China Lung Cancer Research Highlight

Gene alterations, smoking and histology: when the deeper means the rarer

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Editorial to: *She-Juan An, et al. Identification of enriched driver gene alterations in subgroups of non-small cell lung cancer patients based on histology and smoking status. PLoS One 2012;7:e40109.*

Lung cancer is the leading cause of death for solid tumors worldwide with an annual mortality of over one million (1). Despite advances in defining the molecular mechanisms involved in lung oncogenesis and the remarkable efforts made to improve screening programs for secondary cancer prevention, patients' prognosis remains poor. Lung carcinoma includes a series of different diseases which are roughly divided into two groups based on clinical and histo-pathological features: non-small-cell lung cancer (NSCLC), accounting for almost 80% of lung cancer diagnosis and small cell lung cancer (SCLC) responsible for the remaining 20%. NSCLCs were further classified as: adenocarcinoma (ADC, and its variants); squamous cell carcinoma (SCC) and large cell carcinoma (LCC)—comprising the neuro-endocrine variant (LCNEC). Recently the American Thoracic Society and the European Respiratory Society approved a new classification of lung ADCs which eliminates the former term bronchiole-alveolar (BAC) carcinoma and introduces the new concepts of adenocarcinoma *in situ* (AIS) and minimally invasive adenocarcinoma (MIA) for small solitary ADCs with either pure lepidic growth (AIS) or predominant lepidic growth with ≤5 mm invasion (MIA). Invasive ADCs are classified by predominant pattern after using comprehensive histologic subtyping with lepidic (formerly most mixed subtype tumors with non-mucinous BAC), acinar, papillary, and solid patterns; micropapillary is added as a new histologic subtype (2).

A better understanding of the molecular mechanisms below the complex network between histology, environmental toxics and tumor molecular profile, is mandatory to reach the effective therapeutic treatment and disease control.

From this perspective the paper by She-Juan An and colleagues selected a panel of the most relevant oncogenes and tumor suppressor genes-known to be activated in NSCLC-and aimed to evaluate the incidence of their genetic alterations stratifying a wide number of NSCLC cases according to histology and exposure to cigarette smoking. It is the first paper which investigates a broad spectrum of best known and more novel genes in a more than 500 tumors, obtained after an initial screening of almost 2,000 cases thus proving a clear picture of how molecular lesions vary according to tumor morphology and smoking habit. The results presented allow a number of relevant considerations, firstly in terms of epidemiology, but also for their diagnostic and prognostic implications.

Overall all the genes analyzed are infrequently altered in the Chinese populations with the exception of EGFR (about 40% of cases). Interestingly authors analyzed the expression of a panel of very well known genes together with that of novel genes, such as *DDR2*, *STK11*, *FGFR2* which function is only partially defined but which are emerging as promising actionable NSCLC targets (3).

Although simplistic, tumor genotype is now matched to corresponding phenotype and NSCLC cases can be thus stratified into four classes: (I) ADC not smokers; (II) ADC current smokers; (III) SCC not smokers; (IV) SCC current smokers. Quite unexpectedly, each class features an own asset whit a specific molecular profile. Thus it emerges that *EGFR* is the most frequently altered gene among patients carrying lung ADC both smokers and never smokers; in patients affected by SCC *EGFR* lesions are present among never smokers whereas *PTEN* is the most frequently mutated gene in current smokers. In other words, these findings clearly consent to hypothesize that host life habit (such as exposure to tobacco smoke) may affect and somehow allow the selection and growth of a neoplastic clone enriched by a defined genotype. It should be also be concluded that an even though cancer is a genetic disease (4), a determined cancer genetic profile is prone to be selected, according to a Darwinian law, by a pressure coming from environment.

From this basis, which is the role of driver genes? In which sequence lesions are acquired in different phenotypes?

The paper by She-Juan An and colleagues tries to give an answer by using the approach of incidence analysis through rough molecular screening. For the first time, authors investigate the entire profile of both best known and novel driver genes in such a vast lung cancer population. Although ethnicity may play a role that cannot be ignored, the study provides a clear picture of how and haw frequently genetic lesions affects different NSCLC phenotypes. This approach interestingly points out some pathogenic considerations. For instance, smoking habits might play an active role in selecting *KRAS* mutations or, in other words, these findings confirm lung cancer in never smokers a separate entity. However although for ADC, the findings recall already published data (5), SCC in never smokers seems to have pathogenic mechanisms that differ from known driver genes alterations. Moreover authors recognized a number of overall mutations which involve, as expected, the most frequently altered genes. This observation has implication for both diagnosis and therapeutic management of NSCLC, with also economic consequences. Thus, in front of morphological diagnosis of lung cancer, extensive molecular profiling is mandatory to find an actionable target. Moreover tumor heterogeneity might complicate this scenario since detection of overlap genetic lesions might affect responses to those molecules which are aimed to block only a single mutated target. From this perspective, dedicated screening testing the efficacy of single molecule versus combinatorial approaches is effectively needed.

One of the most relevant consideration emerging by reading this paper, is that tumor heterogeneity creates a number a '*molecular hills*' (in absence of few '*high mountains*') which really complicates the NSCLC landscape. Besides it clearly points out that high-throughput diagnostic approach should be routinely established as soon as possible. Overall, the main message of the paper is that molecular-base epidemiology confirms that NSCLC phenotype (morphology) is the result of a complex and obscure crosstalk between driver genes and environment. The pattern is somehow predictable and derivable by already available epidemiology analysis (e.g., the present work) only in some settings, e.g., smokers *vs.* never smokers, whereas in other cases exhaustive gene expression might be performed. As a consequence, patients carrying lung cancer featuring infrequent lesions must be treated as carrying rare or orphan disease. These findings contribute to underline that NSCLC is a very composite disease and that new classifications based on molecular profile are urgently needed, also for their clinical and prognostic implications.

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