Editorial

Unraveling the genomic complexity of small cell lung cancer

Niki Karachaliou[1,2], Aaron E. Sosa[1], Rafael Rosell[2,3]

[1]University Hospital Sagrat Cor, Oncology Institute Rosell, Barcelona, Spain; [2]Autonomous University of Barcelona, Germans Trias i Pujol Health Sciences Research Institute, Badalona, Spain; [3]Catalan Institute of Oncology, Hospital Germans Trias i Pujol, Badalona, Spain

Correspondence to: Rafael Rosell. IMPPC Campus Can Ruti, Carretera de Can Ruti, Cami de les escoles s/n, 08916, Badalona, Spain.
Email: rrosell@iconcologia.net.

Submitted Jun 03, 2016. Accepted for publication Jun 13, 2016.
doi: 10.21037/tlcr.2016.07.02
View this article at: http://dx.doi.org/10.21037/tlcr.2016.07.02

Significant clinical advances have been made in the last few years regarding lung cancer management. Molecularly targeted therapies have allowed a personalized approach for the treatment of patients with advanced non-small cell lung cancer (NSCLC). Immunotherapy has also advanced with promising results in the treatment of several tumors, including lung cancer. Immune checkpoint inhibitors are now at the forefront of immunotherapy and two antibodies against PD-1 (nivolumab and pembrolizumab) are approved for NSCLC. Despite the significant progress that has been achieved in NSCLC, such progress is rather limited in small cell lung cancer (SCLC). The treatment of SCLC patients has not significantly changed in the last 30 years and no effective targeted therapies are currently available (1). Since curative intent resections are not usually performed in SCLC, there is a paucity of tumor material for the performance of translational research. This problem has now been overcome with the development of new model systems, mainly genetically engineered mouse models (GEMMs) that give us the opportunity to understand the biology and molecular biology of SCLC. It is widely accepted that SCLC is a high-grade neuroendocrine carcinoma with several molecular and cellular abnormalities (2). Tumor suppressor genes, such as retinoblastoma 1 (*RB1*) and tumor protein p53 (*TP53*), are inactivated in the majority of patients with SCLC (2). Somatic inactivation of *RB1* and *TP53* (double knockout) is used to establish GEMMs as models for biological and preclinical studies of SCLC (3). In addition, a vast amount of knowledge has been gained by high throughput molecular profile technologies.

Dowlati and colleagues (4) performed targeted-exome and whole-exome sequencing in 50 SCLC patients, most of whom had extensive-stage disease. As previously reported (5-7), they found that *TP53* and *RB1* were the most frequently mutated genes in 86% and 58% of the cases, respectively (4). There is mounting evidence that almost all SCLCs have an alteration in the *TP53* gene (5). The p53 protein is a tumor suppressor protein that has been characterized as the "guardian of the genome" (8). It is a stress response protein, activated in a variety of stress-inducing signals, like cellular injury, hypoxia, DNA damage or oncogene activation. When activated, p53 controls many biological processes with the main ones being apoptosis, autophagy, cell-cycle arrest and senescence (9,10). At least in NSCLC, the prognostic role of the *TP53* gene is controversial and not all mutated patients represent a clinically homogeneous group (11). We have found that "nondisruptive" *TP53* mutations, may apparently confer oncogenic activities to the mutated p53 protein, and define a group of metastatic NSCLC patients with a dismal prognosis (11). In contrast, patients with 'disruptive' *TP53* mutations characterized by a complete, or almost complete, loss of activity of the p53 protein, have good prognosis, similar to patients with wild-type *TP53* (11). In the study of Dowlati *et al*., SCLC patients with 'disruptive' *TP53* mutations had a significantly better response to first-line chemotherapy compared to patients with wild-type *TP53*. Overall, *TP53* mutations (disruptive or nondisruptive) did not have an effect on progression-free survival (PFS) and overall survival (OS) (4).

SCLC pathogenesis follows the classical "two-hit paradigm" pattern of Knudson-type tumor suppressors (12). Loss of function of both *TP53* and *RB1* is needed for SCLC to be developed in the lung of mice models (3). Dowlati *et al*. found that more than half of the population examined (58%) carried *RB1* mutations (4). This frequency is lower from

what has been reported by researchers in the University of Cologne (13). George *et al.* sequenced 110 SCLC cases and found *RB1* and *TP53* inactivating mutations in all but two of the cases, establishing these two genes as obligatory tumor suppressors in SCLC (13). In the Dowlati study, wild-type *RB1* status was significantly associated with lower response to chemotherapy (4). In the multivariable Cox regression model, *RB1* was the only significant prognostic factor in SCLC patients treated with first-line chemotherapy (4). In addition, SCLC patients with *RB1* mutations had significantly longer PFS and OS, compared to those with wild-type *RB1* (4). SCLC tumor samples and cell lines with wild type *RB1* expressed the Rb1 protein as measured by immunohistochemistry (4).

