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Review Article

The biology of Epidermal Growth Factor Receptor (EGFR) from regulating cell cycle to promoting carcinogenesis: the state of art including treatment options

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Abstract

The current definition of cancer is the creation of atypical cells capable to rapidly grow beyond the normal boundaries and spread to distant organs. To do so tumour cells have to acquire to the ability to proliferate continuously and avoid apoptosis. An important role in this process is played by growth factors and their receptors. Amongst many, one of the most important interaction is between the Epidermal growth factor (EGF) and its receptor (EGFR) which are frequently mutated or upregulated in human cancers particularly in non-small cell carcinoma of the lung (NSCLC). The biding leads to protein activation, cell proliferation and decreased apoptosis. However, in this subset of tumours, the blockage of this interaction by EGFR-targeting drugs has shown an overall outcome improvement leading to the era of target therapy. The result is that patients are now routinely screened for a series of actionable mutations to be given the best possible therapy available for their specific type of tumour limiting the side effect of broad-spectrum chemotherapy. This paper will review the biology of EGFR receptor, the type and role of its mutation and the clinical implication for patients with NSCLC harbouring these mutations.

Abbreviations

EGF: Epidermal Growth Factor; EGFR: Epidermal Growth Factor Receptor; NSCLC: Non-small Cell Carcinoma of the Lung; RTKs: Receptor Tyrosine Kinases; HGF: Hepatocyte Growth Factor; IGF1R: Insulin-like Growth Factor 1 Receptor; FDA: Food and Drug Administration.

Review of the Literature

Structure and function of egfr

Receptor Tyrosine Kinases (RTKs) are cell surface receptors for many ligands such as polypeptide growth factors, cytokines, and hormones for which they have a high affinity [1]. So far 58 RTKs have been identified which are distributed in 20 families and amongst those, the Epidermal Growth Factor Receptor (EGFR) and its other family members (erbB2/ HER2, erbB3/ HER3, erbB4/HER4) have been discovered to play an important role in signalling and cancerogenesis [1]. These receptors can initiate intracellular signalling regulating cell proliferation and survival [2]. The mechanisms through which this happens and can be targeted by specific drugs is related to the structure and biology of the receptor itself [3]. The EGFR gene is located on the short arm of chromosome 7 (7p11.2) and encodes a 170-kDa type I transmembrane growth factor receptor with tyrosine kinase activity. All these trans-membrane proteins are composed of an extracellular ligand-binding domain, a transmembrane lipophilic domain, and an intracellular tyrosine kinase domain and all bind to receptor-specific ligands except HER2 [4].

After biding with its specific ligand, the receptor undergoes dimerization (homo or heterodimerisation according to the type of the other receptor involved in the process). The subsequent phosphorylation of the key tyrosine residues within the COOH-

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term portion creates a docking site for proteins containing Src homology2 and phosphotyrosine-binding domains [5,6]. These proteins activate intracellular signalling by many different pathways: the RAS/RAF/MEK/MAPK pathway, the Phospatidylinositol3-kinase (PI3K)/PTEN/AKT pathway, Phospholipase Cγ and the Signal Transducers and Activators of Transcription (STAT) pathway. Depending on which of these pathways is activated, the final effect is cell proliferation or inhibition of apoptosis [7,8]

The RAS/RAF/MEK/MAPK pathway regulates cell proliferation and survival through the activation of mitogen-activated protein kinases (MAPKs) which migrate in the nucleus and phosphorylate transcription factors involved in cell proliferation [8,9] MAPKs are activated through phosphorylation by Raf-1 which is activated by Ras-GTP after recruitment by Sos [10,11]. Sos is capable to recruit Ras-GDP and activate it to Ras-GTP because of a conformational change following EGFR phosphorylation which creates a docking site for Sos and the adaptor protein Grb2 [12,13].

The PI3K/PTEN/AKT pathway has been linked to cell growth, apoptosis resistance, migration and invasion [8,14]. PI3K is a dimeric enzyme containing a subunit (p85) responsible for binding a docking site present on HER-3 and another subunit (p110) that generate second messengers capable to phosphorylate and activate Akt. Although EGFR doesn't have docking site for p85 it can activate PI3K through dimerization with HER-3 (14). Other pathways involve direct interaction between Phospholipase Cγ and EGFR causing activation of Protein kinase C and subsequent MAPK activation [2,8], or another possibility is the interaction between STAT proteins with their consequent dimerization through their Src homology 2 domains following EGFR activation. The results are their migration into the nucleus and activation of transcription factors promoting cell survival, whereas constitutive activation of STAT proteins has been found in numerous primary cancers [15].

