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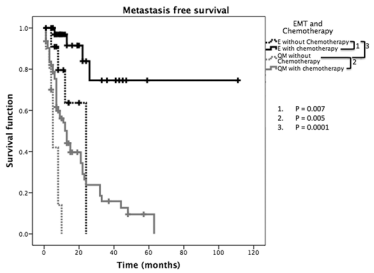
MODERN PATHOLOGY

Predictive power of quasimesenchymal phenotype in epithelial malignancies

https://doi.org/10.1038/s41379-018-0196-2



Mahadevan et al. used RNA in situ hybridization probes for epithelial–mesenchymal transition-related genes expressed in circulating tumor cells to assess the role of this transition in metastasis. Using a panel of 158 pancreatic ductal adenocarcinomas and 205 colonic adenocarcinomas, the group assessed expression of their RNA probes, using SMAD4 expression as a biomarker. They developed an expression signature that signified epithelial phenotypes and a second that signified quasimesenchymal phenotypes and showed that the quasimesenchymal phenotype, in both pancreatic and colonic adenocarcinoma samples, correlated with significantly shorter disease-specific and metastasis-free survival. SMAD4 loss demonstrated the same thing, but proved to be a less robust predictor of metastases. Chemotherapy-naïve epithelial tumors showed a superior metastasis-free survival when compared to chemotherapy-naïve quasimesenchymal tumors. This could allow predictive modeling in clinical care and better assessment for clinical trial entry to better target current therapeutic strategies.

T-cell infiltration in DLBCL patients

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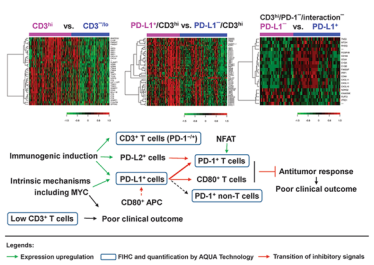

Anti-PD-1/PD-L1 immunotherapy is now a cornerstone in oncology; however, the prognostic significance of PD-1/PD-L1 expression in diffuse large B-cell lymphoma (DLBCL) treated with standard chemotherapy has been inconsistent to the point of contradictory. Using three-marker fluorescent multiplex immunohistochemistry and automated quantitative analysis technology to assess $CD3^+$, $PD\text{-}L1^+$ and $PD\text{-}1^+CD3^+$ expression in diagnostic samples across 414 patients, Li et al. found that low T-cell tissue cellularity, tissue $PD\text{-}L1^+$ expression, $PD\text{-}1^+CD3^+$ expression and PD-1/PD-L1 interaction showed hierarchical adverse prognostic effects. PD-1/PD-L1 interaction showed favorable prognostic effect in $PD\text{-}L1^+$ patients without high $CD3^+$ tissue cellularity and vice versa. The group was able to discern several features that when combined resulted in more convincing prognostic conclusions for DLBCL patients in their test cohort. They conclude that only DLBCL patients with sufficient T-cell infiltration would likely see benefit from PD-1/PD-L1 blockade.

LABORATORY INVESTIGATION

Surfactant therapy supports fuctional remodeling in pulmonary fibrosis

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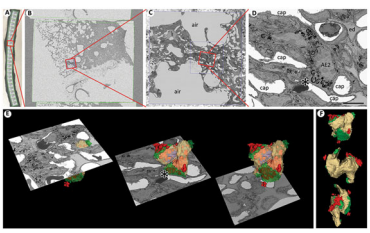

Beike et al. evaluated the role that surfactant dysfunction played in alveolar collapse preceding fibrosis and loss of alveolar epithelial type II (AE2) cells in idiopathic pulmonary fibrosis (IPF) using an overexpressed-TGF-β1 mouse model, which mimics this alveolar collapse. Treating TGF-β1-overexpressing mice with either intratracheal surfactant (Surf group) or 0.9% NaCl (Saline group) and assessing lung mechanics on day 7 and day 14 they showed that the Surf group had significantly improved tissue elastance, higher numbers of open alveoli and increased alveolar size on day 7; these features remained significantly improved on day 14. The surface area of AE2 cells was increased in the Surf group. Using 3D

reconstruction by scanning electron microscope they were able to demonstrate that AE2 cells were trapped without contact to airspaces in both the TGF-β1 mice and human IPF. Surfactant therapy and control of TGF-β1 signaling may reduce pro-fibrotic remolding in these patients.

