and sensitizes established pancreas tumors to gemcitabine. LIF activates a unique set of downstream pathways, distinct from IL-6 and other members of this family of cytokines. This pathway may account for K-Ras’ unique ability to promote stem-ness. The existence of a new effector pathway specific for KRAS therefore offers new opportunities for therapeutic intervention.

Immunomodulatory effects of radiotherapy: Magical effects of the healing beam?

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Immunotherapy is changing the management of metastatic lung cancer. Checkpoint inhibitors have demonstrated promising response in non-small cell lung cancer and are emerging as amongst the most efficacious anticancer agents ever discovered. Checkpoint inhibitors are aimed at reversing mechanisms of T-cell suppression by blocking signaling through regulatory T-cell co-receptors (e.g., CTLA-4 or PD-1) or blocking T-cell suppressive enzymes (e.g., Indolamine 2,3 Dioxygenase (IDO)). These therapies can achieve durable long-term remissions, however, most patients fail to respond, and some can experience significant immune-mediated toxicities (1-3). Combinatorial strategies employing immunotherapy and standard-of-care therapies may increase the efficacy of immunotherapy and extend its benefit to a larger proportion of patients. Little data is available on how best to achieve this goal.

Radiotherapy (RT) is an ideal candidate for combinatorial immunotherapy strategies. In addition to debulking tumor and releasing tumor antigens, RT has well-established immunomodulatory effects (4). These interdependent and overlapping effects include increasing homing and effector function of tumor infiltrating lymphocytes (TILs) including T-cells (5) and natural killer (NK) cells (6), increasing the diversity of the T-cell response (7), destruction of immunosuppressive cells in the tumor microenvironment (8), induction of immunogenic cell death (9,10), increased dendritic cell (DC) trafficking and presentation of tumor antigen (11), and upregulation of immunogenic cell surface receptors (12) and stress ligands (6). Additionally our recent data demonstrate that RT can induce chemokines such as CCL3, 4, and 5 and the critical nature of these chemokines to an anti-tumor immune response and the effectiveness of checkpoint blockade immunotherapy has recently been highlighted (13). The immunomodulatory effects of radiotherapy are complex and some of these effects can be suppressive such as induction of TGF-beta (14), accumulation of immunosuppressive cells (15), upregulation of PD-L1 (16), and upregulation of IDO.

Clinical reports confirm the safety and efficacy of multimodality strategies employing RT and CpG or IL-2 immunotherapy (17,18). There is also data to suggest synergy between RT and checkpoint inhibition (16,19,20). Dozens of clinical trials testing such combinatorial strategies are underway with countless others in preparation, which will together likely accrue thousands of patients. There is considerable variability in “standard-of-care” RT regimens and combinatorial strategies could employ a wide variety of dose/fractionation regimens, sequencing/timing regimens, and even RT quality (i.e. photons vs. protons). There is limited mechanistic data available to guide how to best combine these modalities (21,22). These variables can substantially alter the efficacy of combined RT + immunotherapy strategies. A framework for appropriately combining these therapies is needed and will have an immediate impact on patient care. It is possible that different immunotherapies and different tumors will behave differently in response to these RT variables. The mechanistic immune effects of RT and immunotherapy are complex. Identifying the best strategies to combine these immune effects will likely be similarly complex.

References
Sox2 cooperates with Lkb1 loss to promote squamous cell lung cancer

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Squamous cell carcinoma (SCC) of the lung is the second most common subtype of lung cancer with limited treatment options and a poor survival rate. Until recently, mouse models of SCC have been limited. Using lentiviral delivery of Sox2 to the mouse lung, we tested the ability of Sox2 to promote tumorigenesis in multiple tumor suppressor backgrounds. Expression of Sox2 specifically cooperates with loss of Lkb1 to promote squamous lung tumors. Importantly, Sox2 expression and mTOR pathway activation frequently co-occur in human squamous tumors. Mouse squamous tumors exhibit characteristic histopathology and biomarker expression similar to human SCC. Murine SCCs also mimic human SCCs by activation of therapeutically relevant pathways including STAT and mTOR. We show that Sox2 expression is sufficient to induce phosphorylated Stat3 in vitro (Mukhopadhyay et al, Cell Reports, 2014). An inducible genetic model of Sox2 expression and Lkb1 have been generated and are being used to interrogate the cell of origin for squamous cell lung cancer. In addition, Sox2-driven tumors exhibit innate and adaptive immune cell infiltration, similar to the recent PTENfl/flLkb1fl/fl model of SCC. These models may be useful to study immunotherapies and their mechanism of action, and to test the contribution of additional driver alterations in SCC.

Proximalization therapy for KRas mutant adenocarcinoma

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KRAS activating mutations are common in lung adenocarcinoma and are currently not able to be directly targeted. These are most likely early mutations in the adenoma-adenocarcinoma sequence and may be present in phenotypically normal lung. Thus, targeted therapy would be useful in early stage and/or screened patients. In order to begin to develop agents targeting these early lesions, we have used cell lineage specific CreER mouse models to analyze cell-of-origin in the mouse lung. When KrasG12D is induced in various cells throughout the respiratory epithelium, Type II cells are the primary cell-of-origin of lung adenocarcinoma. To delve into mechanism, using gain and loss of function genetic models, we discovered that low Sox2 expression with resulting active Notch signaling dictate the ability of Type II cells to proliferate and progress into adenocarcinoma upon KrasG12D activation. Because low Sox2 and high Notch expression characterize a distal lung epithelial progenitor state, we hypothesized that Kras activation leads to dedifferentiation of Type II cells. We demonstrated that Kras activation in Type II cells leads to Spc+Rage+ bipotent progenitor-like cells that also express specific the lung embryonic development markers Sox9 and Ezh2. Next, we use a mouse genetic approach to show that this dedifferentiation requires Notch signaling. Additionally, Sox2 upregulation genetically and chemically profound inhibit KrasG12D-induced...