The Role of egfr mutations in cancerogenesis

All these effects are initiated by EGFR activation which can happen in three ways: ligand-dependent activation, ligand-independent activation and overexpression. Six EGFR ligands have been identified which causes the dimerization of the receptor and its autophosphorylation [2,16]. On the contrary, ligand-independent activation is caused by stress such as radiation and finally overexpression of the EGFR which is mediated with interaction with integrins [2].

EGFR has long been studied with important discoveries regarding its role in cell signalling and potential oncogenic role dated back in the 1980s [17,18].

Through the years and with a better understanding of those pathways [19], it has been recognised that EGFR plays an important role in tumorigenesis with at least three different mechanisms: overexpression of EGFR ligands, receptor amplification or activating mutation of EGFR [20]. The overall effect is the acquired ability of cells to proliferate continuously and avoid apoptosis which is one of the hallmarks of cancer described by Hanahan and Weinberg [21,22]. This involves bypassing a series of check-point that control the main phases of the replication cycle such as cell size control, DNA damage responses or monitoring DNA replication [23]. Besides playing an important role in initiating tumorigenesis in many solid tumours, genetic alteration of growth factor receptors has also clinical relevance in particularly in a subtype of carcinoma of the lung were is considered a predictive marker [24].

Types, frequency and effect of egfr mutations

In their comprehensive metanalysis, Pao, et al. [20], have summarised all type of mutations affecting EGFR tyrosine kinase domain known to date.

According to their review, 85.9% of the mutations reported happening in two "hot spots" in the EGFR gene between exon 19 and exon 21.

Exon 19 encodes highly conserved amino acids (LREA) which in the majority of those mutations (55.8%) are eliminated by multi-nucleotide in-frame deletions. This occurs in the activation loop, adjacent to a highly conserved DFG motif [25]. The remaining 44.2% of mutation are point mutations on exon 21 causing substitution between leucine and arginine at position 858 (L858R). The rest of the mutations amounting to 14.1% includes non-synonymous mutations between exons 18-21, a multi-nucleotide in-frame deletion in exon 19 downstream LREA and ultimately in-frame duplications/insertions in exon 20 [20]. It has been postulated that all these mutations lead to conformational change (for example affecting the alfa C-helix or phosphate-binding loop) resulting in increased activity of the receptor and some cases to sensitivity to TK inhibitors [26-28]. In their study Shan et al. have gone into the depth of how mutations affect the receptor structure and function [29]. They started from the observation that the extracellular domain has a very low tendency for dimerisation in the absence of interaction with its ligand [30]. Then they described the conformational changes of the receptor, adding new data to those previously reported [31-33].

Amongst those, Zhang et al. described how asymmetric dimers are created upon stabilisation of one EGFR kinase (the receiver) by another EGFR kinase (the activator) through the placement of the alpha-C helix in a way that the catalytic KE salt bridge between Lys721 and Glu738 is maintained (alphaC-inactive) [33]. However, EGFR can adopt also alphaC-out active conformation where the above-mentioned bridge is broken and the receptor is inactive [31,32]. Shan et al. have shown a third conformation, in which EGFR kinase exhibits a partial unfolding at the alphaC helix or local intrinsic disorder [29]. Intrinsic disorder has been shown to have an important role for the function of proteins [34] and the experiment conducted by Shan et al. not only enforced this concept but showed a possible mechanism through which EGFR mutations can act as a cancer promoter. The authors focused on how L834R mutation may cause aberrant activity by suppressing the local intrinsic disorder, increasing the dimerization affinity of the receptor and lowering the threshold for its activation [29]. This is

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supported by the higher dimerisation affinity that the mutant receptor as compared to the wild-type counterpart. Eventually, they also discussed the possibility of lateral signal propagation involving the cytoplasmic portion of the receptor which happens during the dimerisation through the phosphorylation of a tyrosine residue (tyr845) in the activation loop which suppresses the intrinsic disorder [29].

