Cancer Research
Breaking Insights
Highlights from Recent Cancer Literature
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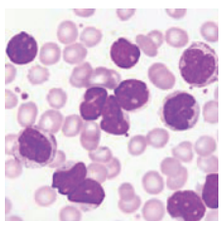
Mechanisms of Therapy Resistance in T-ALL

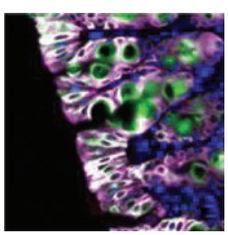


Using a model of T-cell acute lymphoblastic leukemia (T-ALL) in living mice, Tremblay and colleagues demonstrated that self-renewal, clonal evolution, and resistance to therapy were limited to a rare subpopulation of cell-cycle-restricted pre-leukemic stem cells (pre-LSC). These cells activated both p53 and its target p21, a cell-cycle inhibitor, and acquired oncogenic *Notch1* mutations necessary for evolution to T-ALL. Deletion of *p21* led to proliferation of pre-LSCs, followed by clonal extinction through loss of asymmetric cell division and terminal differentiation. Thus, cell-cycle restriction is a fundamental property of pre-LSCs that underlies their relapse following chemotherapy.

Expert Commentary: These data suggest inducing proliferation of pre-LSCs as a promising approach to improve outcomes for acute leukemia.

Tremblay CS, Saw J, Chiu SK, Wong NC, Tsyganov K, Ghotb S, et al. Restricted cell cycle is essential for clonal evolution and therapeutic resistance of pre-leukemic stem cells. Nat Commun 2018;9:3535. doi: 10.1038/s41467-018-06021–7.

Wnt Signaling Drives Macropinocytosis in Cancer



Activation of macropinocytosis has recently been demonstrated as a means by which Ras-transformed cancers take up nutrients. Inhibiting macropinocytosis could be a potential strategy to deprive Ras-driven cancers of nutrients. Redelman-Sidi and colleagues performed a genome-wide shRNA screen for activators of macropinocytosis in *RAS* WT cancer cells. They identified and validated the canonical Wnt pathway as a pivotal activator of this process, enabling absorption of essential amino acids. Macropinocytosis in mutant *RAS*-driven cancer cells also required Wnt signaling across mutant *RAS* cells from diverse tissues of origin. They hypothesized that Wnt-driven macropinocytosis results in increased bacterial translocation into the colon wall, a known early driver of colon tumorigenesis. Using an inducible *APC* knockdown mouse model of polyposis, they showed an increase in macropinocytosis after 8 days, prior to polyp formation, and a 9-fold increase in intraluminal bacteria in the wall of the colon.

Expert Commentary: Therapeutic targeting of macropinocytosis could leverage the Wnt-dependent uptake of essential amino acids by cancer cells. (*Image from cited article courtesy of publisher.*)

Redelman-Sidi G, Binyamin A, Gaeta I, Palm W, Thompson CB, Romesser PB, et al. The canonical Wnt pathway drives macropinocytsis in cancer. Cancer Res 2018;78:4658–70.

Reconstructing the Natural History of Childhood Sarcomas

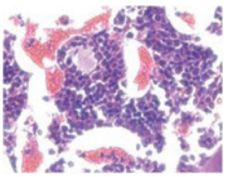
Ewing sarcoma (ES) is a bone and soft tissue tumor, which is often characterized by aberrant gene fusions. Anderson and colleagues analyzed 124 Ewing sarcoma tumors using whole genome sequencing to identify how these gene fusions are generated. The key fusion EWSR1-ETS arose in 42% of cases through complex loop-like rearrangements called chromoplexy, involving multiple chromosomes and partners. These events revealed remarkably low numbers of different breakpoints, suggesting an early burst of rearrangements lead to these loops. Although the rearrangement was conserved from diagnosis to relapse, mutational patterns were highly divergent, suggesting that divergence between primary and relapse clones occurred 1-2 years before diagnosis, with subsequent clonal evolution occurring in parallel.

Expert Commentary: By studying the clonal evolution of structural rearrangements compared with somatic nucleotide variants, insights into tumor latency can potentially be leveraged to identify clinically undetectable early relapse tumors through analysis of biomarkers such as circulating tumor DNA. *(Image by Biswarup Ganguly courtesy of Wikimedia Commons.)*

Anderson ND, de Borja R, Young MD, Fuligni F, Rosic A, Roberts ND, et al. Rearrangement bursts generate canonical gene fusions in bone and soft tissue tumors. Science 2018;361. doi: 10.1126/science.aam8419.

