

Understanding the Biology Behind the EGFR to Improve NSCLC Patients' Treatment

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Abstract

Epidermal growth factor receptor (EGFR) is a member of the EGFR tyrosine kinase family, which consists of EGFR (erbB1/Her1), Her2/neu (erbB2), Her3 (erbB3) and Her4 (erbB4). HER receptors are ubiquitously expressed in various cell types, under homeostatic conditions, receptor activation is tightly regulated by the availability of ligands, which collectively form the EGF family.

Keywords: Angiogenesis; Mutant tumours; Endothelial growth; Lung cancer

Introduction

Several intra cellular pathways are tightly connected to the EGFR status, among them the two main signalling pathways activated by GFR include the ras/raF/meK/erK and the Pi3K/aKt axes; however, Src tyrosine kinases, PI3 γ , PKC, and STAT activation and downstream signalling have also been well documented [1,2].

Literature Review

A direct link between EGFR activation and angiogenesis has been described. EGFR activation can contribute to the production of several proangiogenic factors in tumours, including VEGF and basic fibroblast growth factor [3,4].

Tumours that harbour activated oncogenes show often dependence on the prolonged activity of oncogenes and to the signalling pathways which makes them sensitive to drugs that target such pathways [5,6].

Several approaches have been developed to target the EGFR to interfere with EGFR-mediated cellular effects and the most utilised are monoclonal antibodies directed against the extracellular receptor domain and small-molecule compounds that interfere with intracellular EGFR tyrosine kinase activity [7].

Despite the initial response to such treatments virtually all the patients carrying an EGFR mutated progress. Several resistant mechanisms have been identified reflecting nonuniform response to treatment and a possible role for intratumor heterogeneity [8].

The response rate (RR) to the Tyrosine Kinase Inhibitors (TKIs) in patients with EGFR-mutated about 75%, which indicates a 25% of primary resistance to such treatments.

Several mutations, even within exons 18 to 21, the most common site for mutations, could be responsible for primary resistance to EGFR TKIs (e.g. small insertions or duplications in exon 20) [9]. *In vitro* and *in vivo* studies have shown that such mutations are less sensitive to EGFR TKIs than the exon 19 deletion and L858R mutants [10,11].

Another possible mechanism of resistance is the presence of other genetic lesions that affect signaling downstream of EGFR such as PI3K mutations, loss of PTEN and crosstalk between EGFR and insulin-like growth factor receptor 1 (IGF1R) [12-14].

A well-known mechanism of acquired resistance to TKIs in EGFR mutated non-small cell lung cancer (NSCLC) patients (incidence up to 50%) is the development of a second-site mutation in the threonine gatekeeper residue at position 790, T790M [15]. Interestingly in 2011 Rosell et al. found that in 35% of patients with EGFR mutated NSCLC the T790M mutation can be detected prior to EGFR TKI treatment [16].

Discussion

In preclinical model of adenocarcinoma with exon 21 missense mutation (L858R) and exon 20 missense mutation (T790M) the combination of gefitinib with the vascular endothelial growth factor (VEGF) inhibitor bevacizumab was showed to inhibit tumour growth [17] and to overcome the primary resistance to TKIs. Level of signal transducer and activator of transcription 3 (STAT3) are increased almost immediately after starting erlotinib treatment in EGFR-mutant NSCLC cells [18]. Furthermore, STAT3 activation through IL-6R and FGFR, in response to inhibition of an oncogenic kinase might significantly contributes to resistance of the cell population to drug treatment and consequently limits the efficacy of such agents [19]. It was also noted to play a key role in the interleukin 6 induced expression of VEGF in cervical cancer. VEGF was found to be inhibited by blocking STAT3 or by treatment with an anti-VEGF antibody [20]. IL-6 also play an essential role in activating the Scr family kinase and subsequently YES-associated protein 1 (YAP1) [21]. In a recent publication Chaib et al. [22] showed that Scr-YAP1 signalling limits EGFR TKI response, in conjunction with STA3, in lung cancer. This has strengthened the idea that EGRF TKI monotherapy is inadequate for NSCLC patients EGFR mutant. The co-activation of a broader network of signalling events limits the EGFR response.

Conclusion

Based on those findings combining EGFR-TKIs with VEGF-neutralising antibodies might potentially delay or even inhibit the development of resistance driven by the interleukin 6-STAT3-VEGF pathway in EGFR-mutant NSCLC and represents a new therapeutic approach that is warranted clinical studies.

Conflict of Interest

Both the authors declare no conflict of interests.

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