in normal tissues. Indeed, to date, there is still no MYC inhibitor in the clinic. We previously designed a dominant negative form of MYC called Omomyc and used its conditional transgenic expression to inhibit MYC function both in vitro and in vivo, demonstrating a potent therapeutic impact in various mouse models of cancer, including non-small cell lung cancer (NSCLC), causing only mild, well-tolerated, and reversible side effects. Importantly, we recently showed that the purified Omomyc mini-protein displays unexpected cell-penetrating properties and can be used by direct tissue delivery or systemic administration to target NSCLC harboring different oncogenic mutation profiles, indicating its potential for clinical development for the treatment of NSCLC patients. Clinical trials testing this use are due to begin in 2020.

IA17

Druggable Vulnerabilities in Therapy-Resistant Lung Cancers

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Oncogene-targeted therapies often drive therapeutic responses in patients with advanced lung cancers, but frequently these responses eventually give way to acquired resistance. Blocking acquired resistance is a substantial and open-ended challenge whose difficulty is underscored by the fact that resistance within individual patients is often polycylic in nature, driven by diverse and co-occurring mechanisms. Here, I will discuss two broad approaches we are employing in the search for therapeutic strategies that delay or circumvent resistance evolution. In the first area, we have identified vulnerabilities present in tumors at minimal residual disease states. For example, we have identified a molecular pathway through which targeted therapies such as EGFR, ALK, and BRAF inhibitors trigger double-strand DNA breaks in the cancer cells that comprise the minimal residual disease state. These cells rely upon an ATM-dependent DNA repair process for their survival and are thus hypersensitive to ATM inhibition. As such, combining oncogene-targeted therapies with an ATM inhibitor leads to more penetrant and durable responses to these agents in vivo. In the second area, we have identified vulnerabilities that arise specifically in tumor cells that develop acquired resistance to oncogene-targeted therapies. Importantly, we have identified scenarios in which these “collateral sensitivities” are conserved across heterogeneous resistant clones with distinct resistance mechanisms, implying that targeting these mechanisms may simultaneously eradicate diverse clones. I will describe examples of mechanism-based collateral sensitivities we have uncovered in lung cancers, melanomas, and leukemias, then demonstrate that by targeting these mechanisms in the upfront setting, it is possible to construct combination therapies that select against resistance.

IA18

A New World for Lung Cancer Vaccines: Beyond Picking a Single Antigen for Everyone

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Immunotherapy was hypothesized as an effective approach for the treatment of lung cancer for decades. Until the last decade, this enthusiasm was met with the cold reality of clinical trials, showing no impact in various mouse models of cancer, including non-small cell lung cancer (NSCLC), which, until recently, was always considered to be immune quiescent. Blockade of the inhibitory PD1-PDL1 pathway on CD8+ and CD4+ tumor-infiltrating lymphocytes (TILs) has revolutionized standard of care for NSCLC patients. Anti-PD1 can specifically target tumor cells without harming normal lung epithelial cells, which ultimately allows for fewer adverse events compared to standard chemotherapy or radiation. However, these approaches do not work in 80% of NSCLC patients; thus, a better understanding of the immune response prior to the development of cancer (heavy smokers and patients with chronic obstructive pulmonary disease [COPD]) compared to active disease (adenocarcinoma [LUAD] and squamous cell carcinoma [LUSC]) is necessary to develop new therapeutic approaches to enhance the antitumor immune response but also to assemble additional noninvasive, accurate screening methods for patients. The current immunotherapies for NSCLC patients do not consider or target B cells despite their predominance in the tumor microenvironment (TME) and key role in the adaptive immune response. Further, in NSCLC patients, current evidence suggests an antitumor role for B cells as they can generate tumor-specific antibodies, present antigens to CD4+ TILs, and are detected within tertiary lymphoid structures (TLS), which also correlate with better prognosis. TLS predominantly contain B cells, CD4+ T conventional cells, and CD14+ myeloid cells; however, unlike normal lymphoid tissues, i.e., lymph node or tonsil, TLS in cancer patients do not always have well-defined germinal centers (GCs). GCs are paramount for proper B-cell development and function. Thus, in order to successfully implement B-cell targeting into future immunotherapies, we must increase our understanding of B-cell function in TLS within premalignancy and overt cancer. We hypothesize that B cells help generate potent, long-term immune responses against lung tumor cells by educating CD4+ T cells in TLS and producing tumor-specific antibodies. Toward this hypothesis, we have evaluated B cells and TLS in premalignancy and overt cancer via single-cell RNA sequencing, advanced spectral cytometry (Cytek Aurora), and multispectral imaging ( Vectra and Nanostring GeoMx platforms). These analyses have revealed key differences in B-cell infiltration and TLS formation as lung cancer develops and progresses. We have utilized our results to create an objective signature for TLS identification. Specifically, we have observed an increase in GC-like TLS as patients develop cancer. We have also begun to evaluate the ex vivo function of B cells in patient tumors via antigen presentation and antibody production assays. We have evidence for a differential function for B cells within the TME that correlates with activation status. Since B cells and TLS are great prognostic indicators in NSCLC patients, an improved objective measure of the different tiers of these structures and how they correlate with disease progression could offer new and viable (a) biomarkers to predict lung cancer progression, (b) targets for early immunotherapeutic intervention in COPD patients that might trigger better antitumor immunity as patients develop lung cancer, and (c) immunotherapeutic targets in patients with already established NSCLC.