small differences between these studies might be explained by differences in sample preparation; for example, Griese and colleagues used centrifugation of BAL to remove cells from the surfactant before analysis, which was not done in the prior studies. Importantly, esterified cholesterol is produced within alveolar macrophages in PAP, and thus they may have underestimated the true proportion of esterified cholesterol present in the alveolar macrophages from patients with PAP. One limitation of the study is that inhibitors of lipid oxidation were not included in the sample preparation and storage, which could have affected the concentration of oxidized lipid species. Such lipid species have specific roles in modulating macrophage functional processes, particularly oxidized derivatives of cholesterol (oxysterols), which act through the LXRA pathway (10). It is also unclear whether the lipidomic profile in individuals correlates with their clinical phenotype, including the presence or absence of fibrosis—this is an area that requires further exploration. Finally, assessing dynamic changes in the alveolar lipidome may be a novel method to monitor the therapeutic response to inhaled GM-CSF or emerging cholesterol-targeted strategies.

Author disclosures are available with the text of this article at www.atsjournals.org.

Bruce C. Trapnell, M.D.
 Translational Pulmonary Science Center
 Division of Pulmonary Biology and
 Division of Pulmonary Medicine
 Cincinnati Children’s Hospital Medical Center
 Cincinnati, Ohio
 and
 Division of Pulmonary, Critical Care and Sleep Medicine
 University of Cincinnati College of Medicine
 Cincinnati, Ohio

Cormac McCarthy, M.D., Ph.D.
 St. Vincent’s University Hospital
 University College Dublin
 Dublin, Ireland

ORCID IDs: 0000-0003-2817-6254 (B.C.T.);
 0000-0003-2896-5210 (C.M.).

References

1. Trapnell BC, Whitsett JA, Nakata K. Pulmonary alveolar proteinosis. N Engl J Med 2003;349:2527–2539.

2. Trapnell BC, Nakata K, Bonella F, Campo I, Griese M, Hamilton J, et al. Pulmonary alveolar proteinosis. Nat Rev Dis Primers 2019;5:16.

3. Daniels CB, Barr HA, Power JH, Nicholas TE. Body temperature alters the lipid composition of pulmonary surfactant in the lizard Ctenophorus nuchalis. Exp Lung Res 1990;16:435–449.

4. Dranoff G, Crawford AD, Sadelain M, Ream B, Rashid A, Bronson RT, et al. Involvement of granulocyte-macrophage colony-stimulating factor in pulmonary homeostasis. Science 1994;264:713–716.

5. Ikemig M, Ueda T, Hull W, Whitsett JA, Mulligan RC, Dranoff G, et al. Surfactant metabolism in transgenic mice after granulocyte-macrophage colony-stimulating factor ablation. Am J Physiol 1996;270:L650–L658.

6. Stanley E, Lieschke GJ, Grill D, Metcalf D, Hodgson G, Gall JA, et al. Granulocyte/macrophage colony-stimulating factor-deficient mice show no major perturbation of hematopoiesis but develop a characteristic pulmonary pathology. Proc Natl Acad Sci USA 1994;91:5592–5596.

7. Robb L, Drinkwater CC, Metcalf D, Li R, Köntgen F, Nicola NA, et al. Hematopoietic and lung abnormalities in mice with a null mutation of the common beta subunit of the receptors for granulocyte-macrophage colony-stimulating factor and interleukins 3 and 5. Proc Natl Acad Sci USA 1995;92:9565–9569.

8. Malur A, Mccoy AJ, Arce S, Baran BP, Kavuru MS, Malur AG, et al. Deletion of PPAR gamma in alveolar macrophages is associated with a Th-1 pulmonary inflammatory response. J Immunol 2009;182:5816–5822.

9. Kennedy MA, Barrera GC, Nakamura K, Baldwin A, Tarr P, Fishbein MC, et al. ABCG1 has a critical role in mediating cholesterol efflux to HDL and preventing cellular lipid accumulation. Cell Metab 2005;1:121–131.

