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New insights into the molecular profile of lung adenocarcinoma and implications for therapy

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Lung cancer is a molecularly heterogeneous disease. The advent of next-generation sequencing techniques has significantly advanced our understanding of the complex molecular underpinnings of lung cancer. Furthermore, the development of targeted therapies has significantly altered the landscape of lung cancer therapy over the past decade. There is hence an increasing interest in developing a classification system that guides clinical management and also incorporates relevant genomic information. Here, we highlight the molecular features of lung adenocarcinoma as highlighted by several independent groups, and more recently The Cancer Genome Atlas and discuss their potential clinical significance.

Lung cancer is the leading cause of cancer-related mortality in the world [1]. Non-small cell lung cancer (NSCLC) is the most common histological subtype of lung cancer [2]. Broadly, the histological subtypes of NSCLC include adenocarcinoma, squamous cell carcinoma and large cell carcinoma. The genomic landscape of a typical lung cancer caused by tobacco smoking is quite complex [3,4].

Summary of findings from genomic studies on lung adenocarcinoma

Comprehensive genomic studies involving lung adenocarcinoma show several striking features [4–8]. The mutational burden in tobacco-related lung adenocarcinoma is significantly higher than many common cancers (median of ~10.5 mutations/Mb of the genome) [5]. In contrast, lung adenocarcinoma from never smokers is associated with a very low mutational burden (median of 0.6 mutations/Mb of the genome). Smoking history also correlates with the prevalence of nucleotide transversions within tumors [4]. Transversion-high (smokers) and transversion-low (never-smokers) tumors are associated with different gene mutations, suggesting that distinct mechanisms drive these tumors. Furthermore, significant intra- and inter-tumoral heterogeneity has been observed in lung adenocarcinomas through next-generation sequencing. The evolutionary history of lung cancer clones constructed through multi-region sequencing suggests that driver alterations in lung cancer occur early in cancer development [7,8]. Although RAS/RAF/AKT pathways are the most commonly involved (76% cases) in the molecular pathogenesis of lung adenocarcinoma, alterations in the TP53 and cell cycle regulator pathways are observed in approximately two-third of cases [4].

Molecular classification of lung adenocarcinoma

Based on tumor expression profiling, Hayes *et al.* [9] demonstrated that lung adenocarcinomas cluster into three groups – bronchioid, magnoid and squamoid. The Cancer Genome Atlas (TCGA) investigators have validated these findings and identified correlation between molecular subtypes of adenocarcinoma with clinical features [4]. For instance, bronchioid tumors harbor *EGFR* mutations and tyrosine kinase (TK) fusions more frequently than other subtypes, are seen more frequently in never-smokers and associated with better prognosis. When applied to

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tumor samples that were a part of the JBR.10 trial, which demonstrated benefit with adjuvant cisplatin and vinorelbine in early-stage NSCLC, this classification system demonstrated that only magnoid subtype tumors showed a significant disease-free survival benefit with adjuvant therapy [10]. It is speculated that magnoid tumors, which show a high degree of chromosomal instability compared with other subtypes, harbor DNA repair pathway defects that render them more sensitive to platinum therapy. TCGA investigators have proposed to change the nomenclature from bronchioid, magnoid and squamoid subtypes to terminal respiratory unit, proximal proliferative and proximal inflammatory subtypes respectively [4]. Integrative clustering using copy-number, mutation, DNA methylation and mRNA expression data suggested the presence of six clusters that were associated with distinct molecular profiles.

