Mechanisms of acquired drug resistance to targeted therapies

Lung cancers that harbor activating EGFR mutations and ALK fusions are exquisitely sensitive to small molecule EGFR and ALK tyrosine kinase inhibitors, respectively. However, even though most patients experience dramatic responses, drug resistance invariably develops leading to disease relapse. Similar patterns of sensitivity and acquired resistance are also observed in other subsets of oncogene-addicted lung cancers treated with molecularly targeted therapies (e.g. ROS1 fusions, RET fusions, BRAF mutations, MET exon 14 skipping mutations). We work closely with oncologists in the MGH Center for Thoracic Cancers to identify and characterize mechanisms of acquired resistance in lung cancer patients treated with targeted therapies. By analyzing tumor biopsies or tumor DNA isolated from blood, we have identified acquired secondary mutations and other genomic alterations that cause drug resistance. To functionally interrogate mechanisms of drug resistance, we have developed a robust infrastructure for generating patient-derived cell lines and mouse tumor xenograft (PDX) models from lung cancer patients treated with targeted therapies at the MGH Cancer Center. These models have allowed us to identify novel mechanisms of acquired resistance and test potential new therapies to overcome them.

Targeting KRAS mutant lung cancers

Mutant-selective KRAS inhibitors have recently entered the clinic, however responses are seen in only a minority of patients. Work by our group revealed that many KRAS mutant lung cancers exhibit decreased oncogenic dependency and a dampened apoptotic response that contributes to intrinsic resistance to KRAS targeted therapy. To overcome this limitation, we are exploring novel therapeutic combinations that can overcome these
Selected Publications:


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EGFR mutant lung cancers can develop acquired resistance to EGFR inhibitors [e.g. acquisition of the gatekeeper EGFR**T790M** mutation] by selection of pre-existing EGFR**T790M** cells, or via evolution of initially EGFR**T790M**-negative drug tolerant cells that then develop the mutation during the course of treatment. EGFRi denotes EGFR inhibitor treatment, such as gefitinib or erlotinib. Reproduced from Hata and Niederst, et al. Nature Medicine 2016.

**Tumor adaptation and evolution during treatment**

Despite the development of successive generations of targeted therapies with improved selectivity and potency, acquired resistance inevitably develops. To halt this perpetual cycle of drug resistance, we are investigating novel therapeutic strategies to alter the tumor evolution prior to the development of drug resistance. Our discovery that drug tolerant clones that survive initial therapy can acquire a "second genomic hit" enabling outgrowth of fully resistant clones suggests that these cells may comprise a cellular reservoir from which heterogeneous mechanisms of resistance may arise. Ongoing efforts are focused on characterizing persistent tumor cells that survive during drug treatment in both experimental models and patients and defining mechanisms that drive drug adaptation. By identifying targetable vulnerabilities of these cells, we hope to develop novel therapeutic strategies that will prevent acquired drug resistance.

**Developing novel immunotherapy approaches for lung cancers with low mutation burden**

EGFR mutant and ALK fusion lung cancers typically occur in never-smokers and consequently have low tumor mutation burden and poor response to currently approved immune checkpoint inhibitors. We are developing TCR cellular therapies and novel methods for reprogramming tumor cell antigenicity to direct the immune system to recognize and fight EGFR and ALK lung cancers.

mechanisms and increase sensitivity to KRAS inhibitors. In addition, we are focused on understanding how both inter-patient and intratumoral heterogeneity may influence initial drug response and the development of acquired drug resistance.