Differential roles of BMP and Wnt pathways in cardiac development

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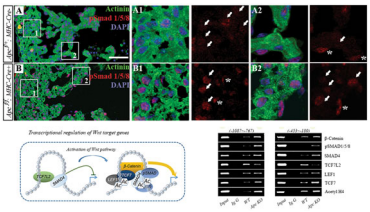

BMP and Wnt pathways regulate cell proliferation and differentiation, but their combined role during late cardiac development remains poorly defined. Two families of nuclear mediators, T-cell factor (TCF) and lymphoid enhancer factor (LEF), are known to mediate Wnt/β-catenin signaling throughout cardiac development. Ye et al. demonstrate that temporal and spatial control of heart maturation is regulated by these factors. The relative levels of each family member throughout cardiac development, along with their relative locations, define an intensity gradient of TCF7L2 that opposes β-catenin in fetal hearts. Wnt signaling differentially regulates LEF1, TCF7, TCF7L1 and TCF7L2 expression in response to *Apc* deletion, and this activation is responsible for target gene activation by switching between enhancers and recruiting pSMADs. The network is a tightly balanced and interwoven system that when dysregulated can lead to proliferation defects and congenital heart abnormalities.

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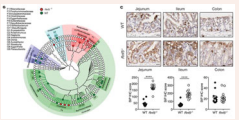
11 Bacterial strains from *Rnf*$^{-/-}$ mice restrict melanoma growth in Wt mice

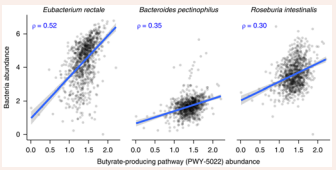
Mice lacking the ubiquitin ligase RNF5 were shown to exhibit attenuated activation of the unfolded protein response (UPR) components, which has downstream effects on inflammasome, recruitment of dendritic cells and expression of antimicrobial peptides in intestinal epithelial cells. Curiously, reduced UPR expression is also seen in both mouse and human melanoma specimens that responded to immune checkpoint therapy. A subset of 11 bacterial strains were identified as being enriched in *Rnf5*$^{-/-}$ mice. These specific bacteria, when introduced orally to germ-free WT mice, conferred a previously unseen antitumor immunity and restricted melanoma growth through increased expression of Toll-like receptors. This study identifies an unexpected relationship between the UPR and gut microbiome and opens doors for further analysis of the relationship between the UPR, gut microbiota and immune checkpoint activity in the clinic.



Nature Communications 2019;10:1492; https://doi.org/10.1038/s41467-019-09525-y

Manipulation of gut microbiome in metabolic diseases

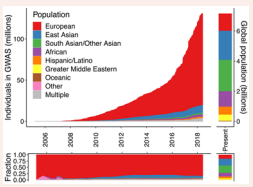
Data are accumulating that link the human gut microbiome to immune function and metabolic disease, including type 2 diabetes and obesity. Sanna et al. show a causal effect of butyrate-producing activity of the gut following a glucose-tolerance test, with specific bacteria increasing in abundance in sharp correlation with butyrate abundance. Using bidirectional Mendelian randomization on a normoglycemic patient group, 17 traits were identified to increase fecal propionate levels and to be causally associated with an increase in body mass index. Larger sample sizes will be required to fully assess microbiome features and better understand the interplay between the gut microbiome and host metabolism. This group explored whether manipulation of the gut microbiome might offer an alternative to pharmacological interventions. Should such manipulation be demonstrated to lead to clinical benefit, it could represent an important avenue of intervention in common metabolic diseases.



Nature Genetics 2019;51:600–605; https://doi.org/10.1038/s41588-019-0350-x

Current polygenic risk scores can exacerbate health disparities

The development of polygenic risk scores as a way to predict complex traits based on genetic data is a growing field, but Martin et al. elaborate some complex ethical considerations to be addressed before they can be widely utilized. Historic biases have been seen in European genome-wide association studies, which have far greater sample sizes than those undertaken in other regions. The use of polygenic risk scores in precision medicine would therefore bias benefit towards those of European descent, not because of inferred clinical benefit but because of data availability. The authors illustrate that understudied populations reveal variants that could be common in these groups but rare/absent in European populations and would not, therefore, be visible even with larger European sample sizes. They encourage researchers to seek greater diversity in genetic studies and an open system for public dissemination of data to allow more equitable applications of polygenic risk scores.



Nature Genetics 2019;51:584–591; https://doi.org/10.1038/s41588-019-0379-x