

Genotype-directed diagnosis and treatment of lung cancer: EGFR and HER2 as molecular paradigms

Lung cancer is the leading cause of cancer mortality worldwide. Great strides have been made against this disease through the identification and therapeutic targeting of oncogenic driver alterations. A paradigm-defining example of the success of this targeted therapy approach is EGFR-mutated lung adenocarcinoma. EGFR-mutated lung adenocarcinoma afflicts approximately 10-30 percent of patients and illustrates both the success and challenges facing the field of precision medicine in oncology.

EGFR inhibitor treatment is widely effective in many EGFR-mutated lung adenocarcinoma patients. However, not all patients respond to treatment and all patients who do respond eventually succumb to disease progression that arises due to acquired resistance to the targeted treatment. Understanding the basis of primary and acquired resistance to EGFR inhibitor treatment is essential in order to devise strategies to prevent or delay this resistance, thereby prolonging patient survival.

In this comprehensive book, we review the current knowledge of the genetic and epigenetic factors that underlie both the response and resistance to EGFR inhibitor treatment in EGFR-mutated lung adenocarcinoma. The underlying biological events contributing to the lack of complete and sustained response to treatment in EGFR-mutated lung cancer are multifactorial. Therefore, the discussion presented in the chapters in this book highlights both tumor-cell intrinsic and extrinsic factors, the role of on-target secondary mutations in EGFR in causing resistance to first- and later-generation EGFR inhibitors, and the emerging understanding of the role of intra- and inter-tumor heterogeneity in modulating response and resistance to first and later-generation EGFR inhibitors.

As the related EGFR family member HER2 is also recurrently mutated as an oncogenic driver in lung cancer, this book also contains the state of the art view on the diagnostic role and therapeutic targeting of mutant HER2 in this disease. Themes arising in EGFR-mutated lung adenocarcinoma are echoed and expanded in the discussion of HER2-driven lung cancer.

In conclusion, the discussions presented herein will serve to summarize the important progress made through genotype-directed therapy in lung cancer through the lens of the EGFR- and HER2-driven molecular subtypes of this disease. Furthermore, factors limiting response and preventing cure are highlighted with the overall goal of charting the future course of basic and translational research that holds promise for improving the depth and duration of therapy response. Ultimately, the goal of these discussions is to stimulate the research community to devise novel strategies that can help transform lung cancer from a lethal disease into a chronic, or even curable condition.



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