Implications for therapy

Targeted therapies directed against lung cancers harboring mutations in *EGFR* TK and rearrangements involving anaplastic lymphoma kinase (*ALK*) have significantly improved outcomes in a subset of patients [11–14]. These alterations are particularly prevalent among never- or light-smokers [11,15,16]. Unfortunately, EGFR mutations are present in the tumor cells in only about 16% of patients with advanced stage NSCLC [17]. Similarly, about 5% of patients with lung adenocarcinoma have *ALK* gene rearrangements in the tumor cells. A median progression-free survival of 7.7 and 11 months has been associated with the use of crizotinib in previously treated and chemotherapy naïve patients [18–20]. Ceritinib has recently been approved for use in ALK rearranged NSCLC [21]. A number of novel ALK inhibitors are under development. Similarly, fusions involving *RET* and *ROS1* oncogenes have also been reported in 1–2% of patients with NSCLC, and partial responses with crizotinib and cabozantinib have been reported in these patients, respectively [22]. Shaw *et al.* [23] recently reported an objective response rate of 72% with a median PFS of 19.2 months with crizotinib in *ROS1* rearrangement-positive NSCLCs.

An issue of considerable clinical importance with the use of targeted therapies is the eventual emergence of resistance to these drugs. Mechanisms of resistance include the development of alterations that affect drug binding through steric hindrance or loss of affinity, such as the *EGFR* gatekeeper T790M or *ALK* L1196M mutations [24]. Few patients with resistance to ALK inhibition demonstrate copy-number gains in rearranged *ALK*. Activation of bypass signaling pathways and phenotypic transformation of tumors, including epithelial-mesenchymal transformation or differentiation to a small cell histology, represent other mechanisms of acquiring resistance to targeted therapies. TK inhibitors such as AZD9291 and CO1686 have recently demonstrated significant activity in NSCLCs harboring the *EGFR* T790M mutation [25,26]. Similarly, encouraging response rates with several novel agents have been reported in crizotinib-resistant *ALK* rearranged tumors [24,27]. These are currently being actively investigated in clinical trials [28–31].

The introduction of next-generation sequencing technologies has enabled an unbiased characterization of cancer genomes on a massive scale. This has led to the discovery of several potentially targetable genetic alterations in lung cancer over the past few years, giving rise to newfound optimism and promise in the field of cancer therapeutics. Such efforts have led to the identification of new driver alterations in 'oncogene negative' lung adenocarcinomas – a subset of tumors that lack known somatic driver alterations capable of activating the RTK/RAS/RAF pathway [4]. Among these, *RIT1* mutations were reported in 2% of adenocarcinomas by TCGA. Berger *et al.* [32] demonstrated a potential role for combined MEK and PI3K inhibition in these tumors. Similarly, Vaishnavi *et al.* [33] reported oncogenic *NTRK1* gene fusions in 3% of oncogene-negative tumors. Cells expressing the fusion protein were sensitive to CEP-701 (lestaurtinib) and crizotinib. Comprehensive genomic analysis by TCGA also suggests that distinct mechanisms underlie oncogene activation. For instance, MET activation through exon 14 skipping as a consequence of splice site alterations was reported in 10 sequenced adenocarcinoma samples [4]. Overall, these findings emphasize the utility of next-generation sequencing technologies in unraveling the complex molecular mechanisms that drive oncogenesis, and identifying targetable alterations. Such characterization of molecular alterations in tumors through 'multiplexed assays' can potentially aid in the administration of genotype-matched therapies to patients harboring specific mutations – an approach that was recently demonstrated by the Lung Cancer Mutation Consortium [34]. Tumors from 1007 patients were tested for at least 1 and 733 patients for 10 genetic alterations as a part of this initiative. These results were used to select a targeted therapy or trial in 275 (28%) of 1007 patients. The median survival was 3.5 years among 260 patients with an oncogenic driver who received genotype-directed therapy, compared with 2.4 years in patients with oncogenic drivers who did not receive such therapy. Next-generation sequencing also carries the potential to determine occult biomarkers that underlie drug sensitivity. Whole genome sequencing of the tumor of a patient with metastatic bladder carcinoma who achieved a durable remission with everolimus aided in the identification of a loss-of-function *TSC1* mutation that correlated with drug sensitivity [35]. Similarly, Lovly *et al.* [36] recently identified a therapeutic synergism between ALK and IGF 1 receptor (IGF-1R) inhibitors through whole genome sequencing of an *ALK* fusion-positive tumor that had an exceptional response to IGF-1R-specific antibody.