Targeting egfr mutations: the advent of tyrosine kinase Inhibitors

The investigation of the structure of EGFR during the early 1990s, initially led to the identification of a new molecule: gefitinib, an anilinoquinazoline with antineoplastic activity targeting the EGFR-TK activity and other similar receptors [35]. Gefitinib inhibits the catalytic activity of other tyrosine kinases, which may result in inhibition of tyrosine kinase-dependent tumour growth. It competes with the binding of ATP to the tyrosine kinase domain of EGFR and inhibits receptor autophosphorylation. The final result is inhibition of signal transduction, cell cycle arrest and inhibition of angiogenesis [35,36]. The growth inhibition was particularly seen in different solid tumours including lung, prostate, breast, colon and ovarian cancer in preclinical studies of cell lines and human tumour xenografts [37]. The results seen in the treatment of NSCLC led to two clinical trials (IDEAL 1 and 2) and in 2003 the drug received US Food and Drug Administration approval in patients with advanced NSCLC as monotherapy treatment after failure of standard chemotherapy regimen [20]. At this time the role of a second molecule, a quinazoline derivative (erlotinib), was also investigated. Similarly, to the previous inhibitor described, erlotinib is an orally ATP- competitive inhibitor capable to block EGFR phosphorylation and delay tumour growth. It has also been shown to block the cell cycle in G1, to reduce RB phosphorylation and to induce apoptosis [20]. It gained FDA approval a year later (2004) for the treatment of patients with disease progression at least after one cycle of chemotherapy [38].

All EGFR TKIs competitively block the binding of ATP to the catalytic site in the tyrosine kinase domain of EGFR, subsequently inhibiting autophosphorylation. The binding is reversible for gefitinib and erlotinib whilst afatinib, a second-generation TKI has an irreversible binding [39].

Overcoming egfr tki resistance

Despite promising results, the response to these inhibitors was different amongst the patients therefore additional studies were conducted focusing on how to improve patient selection for these treatments [20]. A milestone, of course, was the discovery of somatic driver mutations in EGFR which led to a drastic shift in the clinical management of NSCLC from standard chemotherapy to precision medicine [38]. Additional studies and clinical trials (most relevant was IPASS study) were carried out and the most important finding was that presence of EGFR mutation is the best rationale to select patients to treat with TKI rather than clinic-pathological parameters [40]. Nevertheless, a higher frequency of those mutations was reported in Asiatic female, never smoker and with adenocarcinoma as histological type [40]. Even though most NSCLC patients harbouring TKI-sensitizing EGFR mutations show an initial pronounced response to EGFR-TKI treatment, they acquire resistance to these drugs after ~9 to 14 months of such therapy [38]. Many studies have been conducted to investigate the underlining mechanisms of acquired resistance to EGFR-TKIs: Amongst these are mutation in exon 20 of EGFR, MET amplification, overexpression of hepatocyte growth factor (HGF), and activation of the Insulin-like Growth Factor 1 Receptor (IGF1R) [41].

The T790M mutation of EGFR is the most common mechanism of such an acquired resistance, having been detected in up to 50% of patients treated with either the first-generation EGFR-TKIs (erlotinib or gefitinib) or in patients receiving first-line treatment with the second-generation EGFR-TKI (afatinib) [42]. This point mutation which involves a threonine-to-methionine substitution in exon 20, increases the affinity of EGFR for ATP and consequently reduces the binding efficacy of EGFR-TKIs: the clinical implication is poor clinical outcomes in patients treated with EGFR-TKIs [43]. In 2009 Zhou et al. studied three closely related pyrimidines (WZ3146, WZ4002, and WZ8040) to specifically target the T790M mutation and spare the WT-EGFR [44]. Despite one of the three compounds being very effective (WZ4002), it was never developed into a commercial drug (38). Osimertinib was recently approved for patients with T790M mutation resistance to a first- or second-generation EGFR TKI and is the only commercially available third-generation EGFR TKI. It has been approved by the FDA in 2017 for the treatment of metastatic EGFR T790M mutation-positive NSCLC, as detected by the FDA-approved test, and disease progression during or after EGFR TKI therapy [38]. In a randomized phase III trial (AURA 3), osimertinib was compared with standard chemotherapy (platinum-based doublet chemotherapy) in patients with T790M-positive lung cancer [45]. The results reported by Mok et al. showed better progression-free survival and less toxicity of osimertinib compared to chemotherapy. Therefore patients experiencing failure after a first-line EGFR TKI should be tested for the presence of a T790M mutation and considered for third-line TKI. Following these results, osimertinib was compared to a first-generation EGFR TKI as a first-line treatment for EGFR mutation-positive NSCLC in the FLAURA trial. This study demonstrated a significant improvement in Progression-Free Survival (PFS) with osimertinib [46] and it obtained from FDA an additional indication for the first-line treatment of patients with metastatic NSCLC positive for exon-19 deletions or the L858R point mutation of EGFR.