The Rb1 protein has an important role as a negative regulator of the cell cycle through its ability to repress E2F target genes. Several studies on different cancer types have previously examined how *RB1* status affects tumor sensitivity to treatments and clinical outcome. The disruption of Rb1 function enhances response to DNA-damaging agents in breast, prostate, bladder, hepatocellular and ovarian cancer as well as in childhood acute lymphoblastic leukemia (14). In SCLC, a major prognostic factor, quite useful as a predictor for long-term survival, is the female sex, especially when restricted to younger patients (15). This may explain why, when Dowlati and colleagues controlled their analysis for the effects of gender and age, the significant effect of *RB1* status on PFS and OS was lost (4).

Other alterations detected in this small cohort of 50 SCLC patients were in epigenetic genes [*CREBBP*, *MLL2*, *MLL3*, *AT-rich interactive domain 1A* (*ARID1A*) and *ARID1B*] and in the PIK3/mTOR pathway genes (*PTEN*, *RICTOR*, *RPTOR*, *TSC2*) (4). It is worth mentioning that *ARID1A*, a tumor suppressor of the SWI/SNF chromatin remodeling complex, has been recognized as one of the most frequently mutated genes in human cancers (16). ARID1A has been found to interact with ataxia telangiectasia and RAD3-related protein (ATR). It facilitates efficient processing of double-strand DNA breaks (DSB) to single-strand ends and sustains DNA damage signaling. The predictive value of the expression of DNA repair genes on the response and survival of SCLC patients treated with chemotherapy has been previously reported (17). When *ARID1A* is lost, the DNA DSBs repair process is impaired and tumor cells are sensitized to DSB-inducing therapies such as radiation or PARP inhibitors (18). PARP1 has been described as the most overexpressed protein in SCLC and targeting PARP reduced tumor growth in preclinical models (19). However, SCLC cells with the PIK3/mTOR pathway activated were less sensitive to PARP inhibition (19). Therefore, both *ARID1A* mutations and alterations in the PIK3-AKT-mTOR pathway can be useful biomarkers to predict response to PARP inhibition. Furthermore, as the group of Byers demonstrated, combined PARP and PI3K inhibition can be more efficient in SCLC than either drug alone (20).

In the study of Dowlati *et al.*, fibroblast growth factor receptor 1 (FGFR1) was also frequently amplified (4), as has been reported in several previous studies. The family of the FGF receptors is a promising target for personalized therapies in various types of tumors and several drugs targeting the FGF pathway are in clinical testing (2). In addition, a lot of work is ongoing with the scope to identify other amplification biomarkers than FGFR1 as better predictors of response to FGFR inhibition (2). It is not yet clear whether FGFR1 amplification, or the protein and respective messenger RNA expression of FGFR1 and its ligands FGF2 and FGF9, or a combined analysis of all, can evidence the activation of the FGF pathway and allow the selection of SCLC patients for FGFR1 inhibitor therapy. In addition, the frequency of FGFR1 amplification is low in SCLC and maybe in the future *FGFR1* gene copy number will not be the best biomarker to predict sensitivity to FGFR1 inhibitors.

DNA amplification of the v-myc avian myelocytomatosis viral oncogene homolog (MYC) family of proto-oncogenes has been described in almost 20% of SCLC, with the MYCL being a critical driver in SCLC (2). Dowlati and colleagues did not detect any dysregulation of MYC function, something that cannot be easily explained (2,4). Interestingly, the authors highlight the potential benefit from tyrosine kinase inhibitors targeting the rearranged during transfection (RET) receptor for SCLC patients that carry *RET* somatic mutations (4). Indeed, the group of Dowlati was the first to identify an oncogenic RET M918T mutation in SCLC (21). They also found that in SCLC cell lines with the RET receptor mutated, MYC expression and ERK signaling activity were more evident in comparison to cells with the wild-type receptor (21).

The study of Dowlati (4) is a piece of evidence that next generation sequencing makes precision oncology a reality wherein the treatment of cancer patients is based on their personal genetic profile. Until recently, there was a paucity of therapeutic advances, but now we are on the verge of gaining a better therapeutic approach for SCLC. The promise of immunotherapy for this disease has also been growing (22). Rovalpituzumab tesirine, a drug designed

to bind to the Notch delta-like ligand 3 (DLL3), has demonstrated remarkable early results and it is currently being clinically tested for the third-line therapy of SCLC patients (23). DLL3 is highly expressed in approximately 60% of SCLC patients (23). Novel potential therapeutic targets are continuously identified in molecular studies of SCLC and ongoing or future clinical trials will show which of these targets will be translated into an effective targeted therapy.

Acknowledgements

Funding: La Caixa Foundation and Red Tematica de Investigacion Cooperativa en Cancer (RTICC; grant RD12/0036/0072).