Future directions

It is critical to identify rare variants that have not so far been identified. The ongoing ALCHEMIST study will screen 8000 patients with lung adenocarcinoma for targetable alterations in resected early stage NSCLC. There are plans to study

comprehensively the genomic alterations in this trial to identify rare variants. In addition, the contribution made by clonal evolution in the process of metastases and treatment resistance should be further studied using multi-region and multi-site sampling. It is likely that clinical trials in the future will incorporate genomic studies, to understand the molecular mechanisms underlying exceptional responses to novel therapies.

Financial & competing interests disclosure

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References

1. Ferlay J, Steliarova-Foucher E, Lortet-Tieulent J, et al. Cancer incidence and mortality patterns in Europe: estimates for 40 countries in 2012. Eur J Cancer 2013;49:1374-403
2. Travis WD. Pathology of lung cancer. Clin Chest Med 2011;32:669-92
3. Cancer Genome Atlas Research Network. Hammerman PS, Hayes DN, et al. Comprehensive genomic characterization of squamous cell lung cancers. Nature 2012;489:519-25
4. Comprehensive molecular profiling of lung adenocarcinoma. Nature 2014;511:543-50
5. Govindan R, Ding L, Griffith M, et al. Genomic landscape of non-small cell lung cancer in smokers and never-smokers. Cell 2012;150:1121-34
6. Imielinski M, Berger AH, Hammerman PS, et al. Mapping the hallmarks of lung adenocarcinoma with massively parallel sequencing. Cell 2012;150:1107-20
7. de Bruin EC, McGranahan N, Mitter R, et al. Spatial and temporal diversity in genomic instability processes defines lung cancer evolution. Science 2014;346:251-6
8. Zhang J, Fujimoto J, Wedge DC, et al. Intratumor heterogeneity in localized lung adenocarcinomas delineated by multiregion sequencing. Science 2014;346:256-9
9. Hayes DN, Monti S, Parmigiani G, et al. Gene expression profiling reveals reproducible human lung adenocarcinoma subtypes in multiple independent patient cohorts. J Clin Oncol 2006;24:5079-90
10. Wilkerson MD, Yin X, Walter V, et al. Differential pathogenesis of lung adenocarcinoma subtypes involving sequence mutations, copy number, chromosomal instability, and methylation. PLoS One 2012;7:e36530
11. Zhou C, Wu YL, Chen G, et al. Erlotinib versus chemotherapy as first-line treatment for patients with advanced EGFR mutation-positive non-small-cell lung cancer (OPTIMAL, CTONG-0802): a multicentre, open-label, randomised, phase 3 study. Lancet Oncol 2011;12:735-42
12. Maemondo M, Inoue A, Kobayashi K, et al. Gefitinib or chemotherapy for non-small-cell lung cancer with mutated EGFR. N Engl J Med 2010;362:2380-8
13. Paez JG, Jänne PA, Lee JC, et al. EGFR mutations in lung cancer: correlation with clinical response to gefitinib therapy. Science 2004;304:1497-500
14. Kwak EL, Bang YJ, Camidge DR, et al. Anaplastic lymphoma kinase inhibition in non-small-cell lung cancer. N Engl J Med 2010;363:1693-703
15. Mitsudomi T, Morita S, Yatabe Y, et al. Gefitinib versus cisplatin plus docetaxel in patients with non-small-cell lung cancer harbouring mutations of the epidermal growth factor receptor (WJTOG3405): an open label, randomised phase 3 trial. Lancet Oncol 2010;11:121-8
16. Sequist LV, Yang JC, Yamamoto N, et al. Phase III study of afatinib or cisplatin plus pemetrexed in patients with metastatic lung adenocarcinoma with EGFR mutations. J Clin Oncol 2013;31:3327-34
