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Short communication

Genetic alterations landscape of lung cancer patients and their therapeutic value: an overview

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Lung cancer treatment

Late diagnosis and inefficient treatment lead to poor prognosis for most of the lung cancer patients. Improvement of the survival rate and quality of life requires establishment of efficient treatments through gaining comprehensive knowledge of the prevalence, incidence and clinical importance of known genetic alterations and discovery of novel alterations and targeted and immunotherapeutic agents. Therefore, comprehensive genomic analyses and functional preclinical validation are essential for expanding the potentially actionable genomic aberrations and discovering their therapeutic value.

Most common genetic alterations in lung cancers

EGFR mutations

Epidermal growth factor receptor (EGFR) is a tyrosine kinase normally found on surface of epithelial cells and is often overexpressed in a variety of human malignancies. The most common EGFR mutations in lung cancers include exon 19 deletions, present in 45% of the patients with EGFR mutations and p.L858R point mutations in exon 21, present in 40% of the patients with EGFR mutations, and are associated with responsiveness to oral EGFR tyrosine kinase inhibitors (TKIs) (Miller et al., 2008).

BRAF mutations

V-Raf murine sarcoma viral oncogene homolog B (BRAF) is a serine/threonine kinase, part of the canonical MAP/ERK signaling pathway. The BRAF point mutation with change in amino acid at position 600 (p. V600E) is associated with responsiveness to combined therapy with oral inhibitors of BRAF and MEK, such as dabrafenib and trametinib. Other BRAF mutations are also observed in NSCLC, at a rate approximately equal to p.V600E, but their impact on therapy selection is yet to be understood and thus specific targeted therapy is not available (National Comprehensive Cancer Network, 2022). Other EGFR exon 20 mutations are diverse group of on-frame duplications or insertions, such as insASV, insSVD and insNPH and occur in approximately 2% of NSCLC patients and 4-12% of patients with EGFR mutations.

KRAS mutations

KRAS is a G-protein with intrinsic GTPase activity and activating mutations result in unregulated signaling through the MAP/ERK pathway. KRAS mutation prevalence is associated with cigarette smoking, unlike many other actionable mutations (Slebos et al., 1991). Substitutions on KRAS G12, G13 and Q61 attenuate GTP hydrolysis capacity, while A146T promotes KRAS GTP formation as increased nucleotide exchange, thereby reducing this isoform's oncogenic capacity (Shen et al., 2022). KRAS mutations, most commonly on codon 12 (KRAS G12C), are prognostic for poor survival and reduced responsiveness to EGFR TKI therapy (Miller et al., 2008), but are not predictors of response rate (RR), progression-free survival (PFS) or overall survival in lung cancer patients.

PIK3CA mutations

Mutations of the lipid kinase PIK3, coordinating a diverse range of cell functions (proliferation, cell survival, degranulation, vesicular trafficking and cell migration), are rare in NSCLC (1-4%). Most of them are missense mutations in exon 9 (c.1624G>A (p. E542K), c.1633G>A (p. E545K) and exon 20 (c.3140A (H1047R), M1043I, G1049S) that encode part of helical and kinase domains.

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PIK3CA mutations are correlated with worse overall survival, especially in patients treated with EGFR TKIs (Ludovini, 2011), poor PFS and cancer-specific survival (CSS), as well as poorer lymph node metastasis status (Wang et al., 2020).

ALK and ROS1 rearrangements

Anaplastic lymphoma kinase (ALK) and proto-oncogene tyrosine-protein kinase 1 (ROS1) are receptor tyrosine kinases that play major role in activation of several signaling pathways associated with differentiation, proliferation, cell growth and survival. About 2-7% NSCLC patients have ALK rearrangements, mainly with adenocarcinoma histology and being light or never smokers (Mithoowani and Febbraro, 2022). ALK-(+) patients are resistant to EGFR TKIs and should be treated with targeted agents alectinib, brigatinib, ceritinib, crizotinib and lorlatinib (National Comprehensive Cancer Network, 2022). ROS1 rearrangements occur in 1-2.6% of NSCLC patients (Dugay et al., 2017; Kim et al., 2013).

PD-L1 and HER2 expression

Programmed death-ligand 1 (PD-L1) is a co-regulatory molecule that can be expressed on tumor cells and inhibit T-cell mediated cell death. Although it is not optimal, PD-L1 expression is currently the best available biomarker to asses appropriateness for immunotherapy (Kerr and Hirsch, 2016). The Human epidermal growth factor receptor 2 (HER2), the confirmed emerging driver and therapeutic target in NSCLC, encodes member of the erbB receptor tyrosine kinase family. The incidence of HER2 alterations (mutation, overexpression, amplification) in NSCLC patients is 2.4-38.0% and is more frequent in adenocarcinomas with well-differentiated histology. HER2 overexpression is considered as poor prognostic factor, indicating worse survival (Zhao and Xia, 2020).

Conclusion and recommendations

NSCLC guidelines recommend testing for driver mutations in all non-squamous tumors (Mithoowani and Febbraro, 2022). The international association for the study of Lung Cancer recommends testing for EGFR, ALK and ROS1 as a minimum requirement; newer guidelines also recommend testing for BRAF, KRAS, MET, ERBB2 and RET (National Comprehensive Cancer Network, 2022), as well as ROS1 in all adenocarcinoma patients, BRAF in patients with metastatic non-squamous NSCLC or NSCLC NOS (National Comprehensive Cancer Network, 2022). Therefore, large scale testing for prognostic and predictive somatic genetic alterations is feasible and impacts therapeutic decisions in lung cancer management, and as such, should be routinely performed. In that way, a comprehensive genetic profile of lung cancers in a time and cost-effective manner will be generated.

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