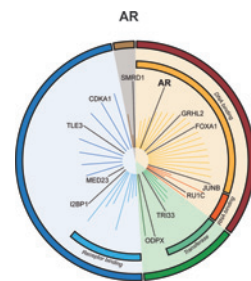


GRHL2: A Novel Androgen Receptor Coregulator

Paltoglou and colleagues employed a novel proteomic technique to identify a new androgen receptor (AR) coregulator, the transcription factor Grainyhead-like 2 (GRHL2), in oncogenic AR signaling. GRHL2 was amplified and overexpressed in human prostate cancer and also colocalized with AR. The authors show in multiple models that GRHL2 maintained AR expression and was required for cell proliferation. Additionally, GRHL2 enhanced AR's transcriptional activity and colocalized with AR on chromatin to regulate genes involved in prostate cancer progression. Further, GRHL2 was regulated by AR, resulting in a positive feedback loop. Interestingly, GRHL2 also suppressed epithelial-mesenchymal transition and prostate cancer cell invasion. In fact, AR aided GRHL2 in maintaining an epithelial phenotype. These authors have identified a novel AR coregulator that enhances oncogenic AR signaling and suppresses metastasis. (Image from cited article courtesy of publisher.)

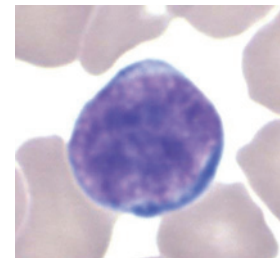
Paltoglou S, Rajdeep D, Townley SL, Hickey T, Tarulli G, Coutinho I, et al. Novel androgen receptor coregulator GRHL2 exerts both oncogenic and antimetastatic functions in prostate cancer. *Cancer Res* 2017;77:3417–30.



Tumor Burden in Check-Point Therapy

Huang and colleagues monitored serial peripheral immune cells from 29 patients with stage IV melanoma treated with anti-PD-1 antibody and age-matched healthy donors using high-dimensional flow cytometry, mass cytometry, and RNA sequencing. CD4, CD8, and memory T-cell subsets were similar between groups, but circulating CD8 T cells with an exhausted-phenotype (T_{ex} cells) showed increased frequency of reinvigorated T cells in anti-PD-1 treated patients. Although >75% of patients demonstrated this peripheral T_{ex} -cell reinvigoration signal, only a third demonstrated clinical response. The ratio of T_{ex} -cell reinvigoration to total tumor burden, assessed radiologically, predicted clinical response even at 6-weeks following treatment, suggesting that immune therapies require low tumor burden. These findings illuminate the utility of blood-based immune monitoring, identifies a candidate predictive reinvigoration score and suggests tumor debulking may augment immune therapy responses. (Image by Glenn Littel courtesy of Wikimedia Commons.)

Huang AC, Postow MA, Orlowski RJ, Mick R, Bengsch B, Manne S, et al. T-cell invigoration to tumour burden ratio associated with anti-PD-1 response. *Nature* 2017;545:60–5.



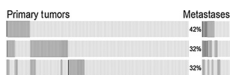
Wnt-Producing Niche in Lung Adenocarcinoma

Wnt signaling is essential for *BRAF*- and *KRAS*-driven lung adenocarcinomas, for which few therapies exist. Tammela and colleagues show that such lung adenocarcinomas consist of two adjacent subpopulations of cells, one that produces Wnt ligands and one that responds to Wnt ligands. The subpopulation that produced Wnt ligands acted as a niche for the Wnt-responding $Lgr5^{+}$ cells, which propagated in response. Perturbation of Wnt signaling, genetically or via a small-molecule inhibitor of the Wnt acyl-transferase Porcupine, significantly attenuated lung adenocarcinoma growth and improved tumor-free survival. *Porcupine* expression was significantly increased in adenocarcinomas relative to adenomas, consistent with inactivation of *Porcupine* attenuating adenocarcinoma growth but having little effect on adenoma formation. The authors then identified a Wnt ligand secretion gene expression signature, which correlated with decreased survival and increased tumor grade of lung adenocarcinoma patients. (Image by Jonathan Wilkins courtesy of Wikimedia Commons.)

Tammela T, Sanchez-Rivera FJ, Cetinbas NM, Wu K, Joshi NS, Helenius K, et al. A Wnt-producing niche drives proliferative potential and progression in lung adenocarcinoma. *Nature* 2017;545:355–9.