Footnote

Provenance: This is a Guest Editorial commissioned by Section Editor Hongbing Liu, MD, PhD (Department of Respiratory Medicine, Jinling Hospital, Nanjing University School of Medicine, Nanjing, China).
Conflicts of Interest: The authors have no conflicts of interest to declare.

Comment on: Dowlati A, Lipka MB, McColl K, *et al*. Clinical correlation of extensive-stage small-cell lung cancer genomics. Ann Oncol 2016;27:642-7.

References

1. Karachaliou N, Pilotto S, Lazzari C, et al. Cellular and molecular biology of small cell lung cancer: an overview. Transl Lung Cancer Res 2016;5:2-15.
2. Bunn PA Jr, Minna JD, Augustyn A, et al. Small cell lung cancer: can recent advances in biology and molecular biology be translated into improved outcomes? J Thorac Oncol 2016;11:453-74.
3. Meuwissen R, Linn SC, Linnoila RI, et al. Induction of small cell lung cancer by somatic inactivation of both Trp53 and Rb1 in a conditional mouse model. Cancer Cell 2003;4:181-9.
4. Dowlati A, Lipka MB, McColl K, et al. Clinical correlation of extensive-stage small-cell lung cancer genomics. Ann Oncol 2016;27:642-7.
5. D'Amico D, Carbone D, Mitsudomi T, et al. High frequency of somatically acquired p53 mutations in small-cell lung cancer cell lines and tumors. Oncogene 1992;7:339-46.
6. Takahashi T, Nau MM, Chiba I, et al. p53: a frequent target for genetic abnormalities in lung cancer. Science 1989;246:491-4.
7. Wistuba II, Gazdar AF, Minna JD. Molecular genetics of small cell lung carcinoma. Semin Oncol 2001;28:3-13.
8. Lane DP. Cancer. p53, guardian of the genome. Nature 1992;358:15-6.
9. Yee KS, Vousden KH. Complicating the complexity of p53. Carcinogenesis 2005;26:1317-22.
10. Green DR, Kroemer G. Cytoplasmic functions of the tumour suppressor p53. Nature 2009;458:1127-30.
11. Molina-Vila MA, Bertran-Alamillo J, Gascó A, et al. Nondisruptive p53 mutations are associated with shorter survival in patients with advanced non-small cell lung cancer. Clin Cancer Res 2014;20:4647-59.
12. Knudson AG. Two genetic hits (more or less) to cancer. Nat Rev Cancer 2001;1:157-62.
13. George J, Lim JS, Jang SJ, et al. Comprehensive genomic profiles of small cell lung cancer. Nature 2015;524:47-53.
14. Indovina P, Pentimalli F, Casini N, et al. RB1 dual role in proliferation and apoptosis: cell fate control and implications for cancer therapy. Oncotarget 2015;6:17873-90.
15. Wolf M, Holle R, Hans K, et al. Analysis of prognostic factors in 766 patients with small cell lung cancer (SCLC): the role of sex as a predictor for survival. Br J Cancer 1991;63:986-92.
16. Wu JN, Roberts CW. ARID1A mutations in cancer: another epigenetic tumor suppressor? Cancer Discov 2013;3:35-43.
17. Karachaliou N, Papadaki C, Lagoudaki E, et al. Predictive value of BRCA1, ERCC1, ATP7B, PKM2, TOPOI, TOPO-IIA, TOPOIIB and C-MYC genes in patients with small cell lung cancer (SCLC) who received first line therapy with cisplatin and etoposide. PLoS One 2013;8:e74611.
18. Shen J, Peng Y, Wei L, et al. ARID1A deficiency impairs the DNA damage checkpoint and sensitizes cells to PARP inhibitors. Cancer Discov 2015;5:752-67.
19. Byers LA, Wang J, Nilsson MB, et al. Proteomic profiling identifies dysregulated pathways in small cell lung cancer and novel therapeutic targets including PARP1. Cancer Discov 2012;2:798-811.
20. Cardnell RJ, Feng Y, Mukherjee S, et al. Activation of the PI3K/mTOR pathway following PARP Inhibition in small cell lung cancer. PLoS One 2016;11:e0152584.
21. Dabir S, Babakoohi S, Kluge A, et al. RET mutation

and expression in small-cell lung cancer. J Thorac Oncol 2014;9:1316-23.
22. Reck M, Heigener D, Reinmuth N. Immunotherapy for small-cell lung cancer: emerging evidence. Future Oncol 2016;12:931-43.
23. Saunders LR, Bankovich AJ, Anderson WC, et al. A DLL3-targeted antibody-drug conjugate eradicates high-grade pulmonary neuroendocrine tumor-initiating cells in vivo. Sci Transl Med 2015;7:302ra136.

Cite this article as: Karachaliou N, Sosa AE, Rosell R. Unraveling the genomic complexity of small cell lung cancer. Transl Lung Cancer Res 2016;5(4):363-366. doi: 10.21037/tlcr.2016.07.02

