapse → Met inhibitors would not be a definitive solution

EMT–like phenotype in NSCLC, acquired by Met aberrant signalling, is a determinant of marked insensitivity to EGFR TKIs. Targeting both Met and EGFR signalling pathways will hinder the early emergence of drug resistance, but they will not probably prevent from an eventually relapse

Methodology

Most data has been taken from scientific articles and reviews that are found in PubMed. To perform the search, some key words were used to select the most useful articles: *epithelial–to–mesenchymal transition*, *non–small cell lung cancer*, *acquired drug resistance*, *EGFR tyrosine–kinase inhibitors*, *Met signalling*, *Met inhibitors*. In addition, publication date and journal were taken into account.