10. Venkateswaran A, Lafitte BA, Joseph SB, Mak PA, Wilpitz DC, Edwards PA, et al. Control of cellular cholesterol efflux by the nuclear oxysterol receptor LXR alpha. Proc Natl Acad Sci USA 2000;97:12097–12102.

11. Griese M. Pulmonary surfactant in health and human lung diseases: state of the art. Eur Respir J 1999;13:1455–1476.

12. Yoshida M, Ikegami M, Reed JA, Chrones ECZ, Whitsett JA. GM-CSF regulates protein and lipid catabolism by alveolar macrophages. Am J Physiol Lung Cell Mol Physiol 2001;280:L379–L386.

13. Doyle IR, Davidson KG, Barr HA, Nicholas TE, Payne K, Pitzchner J. Quantity and structure of surfactant proteins vary among patients with alveolar proteinosis. Am J Respir Crit Care Med 1998;157:658–664.

14. Sallese A, Suzuki T, McCarthy C, Bridges J, Filuta A, Arumugam P, et al. Targeting cholesterol homeostasis in lung diseases. Science 2017;7:10211.

15. McCarthy C, Lee E, Bridges JP, Sallese A, Suzuki T, Woods JC, et al. Statin as a novel pharmacotherapy of pulmonary alveolar proteinosis. Nat Commun 2018;9:3127.

16. Griese M, Bonella F, Costabel U, de Blase J, Tran N-B, Liebsch G. Quantitative lipidomics in pulmonary alveolar proteinosis. Am J Respir Crit Care Med 2019;200:881–887.

© 2019 by the American Thoracic Society

Predictive Biomarkers of Response to Src Inhibitors in Lung Cancer

Getting to YES1

During the last 15 years, predictive molecular pathology and precision medicine have revolutionized the clinical management of non–small cell lung cancer (NSCLC). Mutations that are essential for malignant growth (i.e., driver mutations) are commonly associated with oncogene addiction, or dependence of some cancers on one gene for the maintenance of the malignant phenotype. The discovery of driver mutations in NSCLC has led to the incorporation of tumor molecular genotyping into therapeutic decision making and the development of new therapeutic options, such as TKIs (tyrosine kinase inhibitors) for oncogene-addicted patients with NSCLC (e.g., EGFR, ALK, and ROSI). Unfortunately, despite the identification of new driver mutations and significant advances in targeted therapies, the 5-year survival rate for lung
cancer remains less than 20% (1). Thus, additional strategies to treat lung cancer are urgently needed.

Src family tyrosine kinases regulate multiple genetic and signaling pathways involved in the proliferation, survival, angiogenesis, invasion, and migration of cancer cells (2). Increased Src expression was reported in 60–80% of adenocarcinomas and in 50% of squamous cell carcinomas isolated from patients with NSCLC (3). Src family TKIs have been investigated in clinical trials, but phase 2 trials testing single-agent Src inhibitors in previously treated patients with advanced NSCLC were disappointing (4–6), with one trial showing no activity (6). However, other trials demonstrated marked activity in one patient and prolonged stable disease in several others (4, 5), suggesting there may exist a subset of Src inhibitor–responsive patients with NSCLC that remains molecularly undefined.

In this issue of the Journal, Garmendia and colleagues (pp. 888–899) (7) bring new insight into whether Src family tyrosine kinases may serve as potential therapeutic targets by investigating YES1 genetic alteration in NSCLC. YES1 is a member of the Src family tyrosine kinases and has been shown to play a role in nuclear translocation of EGFR (8) and acquired resistance to EGFR inhibitors in EGFR-mutant lung cancers (9). In this study, Garmendia and colleagues showed using immunohistochemistry that YES1 protein expression is higher in lung cancer cells than normal lung bronchiolar cells. In two cohorts of patients with NSCLC who underwent surgical resection, high YES1 protein expression was an independent predictor of shorter overall survival. Analysis of patients with NSCLC in The Cancer Genome Atlas identified YES1 gene amplification in 15% of lung adenocarcinoma and 25% of patients with lung squamous cell carcinoma. Thus, YES1 is amplified in a significant subset of NSCLC, and its expression correlates with shorter overall survival in patients with NSCLC.