However, management of this subset of patients is still controversial and ongoing research is investigating also the role of immunotherapy in this population.

Egfr and beyond: Is there a rationale for combined therapies?

Many authors have been investigating the relationship between EGFR mutation and the presence of other molecular alterations or immunohistochemical expression of other proteins. The most important are Anaplastic Lymphoma

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Kinase (ALK) and ROS-1 which are often rearranged in NSCLC: in 2007 the first reports of the expression of oncogenic EML4-ALK and SLC34A2/CD74-ROS fusion proteins in lung cancer came out [47,48]. Although oncogenic ALK and ROS1 gene rearrangements in NSCLC are only found in respectively 4% and 2%, there are three drugs (crizotinib, ceritinib, and alectinib) available for the treatment of ALK-rearranged lung tumours, and one drug (crizotinib) is for ROS1-rearranged tumours [49]. Crizotinib became the first ALK inhibitor to receive FDA approval for the treatment of patients with ALK-positive metastatic NSCLC in November 2013 [49]. Other relevant markers which have been investigated are BRAF, MET, RET, ERBB2 (HER2), and KRAS, ERCC1 but currently, no therapy is formally approved [50,51]. EGFR, KRAS, and ALK mutations in NSCLC are mutually exclusive and the presence of one or another can influence response to targeted therapy [52,53]. More recently the focus has been shifted towards the relationship between EGFR and immunotherapy.

Immunotherapy has become another important treatment for NSCLC. In particular, complete activation of T-cells is regulated by direct recognition of antigen through major histocompatibility complex or can be mediated by the antigen-presenting cells and their costimulatory molecules. T-cells can also be negatively regulated as in the cytotoxic T-lymphocyte-associated antigen-4-B7 (CTLA4-B7) pathway and the programmed cell death protein-1 (PD-1)/programmed cell death protein-ligand 1 (PD-L1) pathway. PD-1 is an important immunological checkpoint that can inhibit the activation of T cells and the production of cytokines by binding to its two ligands, PD-L1 and PD-L2. Tumour cells can escape the immune system by upregulating PD-L1 expression and binding to PD-1 on the surface of tumour-specific CD8+ T cells to limit the host's immune response, therefore blockade of the PD-1/PD-L1 signalling pathway using monoclonal antibodies has been investigated in many solid tumours with promising results [54,55]. To date, the FDA has approved multiple anti-PD-1/PD-L1 antibodies for first- and second-line treatment of patients with advanced NSCLC and clinical prognosis has significantly improved [56,57]. Pembrolizumab, the first one approved, is used in combination with carboplatin and pemetrexed for first-line combination therapy as well as for first-line treatment of metastatic non-squamous cell NSCLC(58). However, immunotherapy is only effective for a small number of patients and despite initial response, some of them show a subsequent rapid disease progression. Therefore, clinical trials and further studies on biomarkers are on-going to understand how to better identify patients more likely to respond. But the very big question is whether combined immunotherapy and treatment with TKI can be an option.

Liang and colleagues in their review have given an excellent insight on preclinical studies and clinical trials related to this topic. It has been demonstrated that activation of the EGFR pathway can upregulate the expression of PD-1, PD-L1, and CTLA-4 through p-ERK1/2p-c-Jun, leading to the apoptosis of T cells in the tumour-associated microenvironment (TEM). This brings a state of immunosuppression and the escape of malignant cells from the host immune response [59]. EGFR TKIs besides killing tumour cells enhances the immune response and inhibit the expression of NF-KB reducing the expression of PD-1/PD-L1 [59]. Hence, these preclinical studies that the authors have summarised suggest the use of EGFR-TKIs in combination with immunotherapy to improve clinical outcomes in patients with EGFR positive NSCLC, accompanied by upregulation of PD-L1 expression. However, when translated in a clinical trial the results are not as good and so sharply demarcated. Some early clinical studies confirmed the efficacy of immunotherapy in patients with EGFR-mutant NSCLC; however, toxicity is the main limiting factor (ILD incidence and alanine aminotransferase/aspartate aminotransferase elevated levels resulted in treatment failure). On the contrary results from large randomized Phase III clinical trials have not demonstrated clinical benefit from this combined treatment. The reasons are difficult to understand given the association with smoking history, lymphocytic infiltrate and tumour mutation burden amongst other variables [59].