17. Rosell R, Moran T, Queralt C, et al. Screening for epidermal growth factor receptor mutations in lung cancer. N Engl J Med 2009;361:958-67
18. Shaw AT, Kim DW, Nakagawa K, et al. Crizotinib versus chemotherapy in advanced ALK-positive lung cancer. N Engl J Med 2013;368:2385-94
19. Mok T, Kim DW, Wu YL, et al. First-line crizotinib versus pemetrexed–cisplatin or pemetrexed–carboplatin in patients (pts) with advanced ALK-positive non-squamous non-small cell lung cancer (NSCLC): results of a phase III study (PROFILE 1014). J Clin Oncol 2014;32(5s Suppl):abstract 8002
20. Solomon BJ, Mok T, Kim DW, et al. First-line crizotinib versus chemotherapy in ALK-positive lung cancer. N Engl J Med 2014;371:2167-77
21. Shaw AT, Kim DW, Mehra R, et al. Ceritinib in ALK-rearranged non-small-cell lung cancer. N Engl J Med 2014;370:1189-97
22. Gainor JF, Shaw AT. Novel targets in non-small cell lung cancer: ROS1 and RET fusions. Oncologist 2013;18:865-75
23. Shaw AT, Ou SH, Bang YJ, et al. Crizotinib in ROS1-rearranged non-small-cell lung cancer. N Engl J Med 2014;371:1963-71
24. Camidge DR, Pao W, Sequist LV. Acquired resistance to TKIs in solid tumours: learning from lung cancer. Nat Rev Clin Oncol 2014;11:473-81
25. Janne PA, Ramalingam SS, Yang JC, et al. Clinical activity of the mutant-selective EGFR inhibitor AZD9291 in patients (pts) with EGFR inhibitor–resistant non-small cell lung cancer (NSCLC). J Clin Oncol 2014;32(5s Suppl):abstract 8009^
26. Sequist LV, Soria J-C, Gadgeel SM, et al. First-in-human evaluation of CO-1686, an irreversible, highly selective tyrosine kinase inhibitor of mutations of EGFR (activating and T790M). J Clin Oncol 2014; 32(5s Suppl):abstract 8010^
27. Gettinger SN, Bazhenova L, Salgia R, et al. Updated efficacy and safety of the ALK inhibitor AP26113 in patients (pts) with advanced malignancies, including ALK+ non-small cell lung cancer (NSCLC). J Clin Oncol 2014; 32(5s Suppl):abstract 8047
28. AZD9291 in Combination With Ascending Doses of Novel Therapeutics. Available from: https://clinicaltrials.gov/ct2/show/NCT02143466 [Last accessed 15 January 2015]
29. Open Label Safety and Efficacy Study of Rociletinib (CO-1686) in Patients With T790M Positive NSCLC Who Have Failed One Previous EGFR-Directed TKI (TIGER-2). Available from: https://clinicaltrials.gov/ct2/show/NCT02147990 [Last accessed 15 January 2015]
30. LDK378 Versus Chemotherapy in ALK Rearranged (ALK Positive) Patients Previously Treated With Chemotherapy (Platinum Doublet) and Crizotinib. Available from: https://clinicaltrials.gov/ct2/show/NCT01828112 [Last accessed 15 January 2015]

31. A Phase 2, Multicenter, Randomized Study of AP26113 (ALTA). Available from: https://clinicaltrials.gov/ct2/show/NCT02094573 [Last accessed 15 January 2015]
32. Berger AH, Imielinski M, Duke F, et al. Oncogenic RIT1 mutations in lung adenocarcinoma. Oncogene 2014;33(35):4418-23
33. Vaishnavi A, Capelletti M, Le AT, et al. Oncogenic and drug-sensitive NTRK1 rearrangements in lung cancer. Nat Med 2013;19:1469-72
34. Kris MG, Johnson BE, Berry LD, et al. Using multiplexed assays of oncogenic drivers in lung cancers to select targeted drugs. JAMA 2014;311:1998-2006
35. Iyer G, Hanrahan AJ, Milowsky MI, et al. Genome sequencing identifies a basis for everolimus sensitivity. Science 2012;338:221
36. Lovly CM, McDonald NT, Chen H, et al. Rationale for co-targeting IGF-1R and ALK in ALK fusion-positive lung cancer. Nat Med 2014;20:1027-34