Tracing the origin, tracking the evolution, and the treatment of the future

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The classic approach of using hematoxylin and eosin staining for tumor slides is a cornerstone in the management of non–small cell lung cancer (NSCLC). Although this modality provides valuable histologic information, it does not delve into the biologic determinants of NSCLC. With the advent of gene mutation analysis, driver alterations, such as *EGFR*, *ALK*, and *KRAS*, can predict response to select targeted therapies.¹ As this mutational information had been garnered from patients with advanced metastatic disease, there is little clarity regarding the origins of these mutations in early-stage malignancy as well as the effects that early gene aberrancies have on the course of the disease. Furthermore, given the variable morphologic appearance and prognostic behavior of NSCLC, genetic mutations may not present uniformly throughout the tumor (ie, intratumor heterogeneity [ITH]).

The TRACERx (TRACking Cancer Evolution through therapy [Rx]) clinical trial was developed to help close this knowledge gap. TRACERx is a multicenter cohort study that prospectively seeks to elucidate genetic ITH by performing whole-exome sequencing on early-stage NSCLC tumors that have been treated initially with resection. The ultimate goal of this study lies in performing longitudinal genetic analyses, both during treatment and at time of disease relapse, to allow for a wholistic appreciation of the genetic evolution of these tumors. In turn, the results of this examination can facilitate discovery of new potential drug targets, more accurate prognostication, and increased precision in treatment response assessment. The current publication represents the analysis of 100 enrolled patients.²

In reviewing the TRACERx study in this issue of the *Journal*, Negrão and colleagues³ highlighted the following concepts in the early stages of NSCLC: (1) genetic heterogeneity can impact recurrence and survival; (2) use of multiregional sequencing introduces a significant proportion of patients who have subclonal mutations, thus challenging the paradigm of relying on driver mutation analysis from single-region biopsy specimens; (3) genetic

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Central Message

Elucidating the genetic determinants of the origin and evolution of specific subclonal populations of tumor cells by investigating early-stage lung cancers can help develop new treatment strategies.

See Article page 1199.

ITH may be a suitable therapeutic target by itself; (4) ITH may be rooted in epigenetics, protein expression, and the tumor microenvironment; and (5) the discovery of poor prognostic markers, such as subclonal copy number alterations, may improve patient selection for adjunct therapy.

We and others have shown that the specific histologic composition (eg, solid and micropapillary subtypes) and the immune microenvironment are associated with worse outcomes in early-stage lung adenocarcinoma.⁴⁻⁷ For example, we have found that *KRAS* mutations correlate with the solid histologic subtype.⁸ Subsequent analysis of results from TRACERx may lead to a more complete understanding of the correlation between early-stage genetic variations and histologic subtypes; this will allow for more accurate rationale- and/or biology-based therapies.⁹ Furthermore, the growing knowledge of tumoral genetic, molecular, immunologic, and metabolic factors necessitates a comprehensive analytical platform, which is similar to what was used in TRACERx. Such comprehensive information can yield personalized stratification and treatment response predictions. TRACERx provides the potential for elucidating the genetic determinants of malignant evolution and, when combined with the current understanding of NSCLC prognosis and the development of novel therapeutics, a more effective targeted treatment for various thoracic malignancies.

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