Dissecting Clonal Hematopoiesis in Tissues of Classical Hodgkin Lymphoma Patients

- Microdissection of tumors, matching normal tissue, and blood identifies 5 cases of clonal hematopoiesis among 40 patients with classical Hodgkin lymphoma.

- These cases illustrate scenarios of shared as well as distinct clonal composition of the tumor micro-environment and systemic hematopoiesis.

- Clonal evolution during progression to secondary AML is described in a case with KRAS^{G60D} mutation in tumor microenvironment and nonoverlapping DNMT3A^{R882H} in the tumor.

Clonal hematopoiesis of indeterminate potential (CHIP) carries increased risk of hematologic malignancy and harbors oncogenic driver mutations. Variant allele frequencies (VAF) determined by bulk sequencing suggest CHIP is common in lymphoma. It remains unclear whether CHIP is a preneoplastic state directly progressing to malignancy, promotes lymphomagenesis through shaping the microenvironment, or contains independently coexisting clones. This study dissects clonal composition within the tumor by laser-capture microdissection of classical Hodgkin lymphoma (cHL) cells and their lymph node microenvironment. The five characterized cases encompass all of these scenarios. In some cases, mutations are found exclusively in lymphoma cells; in others, they are shared with the microenvironment. In two cases, cHL cells exist within clonal territories of nonmalignant cells with different genetic lesions, demonstrating that an expanded clone with oncogenic mutation may coexist with lymphoma rather than initiate it. By combining these data with blood VAF for the same lesions, the authors infer developmental trajectories and reveal differences between local and systemic clonal composition. This work documents a spectrum of possibilities by which CHIP contributes to cHL at local and systemic levels, expanding current understanding of clonal hematopoiesis in blood cancers. ∎

Large-scale Identification of Clonal Hematopoiesis and Mutations Recurrent in Blood Cancers

- A total of 434 significantly recurrent blood cancer mutation hotspots are identified by analyzing 48 published somatic mutation landscape studies of hematologic malignancies.

- Prevalence of clonal mutations at these hotspots is 1.8% among 4,538 persons from noncancer cohorts.

- Blood cancer–associated clonal mutations are found in both children and adults from noncancer cohorts, highlighting potential for improved precancer surveillance.
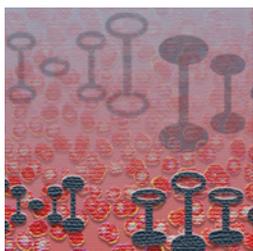
Clonal mutations within hematopoietic genes indicate increased risk of cancer development, while mutations at hotspots may be even more specific. The largest pan-cancer analyses have identified somatic mutations showing low but significantly recurrent mutations across predominantly nonhematologic cancers. However, the landscape of blood cancer–specific somatic mutations remains to be fully characterized. Feusier and colleagues examined datasets from 48 studies across 7,430 patients at diagnosis of leukemias, myeloproliferative neoplasms, and myelodysplastic syndrome. They identified 434 hematologic cancer mutation hotspots, 364 of which can be confidently used for detection of clonal hematopoiesis of indeterminate potential (CHIP). The authors then analyzed the whole-exome sequencing data of 4,538 persons from three noncancer cohorts and determined the prevalence of CHIP identical to hotspot mutations to be 1.8%. Notably, clonal mutations at leukemic hotspots were also found in 3 out of 413 children from noncancer cohorts. Taken together, this study provides the landscape of hematologic cancer hotspot mutations shared in clonal hematopoiesis and leukemia, which could improve screening of individuals susceptible to develop blood cancer. ∎

Machine Learning Improves Evaluation of Bone Marrow Histopathology in MDS Patients

- Convolutional neural networks were applied to improve the evaluation of MDS patient–derived bone marrow biopsies, producing "deep BM histopathology" revealing features that may elude the human eye.

- Extracted features correctly identified the patient age, gender, prognosis, as well as the underlying genetic lesions.