Conclusion

EGFR and its ligand have a pivotal role in controlling cell proliferation and somatic mutations of the receptor can lead to neoplastic transformation. However, in a subset of lung cancers, the presence of these mutations can be targeted by specific drugs. In clinical practice patients are now routinely tested for predictive biomarkers making precision medicine a reality. Despite many clinical trials showing better efficacy and fewer side effects in patients treated with TKIs compared to standard chemotherapy, many questions are still unanswered. For example, how to better tailor the treatment of WT-EGFR lung cancer or those with T790M germline mutation. Research is still ongoing and immunotherapy seems to be a promising option, however, their role and its association with TKIs in EGFR positive NSCLC has still to be addressed.

References

1. Robinson DR, Wu YM, Lin SF (2000) The protein tyrosine kinase family of the human genome. Oncogene 19: 5548-5557. Link: https://bit.ly/2WiXuYL
2. Scaltriti M, Baselga J, (2006) The Epidermal Growth Factor Receptor Pathway: A Model for Targeted Therapy. Clin Cancer Res 12: 5268-5272. Link: https://bit.ly/3c8W3CQ
3. Hynes NE, Lane HA (2005) ERBB receptors and cancer: The complexity of targeted inhibitors. Nat Rev Cancer 5: 341-354. Link: https://bit.ly/3d9BWVy
4. Normanno N, De Luca A, Bianco C, Strizzi L, Mancino M, et al. (2006) Epidermal growth factor receptor (EGFR) signalling in cancer. Gene 366: 2-16. Link: https://bit.ly/2KUri92
5. Yarden Y, Sliwkowski MX (2001) Untangling the ErbB signalling network. Nat Rev Mol Cell Biol 2: 127-137. Link: https://bit.ly/35msLOM
6. Ono M, Kuwano M (2006) Molecular Mechanisms of Epidermal Growth Factor Receptor (EGFR) Activation and Response to Gefitinib and Other EGFR-Targeting Drugs. Clin Cancer Res 12: 7242-7251. Link: https://bit.ly/35ogGbP
7. Bromberg J (2002) Stat proteins and oncogenesis. J Clin Invest 109: 1139-1142. Link: https://bit.ly/2yXUXvb
8. Wee P, Wang Z (2017) Epidermal growth factor receptor cell proliferation signalling pathways. Cancers 9. Link: https://bit.ly/2WhSdkq

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9. Gaestel M (2006) MAPKAP kinases - MKs - Two's company, three's a crowd. Nat Rev Mol Cell Biol 7: 120-130. Link: https://bit.ly/3d2po1Y

10. Hallberg B, Rayter SI, Downward J (1994) Interaction of Ras and Raf in intact mammalian cells upon extracellular stimulation. J Biol Chem 269: 3913-3916. Link: https://bit.ly/3aWpWVF

11. Liebmann C (2001) Regulation of MAP kinase activity by peptide receptor signalling pathway: Paradigms of multiplicity. Cell Signal 13: 777-785. Link: https://bit.ly/3bYHhPh

12. Lowenstein EJ, Daly RJ, Batzer AG, Li W, Margolis B, et al. (1992) The SH2 and SH3 domain-containing protein GRB2 links receptor tyrosine kinases to ras signalling. Cell 70: 431-442. Link: https://bit.ly/2WnwuY8

13. Batzer AG, Rotin D, Ureña JM, Skolnik EY, Schlessinger J (1994) Hierarchy of binding sites for Grb2 and Shc on the epidermal growth factor receptor. Mol Cell Biol 14: 5192-5201. Link: https://bit.ly/3faTrXh

