Comparisons between Mouse and Human Studies Will Help the Prevention, Diagnosis, and Treatment of the Deadliest Type of Lung Cancer

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Lung cancer is one type of cancer for which treatment has been "personalized" through the use of specific protein tyrosine kinase inhibitors. Several genes encoding protein kinases have been identified as driver oncogenes in lung adenocarcinoma, the most frequent histological type of lung cancer. The activating aberrations of these genes that drive carcinogenesis include *EGFR* mutations, *ALK* fusions, *ROS1* fusions, and *RET* fusions. These aberrations cause oncogenic addiction in cancer cells; this phenomenon makes the aberrations a therapeutic target for tyrosine kinase inhibitors and has been validated in genetically engineered mouse models (GEMMs) in which oncogene activation is artificially reproduced in the lungs (Table 1). Interestingly, secondary genetic aberrations have been detected in GEMM tumors as in human lung adenocarcinoma.[1] Therefore, GEMMs are useful for understanding the carcinogenic processes and for identifying potential diagnostic and treatment seeds.

In this issue, Dr. Gazdar et al. report a pathological study of tumors in five GEMMs that mirror the development of small-cell lung cancer (SCLC), the most aggressive type of lung cancer, which shows neuroendocrine features.[2] Because SCLC metastasizes and disseminates at an early stage, only a small subset of patients are eligible for surgical resection with curative intent. Therefore, the number of tumor specimens available for large-scale Omics analysis is very limited, and only a few studies have performed genome-wide analysis of the genetic aberrations underlying SCLC.[3–6] Unfortunately, to date, druggable genetic alterations, such as *FGFR1* amplification and *PTEN/PIK3CA* alterations, have been detected in only a small subset of cases, thereby preventing us from developing a personalized medicine approach to SCLC.

Notably, however, observation of human SCLC has led to the generation of five GEMMs, in which well-known tumor suppressor genes, *TP53* and *RB1* (and others), have been engineered to be inactivated in the lung.[3–6] Distinguished pathologists from different institutions performed a detailed and uniform pathological analysis of the resulting lung tumors that developed in those GEMMs. The authors found that these GEMMs were extremely useful for studying human SCLC. The GEMM tumors generated by these engineered genetic aberrations display definite characteristics of SCLC and, as such, will aid future research by compensating for the shortage of human SCLC samples. Future comprehensive Omics analysis of these GEMM tumors should identify genes, pathways, and molecules worthy of further study.

Thus, comparative studies of human and mouse lung tumors will facilitate the prevention, diagnosis, and treatment of the deadliest type of lung cancer.

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TABLE 1. Genetically Engineered Mouse Models of Lung Adenoma and Adenocarcinoma

Driver Oncogene	Genetic Aberration Introduced	Molecular Targeting Drugs Tested	References
KRAS	G12D mutation		Jackson et al. (2001), Johnson et al. (2001)
EGFR	ΔL747–S752 mutation, L858R mutation	Erlotinib, cetuximab	Politi et al. (2006), Ji et al. (2006)
BRAF	V600E mutation	PD0325901, PD184352 (MEK inhibitors)	Dankort et al. (2007), Ji et al. (2007)
HER2	YVMA insertion mutation	Afatinib	Perera et al. (2009)
ALK	*EML4-ALK* fusion	2,4-pyrimidinediamine derivative (ALK inhibitor)	Soda et al. (2008)
ROS1	*EZR-ROS1* fusion	Crizotinib	Arai et al. (2013)
RET	*KIF5B-RET* fusion	Vandetanib	Saito et al. (2014)

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