The authors demonstrated that stable YES1 overexpression in human NSCLC cell lines induced proliferation in vitro and increased tumor growth and metastasis in subcutaneous mouse models in vivo. Conversely, genetic depletion of YES1 using siRNAs or CRISPR/Cas9 in human NSCLC cell lines reduced proliferation, survival, and invasion in vitro and tumor growth and lung metastatic growth in vivo. Treatment with the Src inhibitor dasatinib inhibited lung cancer proliferation, invasion, and migration in vitro and growth of subcutaneous tumors in vivo. Garmendia and colleagues also showed that in vivo, dasatinib treatment decreased tumor volume in high YES1-expressing NSCLC cell lines and patient-derived xenograft tumors, whereas low YES1-expressing NSCLC cell lines and patient-derived xenograft tumors were more resistant to dasatinib treatment. These data suggest that YES1 copy number and YES1 protein expression may predict which patients with NSCLC will respond to Src inhibitors.

On the basis of these data, the authors conclude that YES1 should be evaluated clinically as a stratification biomarker for those who may benefit from current or novel Src family TKIs. However, this conclusion must be tempered by experiences targeting kinases with copy number gain and/or overexpression from previous lung cancer trials. Although there has been great success in targeting lung cancer driver mutations in the form of somatic mutations and translocations, disease response to inhibition of potential drivers based on gene amplification and/or protein expression has been less robust. For example, FGFR1 (fibroblast growth factor receptor 1) and MET (hepatocyte growth factor receptor) are two potential therapeutic targets in NSCLC with preclinical studies identifying gene copy number gains and/or overexpression in tissue samples (10–12). However, the initial clinical trials testing inhibition of these targets in patients with NSCLC has been underwhelming.

Ongoing efforts in targeting MET activation have focused on clarifying the exact biomarker needed to determine clinical response (12, 13). Refining the biomarker to focus on MET exon 14 deletion, which leads to MET protein overexpression and activation, as well as clearly defining locus specific amplification and the amount of MET amplification needed to predict response, have led to improved clinical outcomes (13). FGFR1 amplification was also thought to be a potential driving oncogene in squamous cell carcinoma of the lung in preclinical models. However, initial trials of TKIs for FGFR1, based on FGFR1 copy number gain, demonstrated only modest activity in single-group phase 2 trials (14–16). This has led to ongoing studies of additional biomarkers needed to predict clinically meaningful FGFR1 inhibition in patients with NSCLC.

Clearly, additional targeted therapies for NSCLC is an area of great need, particularly in squamous cell carcinoma, for which there has yet to be a successful demonstration of targeted therapy. Members of the Src family tyrosine kinases, including YES1, represent an exciting area of potential future targets for personalized treatment of patients with NSCLC. A full understanding of this proto-oncogene and how it can be measured in a clinically meaningful way is essential to move inhibition of YES1 and other Src family tyrosine kinases forward as effective lung cancer treatment. The work of Garmendia and colleagues has established YES1 as a target worth pursing.

Author disclosures are available with the text of this article at www.atljournals.org.

Howard Y. Li, M.D.
Department of Internal Medicine
Virginia Commonwealth University
Richmond, Virginia
and
Medical Service
Hunter Holmes McGuire Veterans Affairs Medical Center
Richmond, Virginia
Laurie L. Carr, M.D.
Department of Medicine
National Jewish Health
Denver, Colorado

ORCID ID: 0000-0002-1230-2941 (H.Y.L.).