14. Vivanco I, Sawyers CL (2002) The phosphatidylinositol 3-kinase-AKT pathway in human cancer. Nat Rev Cancer 2: 489-501. Link: https://bit.ly/2ynq9nJ

15. Shuai K (2000) Modulation of STAT signalling by STAT-interacting proteins. Oncogene 19: 2638-2644. Link: https://bit.ly/2Ss1YLK

16. Burgess AW, Cho HS, Eigenbrot C, Ferguson KM, Garrett TPJ, et al. (2003) An open-and-shut case? Recent insights into the activation of EGF/ErbB receptors. Mol Cell 12: 541-552. Link: https://bit.ly/35pBgbK

17. Hunter T, Cooper JA (1981) Epidermal growth factor induces rapid tyrosine phosphorylation of proteins in A431 human tumor cells. Cell 24: 741-752. Link: https://bit.ly/2ylsejR

18. Anderson SM, Hayward WS, Neel BG, Hanafusa H (1980) Avian erythroblastosis virus produces two mRNA's. J Virol 36: 676-683. Link: https://bit.ly/2WnkmXn

19. Tynan CJ, Lo Schiavo V, Zanetti-Domingues L, Needham SR, Roberts SK, et al. (2016) A tale of the epidermal growth factor receptor: The quest for structural resolution on cells. Methods 86-93. Link: https://bit.ly/3aZE2pg

20. Pao W, Miller VA (2005) Epidermal growth factor receptor mutations, small-molecule kinase inhibitors, and non-small-cell lung cancer: Current knowledge and future directions. J Clin Oncol 23: 2556-2668. Link: https://bit.ly/2KT52fz

21. Hanahan D, Weinberg RA (2000) The hallmarks of cancer. Cell 100: 57-70. Link: https://bit.ly/2zRl5s9

22. Hanahan D, Weinberg RA (2011) Hallmarks of cancer: the next generation. 144: 646-674. Link: https://bit.ly/35n12xg

23. Barnum KJ, O'Connell MJ (2014) Cell cycle regulation by checkpoints. Methods Mol Biol 1170: 29-40. Link: https://bit.ly/2z4HWjm

24. (2017) The impact of EGFR mutations on the prognosis of resected non-small cell lung cancer: A meta-analysis of literature. Ann Oncol.

25. Huse M, Kuriyan J (2002) The conformational plasticity of protein kinases. Cell 109: 275-282. Link: https://bit.ly/2KTTnNy

26. Lynch TJ, Bell DW, Sordella R, Gurubhagavatula S, Okimoto RA, et al. (2004) Activating mutations in the epidermal growth factor receptor underlying responsiveness of non–small-cell lung cancer to gefitinib. N Engl J Med 350: 2129-2139. Link: https://bit.ly/2xsJNyf

27. Paez JG, Jänne PA, Lee JC, Tracy S, Greulich H, et al. (2004) EGFR mutations in lung, cancer: Correlation with clinical response to gefitinib therapy. Science 304: 1497-1500. Link: https://bit.ly/3fiqvNd

28. Honegger AM, Dull TJ, Felder S, Van Obberghen E, Bellot F, et al. (1987) Point mutation at the ATP binding site of EGF receptor abolishes protein-tyrosine kinase activity and alters cellular routing. Cell 51: 199-209. Link: https://bit.ly/3bWvn8B

29. Shan Y, Eastwood MP, Zhang X, Kim ET, Arkhipov A, et al. (2012) Oncogenic mutations counteract intrinsic disorder in the EGFR kinase and promote receptor dimerization. Cell 149: 860-870. Link: https://bit.ly/2SuhSFo

30. Odaka M, Kohda D, Lax I, Schlessinger J, Inagaki F (1997) Ligand-binding enhances the affinity of dimerization of the extracellular domain of the epidermal growth factor receptor. J Biochem 22: 116-121. Link: https://bit.ly/2Wi4i9b

31. Jura N, Endres NF, Engel K, Deindl S, Das R, et al. (2009) Mechanism for Activation of the EGF Receptor Catalytic Domain by the Juxtamembrane Segment. Cell 137: 1293-1307. Link: https://bit.ly/35r8LKE

32. Wood ER, Truesdale AT, McDonald OB, Yuan D, Hassell A, et al. (2004) A Unique Structure for Epidermal Growth Factor Receptor Bound to GW572016 (Lapatinib). Cancer Res 64: 6652-6659. Link: https://bit.ly/2KT6L4x