Breaking Insights

Bone Marrow–Resident Melanoma Cells

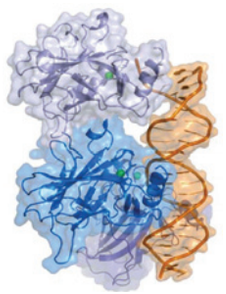


Melanoma is the most aggressive form of skin cancer, with systemic metastasis being the major cause of death. Vishnoi and colleagues hypothesized that melanoma-circulating tumor cells (CTC) home to and reside in the bone marrow during the asymptomatic phase of disease progression. They isolated CTC-enriched cell populations from the blood of patients with metastatic melanoma and expanded these in immunocompromised mice. Comparing the transcriptomes of bone marrow-resident tumor cells (BMRTC) with CTCs, they identified elevated expression of USP7, a key deubiquinating enzyme, as a distinctive gene signature of BMRTCs. Inhibition of USP7 reduced the metastatic potential of BMRTCs by prolonging their arrest in the bone marrow.

Expert Commentary: This study suggests that USP7 inhibitors may be useful in eliminating residual melanoma cells in the bone marrow, thereby preventing further metastatic spread. *(Image from cited article courtesy of publisher.)*

Vishnoi M, Boral D, Liu H, Sprouse ML, Yin W, Goswami-Sewell D, et al. Targeting USP7 identifies a metastasis-competent state within bone marrow-resident melanoma CTCs. Cancer Res 2018;78:5349–62.

Targeting Gain-of-Function p53 Mutants



TP53 missense mutations are prevalent in tumors, including colorectal cancers. Schulz-Heddergott and colleagues show that the most common p53 mutant, $p53^{R248Q}$, exerts gain-of-function activities through hyperactivation of Stat3 signaling in colorectal cancer models. Mechanistically, $p53^{R248Q}$ binds to Stat3, displacing the tyrosine phosphatase SHP2, which dephosphorylates and inactivates Stat3. Gain of function in mutant p53 proteins required stabilization by the heat shock protein 90 (HSP90) chaperone system. Both genetic and pharmacological approaches (HSP90 inhibitors) demonstrate that continued expression of $p53^{R248Q}$ was required for sustained pStat3 signaling and growth of established colorectal cancer.

Expert Commentary: Stabilized mutant p53 in colorectal cancer correlates with enhanced Stat3 signaling and poor patient survival. The destabilization of mutant p53 with HSP90 inhibitors provides a new therapeutic opportunity in colorectal cancer and potentially other solid tumors that express R248Q p53 mutations. *(Image courtesy of Wikimedia Commons.)*

Schulz-Heddergott R, Stark N, Edmunds SJ, Li J, Conradi LC, Bohnenberger H, et al. Therapeutic ablation of gain-of-function mutant p53 in colorectal cancer inhibits Stat3-mediated tumor growth and invasion. Cancer Cell 2018;34:298–314.

Dependencies in *MYCN*-Amplified Neuroblastoma

MYCN-amplified tumors are a particularly high-risk subset of neuroblastomas that are difficult to treat. Targeting tumor-specific gene dependencies could provide effective therapeutic strategies. Durbin and colleagues used genome-scale CRISPR–Cas9 strategies to identify 147 candidate genes selectively essential to the growth and survival of *MYCN*-amplified neuroblastoma cells compared with >300 other human cancer cell lines. Genome-wide chromatin immunoprecipitation, followed by high-throughput sequencing analysis, identified six transcription factors—MYCN, HAND2, ISL1, PHOX2B, GATA3, and TBX2—as part of the core regulatory circuitry (CRC) that maintains *MYCN*-amplified neuroblastoma. BRD4 and CDK7 inhibitors acted in synergy to downregulate expression of the CRC transcription factors.

Expert Commentary: This study identified genes critical for the biology and pathology of *MYCN*-amplified neuroblastoma that are potential therapeutic targets. *(Image courtesy of Wikimedia Commons.)*

Durbin AD, Zimmerman MW, Dharia NV, Abraham BJ, Iniguez AB, Weichert-Leahey N, et al. Selective gene dependencies in MYCN-amplified neuroblastoma include the core transcriptional regulatory circuitry. Nat Genet 2018;50:1240–6.

Note: Breaking Insights 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.