References

1. Howlader N, Noone AM, Krapcho M, Miller D, Brest A, Yu M, et al. SEER cancer statistics review, 1975-2016. Bethesda, MD: National Cancer Institute; 2019 [accessed 2019 May 25]. Available from: https://seer.cancer.gov/csr/1975_2016/

2. Summy JM, Gallick GE. Src family kinases in tumor progression and metastasis. Cancer Metastasis Rev 2003;22:337–358.

3. Mazurenko NN, Kogan EA, Zborovskaya IB, Kisseljov FL. Expression of FGFR1 gene amplification in human small cell and non-small cell lung carcinomas. Eur J Cancer 1992;28:372–377.

4. Laurie SA, Goss GD, Shepherd FA, Reaume MN, Nicholas G, Philip L, et al. A phase II trial of saracatinib, an inhibitor of src kinases, in previously-treated advanced non-small-cell lung cancer: the princess margaret hospital phase II consortium. Clin Lung Cancer 2014;15:52–57.
Life after Pediatric Critical Illness: Risk Factors for Reduced Health-related Quality of Life and Functional Decline

Survivors of a critical illness are at risk to develop physical, cognitive, and psychological impairments that can persist for months to years after they leave the hospital. Health-related quality of life (HRQL) and functional abilities are important measures of outcomes after a critical illness, as they reflect not only the effects of the critical illness, its treatment, and comorbid illness but also physical disability, cognitive impairment, and psychological disorders (depression, anxiety, and post-traumatic stress disorder) after a critical illness in adults (1). A review of HRQL in 557 adult survivors of acute respiratory distress syndrome found a substantially lower HRQL in both physical and mental components compared with age- and sex-matched healthy populations, which was associated with functional disability (2). The preponderance of evidence regarding long-term outcomes after a critical illness comes from adult ICU populations, and less is known about long-term outcomes for children after a critical illness. Children admitted to a pediatric ICU (PICU) have increased vulnerability to develop new or worsening long-term morbidities, including a reduced quality of life and new functional disability. For example, studies of children who had been admitted to a PICU found that they had a reduced HRQL (3) and a high rate of functional disability (up to 82%) after they were discharged from the hospital (4). These findings suggest that, like adult populations, many PICU survivors develop physical, cognitive, and psychological impairments that are associated with reduced HRQL and functional disability.

Although the data regarding HRQL and functional outcomes after a pediatric critical illness have increased in the past 10 years, there are few data regarding risk factors associated with a reduced HRQL or functional decline after pediatric respiratory failure. It is important to understand the risk factors for post-ICU morbidities in pediatric populations in order to understand the full effects of critical illness in children and to identify potential interventions to prevent or improve outcomes. In a study presented in this issue of the Journal, Watson and colleagues (pp. 900–909) evaluated risk factors for a post-PICU decline in functioning and reduced HRQL in children with respiratory failure (5). Children 2 weeks to 17 years of age who were enrolled in the RESTORE (Randomized Evaluation of Sedation Titration for Respiratory Failure) trial were included in the study. Age-appropriate, validated measures of HRQL and functional abilities were assessed at 6 months after PICU discharge via medical record reviews of baseline functioning and parental interviews, and postdischarge functional status and HRQL were assessed by telephone interviews. The parents/guardians of 960 patients were interviewed, and 91% of these patients were discharged home and 6% were discharged to a rehabilitation or assisted-living facility (5).

Post-PICU morbidity was common in pediatric patients with acute respiratory failure. The prevalence of functional decline was 20%, and 19% of the patients had a reduced quality of life. Among patients with normal baseline functioning, 49% had functional decline and 19% had reduced HRQL. Risk factors included sociodemographic factors, preexisting health status, and factors associated with the critical illness factors that occurred during the child’s hospital course (see Table 1 for a summary) (5). The authors found that the magnitude of the new morbidities was similar to that observed in severe underlying diseases such as cancer (5). Similar to findings in adults (6), the trajectories of outcomes were variable and included a continued decline over...