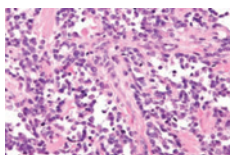
Embryonic TWIST1-HOXA9 Reactivation in Metastasis



The transcription factor TWIST1 has been shown to promote prostate cancer metastasis mediated, in part, by the homeobox transcription factor HOXA9. Malek and colleagues observed that TWIST1 and HOXA9, coexpressed in mouse prostate and silenced postnatally, were reactivated in mouse and human primary prostate tumors, and further enriched in metastases. Coexpression correlated with survival in patients. TWIST1 formed a complex with WDR5 and the lncRNA Hottip/HOTTIP, which regulates chromatin in the Hox/HOX cluster during development. Overexpression of TWIST1 resulted in coenrichment of TWIST1 and WDR5 as well as a WDR5-dependent increase in H3K4me3 at the Hoxa9/HOXA9 promoter. TWIST1 induced upregulation of HOXA9, and aggressive cell phenotypes required expression of WDR5 and Hottip/HOTTIP, with pharmacological inhibitors of HOXA9 suppressing TWIST1-mediated aggressive prostate cancer phenotypes. These authors identified (i) a novel mechanism of chromatin regulation, with TWIST1 increasing H3K4 trimethylation at target gene promoters, and (ii) a potentially therapeutically targetable TWIST1-HOXA9 embryonic prostate developmental program reactivated during prostate cancer metastasis. (Image from cited article courtesy of publisher.)

Malek R, Gajula RP, Williams RD, Nghiem B, Simons BW, Nugent K, et al. TWIST1-WDR5-Hottip regulates Hoxa9 chromatin to facilitate prostate cancer metastasis. *Cancer Res* 2017;77:3181–93.

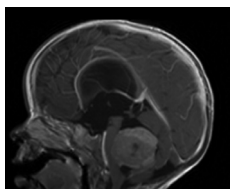
Chimeric Transcription Factors Modulate the Chromatin Landscape



Alveolar rhabdomyosarcoma is characterized by the oncogenic fusion transcription factor PAX3-FOXO1 that comprises the PAX3 DNA binding domain and the FOXO1 transactivation domain. The resulting fusion protein, P3F, drives a myogenic transcription program that sustains a proliferative myoblast-like state. Gryder and colleagues describe how P3F alters the chromatin landscape to support oncogenic transcription. P3F drives formation of super enhancers at key master transcription factors including MYCN, MYOD1, and MYOG, resulting in their high-level expression. Together with P3F, these transcription factors assemble additional super enhancers that regulate myogenic genes and oncogenes. P3F interacts with BRD4 at these super enhancers, an interaction obliterated by the BRD4 inhibitor, JQ1, resulting in rapid degradation of the fusion protein and dampening of P3F mediated oncogenic transcription. This work illustrates how chimeric transcription factors contribute to oncogenic transcription by modulating the chromatin landscape. (Image courtesy of Wikimedia Commons.)

Gryder BE, Yohe ME, Chou HC, Zhang X, Marques J, Wachtel M, et al. PAX3-FOXO1 establishes myogenic super enhancers and confers BET bromodomain vulnerability. *Cancer Discovery*; Published OnlineFirst April 26, 2017; doi: 10.1158/2159-8290.CD-16-1297.

Discerning Cell(s) of Origin for High-Risk Medulloblastoma



Medulloblastoma is the most common type of pediatric malignant primary brain tumor comprised of at least four distinct subgroups. Genetic and phenotypic differences amongst these subgroups are due, in part, to differences in their cellular origin. One of the most aggressive subgroups, MYC-driven medulloblastoma (Group 3, MB_{G3}), is one of the most aggressive subgroups, but the role of Myc in transforming embryonic stem/progenitors into malignant cells has not been tested. Kawachi and colleagues electroporated a conditional MYC-overexpressing and dominant-negative TP53 (Trp53DN) construct into hindbrains of E13.5 Blbp-Cre mice. MB_{G3} formed with 100% penetrance. Lineage tracing of progenitor cells confirmed recombination of transfected genes within Pax6⁺ cells of external granular layer, Sox2⁺ cells in ventricular zone, and Pax2⁺ cells migrating deep into the cerebellum. Transfection of MYC without Trp53DN led to rare choroid plexus carcinomas rather than medulloblastoma. The locations of Blbp-MYC and human MB_{G3} overlapped significantly compared with the other medulloblastoma subgroups, suggesting distinct cells of origin for MB_{G3}. Atoh1-Cre recapitulated MB_{G3}, whereas Gad2-Cre and Ptf1a-Cre led to MB_{G3} with increased latency and decreased penetrance, suggesting resistance of these inhibitory interneuron progenitors to Myc-induced transformation. This study suggests that transformation in MB_{G3} begins in embryogenesis, with distinct cell types showing critical periods of susceptibility to transformation. (Image courtesy of Wikimedia Commons.)

Kawachi D, Ogg RJ, Liu L, Shih DJH, Finkelstein D, Murphy BL, et al. Novel MYC-driven medulloblastoma models from multiple embryonic cerebellar cells. *Oncogene*; Published ahead of print May 15, 2017; doi: 10.1038/onc.2017.110.

Note: Breaking Advances are written by *Cancer Research* editors. Readers are encouraged to consult the articles referred to in each item for full details on the findings described.