- Convolutional neural networks have the potential to better understand how genetic features are reflected in morphology.
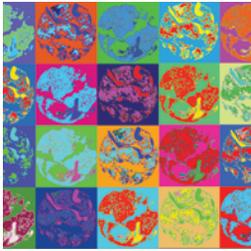
Bone marrow histopathology is a mainstay in diagnostics and monitoring of patients with myelodysplastic syndrome (MDS). Objective evaluation of complex microscopic images has always been difficult and usually requires researchers with years of experience. Now, Brück and colleagues have developed a machine-learning approach to evaluate bone marrow morphology from MDS patients. They applied convolutional neural networks (CNN) to H&E-stained slides, taking segmented nucleated cells, erythrocytes, and lipid droplet intensity as initial parameters for unsupervised image segregation. The approach distinguished healthy subjects and several MDS clusters, which partially overlapped with the World Health Organization (WHO) disease classification, and accurately determined disease score and prognosis. The CNN-based method fared slightly worse than the IPSS-R score in evaluating progression to AML, while for 2-year overall survival, it performed slightly better. A combination of the two gave the most accurate prediction. The algorithm correctly identified TET2, ASXL1, and STAG2 point mutations; spliceosome mutations; and chromosome 7 monosomy. In summary, deep mining of tissue texture will help to better understand MDS pathology and can assist in the classification of patients according to WHO criteria. It may also be helpful to improve stratification of patients by defining disease subtypes. ■

Thalidomide Analogues Induce ZMYM2 Fusion Oncoprotein Degradation

- Avadomide redirects the Ubiquitin ligase Cereblon (CRL4) for targeted degradation of the disease-causing fusion oncoproteins ZMYM2–FGFR1 and ZMYM2–FLT3 *in vitro* and *in vivo*.

- The zinc-chelating N-terminal MYM domain of ZMYM2 was identified as a minimal drug-responsive element.

- Proof-of-concept study for targeted drug-induced degradation of oncogenic fusion proteins using the CRL4^{CRBN} E3 ligase in hematologic malignancies.
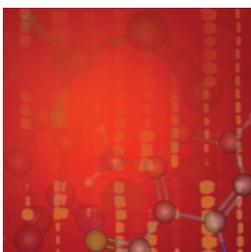
Thalidomide derivatives have attracted attention after they were found to shift the ubiquitin-ligase specificity of the Ubiquitin ligase Cereblon (CRL4) toward non-native targets, termed "neosubstrates." In their study, Renneville and colleagues have used mass spectrometry to identify such neosubstrates, using Hep3B cells treated with avadomide. By doing so, they identified two novel CRL4^{CRBN} substrates, PDE6D and ZYM2—the latter being clinically relevant, as it is expressed as an oncogenic fusion protein in leukemia. In validation experiments, they found that different thalidomide analogues display different target specificity and that CRISPR/Cas9–mediated deletion of CRL4^{CRBN} abolished avadomide response. Using reporter assays and mutagenesis, they demonstrate that the MYM domain is necessary and sufficient for drug-induced degradation of ZMYM2. Using ZMYM2–FGFR1-transformed Ba/F3 cells, efficacy of avadomide treatment was verified *in vitro* and in transplantation experiments in mice. Finally, CD34(+) cells from patients with *ZMYM2–FGFR1*-positive hematologic malignancy responded to avadomide treatment with growth arrest, while cells from healthy donors were unaffected. The findings demonstrate that redirected protein degradation may be a promising strategy to develop therapies targeting proteins previously considered "undruggable." ■

SIRT5 Is a Druggable Metabolic Vulnerability in Acute Myeloid Leukemia

- CRISPR screen identifies SIRT5 as an essential gene in a subset of primary AML blasts and cell lines but not healthy CD34+ progenitors.

- SIRT5 inactivation reduces oxidative phosphorylation and glutamine utilization, increases mitochondrial superoxide, causing apoptosis in cell culture and extending survival in AML mouse models.

- NRD167, a selective cell permeable SIRT5 inhibitor, inhibits leukemia development.

Despite the success of genotype-directed therapy for acute myeloid leukemia (AML), such as inhibitors of FLT3 or mutant IDH1/2, relapse occurs frequently with these drugs, highlighting the importance of identifying shared vulnerabilities in a genotype-agnostic manner for treating AML. Yan and colleagues perform CRISPR-Cas9–mediated shRNA screen on primary AML blasts and identify SIRT5 as one of the top candidates crucial for the survival of AML cells. Inhibition of SIRT5 selectively reduces the survival of AML cells of different genotypes, but it is well tolerated by normal CD34+ cells. In humanized and syngeneic mouse models of AML, SIRT5 is required for leukemogenesis by several myeloid oncogenes. Mechanistically, SIRT5 is required for oxidative phosphorylation and glutamine utilization in SIRT5-dependent AML cell lines, and knockdown of SIRT5 induces mitochondrial reactive oxygen species and apoptosis, which is rescued by ectopic SOD2 expression. A cell permeable SIRT5 inhibitor, NRD167, selectively inhibits cell proliferation, metabolism, and colony formation of AML cells. These results identify SIRT5 as a druggable target for AML or other SIRT5-dependent cancers. ∎

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