Stage I Lung Adenocarcinoma Gene Expression Associated with Aggressive Histologic Features for Guiding Precision Surgery and Therapy


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Background: Stage I lung adenocarcinomas (LUADs) show heterogeneity in histologic patterns that correlate with malignant behavior. Solid, micropapillary, and cribriform patterns are associated with worse survival whereas lepidic (in situ) predominance has the best prognosis. In this study, we sought to characterize histologic pattern-specific gene expression in resected clinical stage I LUADs. We also aimed to train and validate a genomic biomarker predictive of histologic aggressive patterns with the ultimate goal of being able to impact surgical and therapeutic decision making for post-biopsy management.

Methods: A training cohort of 56 tumors from patients with stage I LUAD was included for pathologic annotation and whole-exome RNA sequencing. Histologic pattern subtyping in 5% increments including all diagnostic slides was performed. A single representative FFPE block was chosen for RNA sequencing. Negative binomial models were used to identify gene expression differences associated with percent solid, cribriform, or micropapillary histology, and EnrichR was used for pathway enrichment analysis. A random-forest classifier predicting aggressive histologic patterns was trained using 5-fold cross validation. An independent set of <2.0 cm clinical stage I LUAD was macrodissected into 32 paired components (lepidic + non-lepidic regions) and subjected to RNAseq. Six tumors were defined as low malignant potential (LMP: lepidic + acinar/papillary) and ten tumors were defined as overtly malignant potential (OMP: lepidic + solid/micropapillary/cribriform).

Results: In the training cohort, we identified 1,322 genes associated with tumor histologic composition (FDR q <0.05 and fold-change > 2). Genes whose expression differs with solid histology% were enriched for involvement in DNA replication, cell cycle regulation, and inflammation (FDR q <0.001). Genes associated with microsatellite% were enriched for involvement in tRNA-aminoacylation and decrease of T-cell activity (FDR q <0.001). The functional enrichment of genes associated with cribriform% was less informative. A gene expression classifier was trained to predict the presence of aggressive histology. We validated this classifier on a set of 16 tumor specimens from which we macrodissected and analyzed tissue from the most aggressive histologic pattern (AUC = 0.92). We also found that this classifier could differentiate between lepidic regions isolated from OMP and LMP tumors (AUC = 0.81).

Conclusion: We identified solid-, microsatellite-, and cribriform-specific gene expression among clinical stage I LUADs and developed a classifier predictive of aggressive histologic features using either lepidic (in situ) or nonlepidic components. This biomarker has the potential to predict histologic aggressiveness even from presurgical tumor biopsies where all histologic patterns may not be represented. Such a biomarker may be useful in guiding clinical decision making, including extent of surgical resection.

Immune-Suppressive Microenvironment Induced by Increased Treg During EGFR-TKI Mediated IP-10 and TGF-β

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Background: Studies on the immune microenvironment of EGFR mutant lung cancer have been limited. We analyzed the effect of immune microenvironments on the development of EGFR-TKI resistance in EGFR-mutated lung cancer. Methods: We generated a NINA-antigen-inducible tumor cell line from a KrasG12D/P53-/- mouse lung tumor. Antigen expression in this model is temporally controlled via systemic drug delivery, and generates responses in both transgenic and endogenous CDB T cells. We will use this model to investigate specific T-cell responses to tumors and to assess how therapies such as checkpoint blockade impact T-cell response.

Investigating Antitumor T-Cell Responses Using NINJA: An Inducible Genetic Model for Creating Neoantigens

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Historically, attempts to generate inducible neoantigens in mouse models have been hindered by leaky expression of the antigen in the thymus, leading to central tolerance in developing CD8 and CD4 T cells. We have developed the Inversion Inducible NeoAntigen (NINJA) model to resolve the existing problems of tolerance and leakiness using RNA splicing, DNA recombination, and three levels of regulation to control induction of neoantigen. Furthermore, this inducible model system is compatible with existing Cre-driven models of cancer, and we have generated a NINA-antigen-inducible tumor cell line from a KrasG12D/P53-/- mouse lung tumor. Antigen expression in this model is temporally controlled via systemic drug delivery, and generates responses in both transgenic and endogenous CD8 T cells. We will use this model to investigate specific T-cell responses to tumors and to assess how therapies such as checkpoint blockade impact T-cell response.