33. Zhang X, Gureasko J, Shen K, Cole PA, Kuriyan J (2006) An Allosteric Mechanism for Activation of the Kinase Domain of Epidermal Growth Factor Receptor. Cell 125: 1137-1149. Link: https://bit.ly/2VWy4kQ

34. Dunker AK, Brown CJ, Lawson JD, Iakoucheva LM, Obradović Z (2002) Intrinsic disorder and protein function. Biochemistry 41: 6573-6582. Link: https://bit.ly/2z5WH5O

35. Ward WHJ, Cook PN, Slater AM, Davies DH, Holdgate GA, et al. (1994) Epidermal growth factor receptor tyrosine kinase. Investigation of catalytic mechanism, structure-based searching and discovery of a potent inhibitor. Biochem Pharmacol 48: 659-666. Link: https://bit.ly/2KPFKyY

36. Ae W, Sp G, Wakeling AE, Guy SP, Woodburn JR, et al. (2002) Order Information cancer therapy ZD1839 (Iressa): An Orally Active Inhibitor of Epidermal Growth Factor Signaling with Potential for Cancer Therapy. Cancer Res

37. Sirotnak FM (2003) Studies with ZD1839 in preclinical models. Semin Oncol 30: 12-20. Link: https://bit.ly/3d6S4H3

38. Tony SM, Carbonr PD, Hirsch FR (2017) Iaslc Atlas of Egfr Testing In Lung Cancer [Internet]. Mok TS, Carbone DP, Hirsch FR, editors. Editorial Rx Press, North Fort Myers, FL, USA 79. Link: https://bit.ly/2VUg7TS

39. Cheng L, Alexander RE, MacLennan GT, Cummings OW, Montironi R, et al. (2012) Molecular pathology of lung cancer: Key to personalized medicine. Mod Pathol 25: 347-369. Link: https://bit.ly/3bXzaCx

40. Mok TS, Wu YL, Thongprasert S, Yang CH, Chu DT, et al. (2009) Gefitinib or carboplatin-paclitaxel in pulmonary adenocarcinoma. N Engl J Med 25: 347-369. Link: https://bit.ly/2VXPwFD

41. Takeda M, Nakagawa K (2019) First-and second-generation EGFR-TKIs are all replaced to osimertinib in chemo-naive EGFR mutation-positive non-small cell lung cancer? Int J Mol Sci 20: E146. Link: https://bit.ly/35pqwKt

42. Wu SG, Liu YN, Tsai MF, Chang YL, Yu CJ, et al. (2016) The mechanism of acquired resistance to irreversible EGFR tyrosine kinase inhibitor-afatinib in lung adenocarcinoma patients. Oncotarget 7: 12404-12413. Link: https://bit.ly/3fcalow

43. Morgillo F, Della Corte CM, Fasano M, Ciardiello F (2016) Mechanisms of resistance to EGFR-targeted drugs: Lung cancer. ESMO Open 11: e000060. Link: https://bit.ly/3bSHJhQ

44. Zhou C, Wu YL, Chen G, Feng J, Liu XQ, et al. (2015) Final overall survival results from a randomised, phase III study of erlotinib versus chemotherapy as first-line treatment of EGFR mutation-positive advanced non-small-cell lung cancer (OPTIMAL, CTONG-0802). Ann Oncol Link: https://bit.ly/2KRA5sb

45. Mok TS, Wu YL, Ahn MJ, Garassino MC, Kim HR, et al. (2017) Osimertinib or platinum-pemetrexed in EGFR T790M-Positive lung cancer. N Engl J Med 376: 629-640. Link: https://bit.ly/2KTWK7a

46. Soria JC, Ohe Y, Vansteenkiste J, Reungwetwattana T, Chewaskulyong B, et al. (2018) Osimertinib in untreated EGFR-Mutated advanced non-small-cell lung cancer. N Engl J Med 378: 113-125. Link: https://bit.ly/2YsJ4Im

Citation: Viola P (2020) The biology of Epidermal Growth Factor Receptor (EGFR) from regulating cell cycle to promoting carcinogenesis: the state of art including treatment options. Ann Cytol Pathol 5(1): 048-053. DOI: https://dx.doi.org/10.17352/acp.000015

47. Soda M, Choi YL, Enomoto M, Takada S, Yamashita Y, et al. (2007) Identification of the transforming EML4-ALK fusion gene in non-small-cell lung cancer. Nature 448: 561-566. Link: https://bit.ly/2WnCqjS

48. Rikova K, Guo A, Zeng Q, Possemato A, Yu J, et al. (2007) Global Survey of Phosphotyrosine Signaling Identifies Oncogenic Kinases in Lung Cancer. Cell 131: 1190-1203. Link: https://bit.ly/3faoJxn

49. Tsao MS, Yasushi Y (2016) Iaslc Atlas Of Alk And Ros1 Testing In Lung Cancer. first. Ming Sound Tsao, MD, FRCPC Fred R. Hirsch, MD, PhD Yasushi Yatabe, MD P, editor. Editorial Rx Press, North Fort Myers, FL, U.S.A.

50. Lindeman NI, Cagle PT, Aisner DL, Arcila ME, Beasley MB, et al. (2018) Updated Molecular Testing Guideline for the Selection of Lung Cancer Patients for Treatment With Targeted Tyrosine Kinase Inhibitors. J Thorac Oncol 8: 823-859. Link: https://bit.ly/3c98DSZ

51. Kalogeraki A, Karvela-Kalogeraki I, Tamiolakis D, Petraki P, Saridaki Z, et al. (2014) ERCC1 expression correlated with EGFR and clinicopathological variables in patients with non-small cell lung cancer. An immunocytochemical study on fine-needle aspiration biopsies samples. Rev Port Pneumol 20: 200-207. Link: https://bit.ly/2YoKjYW

52. Keedy VL, Temin S, Somerfield MR, Beasley MB, Johnson DH, et al. (2011) American Society of clinical oncology provisional clinical opinion: Epidermal growth factor receptor (EGFR) mutation testing for patients with advanced non-small-cell lung cancer considering first-line EGFR tyrosine kinase inhibitor therapy. J Clin Oncol 29: 2121-2127. Link: https://bit.ly/3bZ4r7V

53. Stella GM, Scabini R, Inghilleri S, Cemmi F, Corso S, et al. (2013) EGFR and KRAS mutational profiling in fresh non-small cell lung cancer (NSCLC) cells. J Cancer Res Clin Oncol 139: 1327-1335. Link: https://bit.ly/3dd6upn

54. Gong J, Chehrazi-Raffle A, Reddi S, Salgia R (2018) Development of PD-1 and PD-L1 inhibitors as a form of cancer immunotherapy: A comprehensive review of registration trials and future considerations. J Immunother Cancer 6: 8. Link: https://bit.ly/3f9uP0V

55. Šmahel M (2017) PD-1/PD-L1 blockade therapy for tumors with downregulated MHC class I expression. Int J Mol Sci 18 Pii: E1331. Link: https://bit.ly/3d7VYQ1

56. Herbst RS, Baas P, Kim DW, Felip E, Pérez-Gracia JL, et al. (2016) Pembrolizumab versus docetaxel for previously treated, PD-L1-positive, advanced non-small-cell lung cancer (KEYNOTE-010): A randomised controlled trial. Lancet 387: 1540-1550. Link: https://bit.ly/2YxyrEl

57. Reck M, Rodriguez-Abreu D, Robinson AG, Hui R, Csöszi T, et al. (2016) Pembrolizumab versus Chemotherapy for PD-L1-Positive Non-Small-Cell Lung Cancer. N Engl J Med 375: 1823-1833. Link: https://bit.ly/3feLoIK

58. Langer CJ, Gadgeel SM, Borghaei H, Papadimitrakopoulou VA, Patnaik A, et al. (2016) Carboplatin and pemetrexed with or without pembrolizumab for advanced, non-squamous non-small-cell lung cancer: a randomised, phase 2 cohort of the open-label KEYNOTE-021 study. Lancet Oncol 17: 1497-1508. Link: https://bit.ly/2VTnH14

59. Liang H, Liu X, Wang M (2018) Immunotherapy combined with epidermal growth factor receptor-tyrosine kinase inhibitors in non-small-cell lung cancer treatment. Onco Targets Ther 11: 6189-6196. Link: https://bit.ly/2YsMIBR

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