Genotoxic chemotherapy and irradiation are used to treat a broad range of malignancies but can lead to secondary cancers called therapy-induced myeloid neoplasms (t-MN). This link has been initially explained by direct mutagenic effect of the therapy on myeloid progenitors. Later research revealed that genotoxic stress confers selective advantage to preneoplastic progenitors with preexisting mutations in the p53 pathway. Now Stoddart and colleagues reveal that this selective advantage is shaped by chemotherapy-inflicted long-term damage to non-hematopoietic cells such as bone marrow stroma. Recapitulating key genetic events of del(5q) t-MN progression in mice, this study shows that EGR1 and APC double-deficient premalignant hematopoietic progenitors transplanted into chemotherapy-pretreated mice are more likely to develop myelodysplastic syndrome and progress to acute myeloid leukemia (AML). In hosts with chemotherapy-damaged stroma, not only did preleukemic p53-deficient clones expanded more rapidly but they acquired additional mutations in DNA damage response genes as they progressed to AML. These findings uncover how a transient genotoxic stress exposure leads to continuous shift in hematopoietic progenitor fitness by altering both preleukemic cells and their niche, and establish a clinically relevant mouse model for exploring the underlying mechanisms and therapeutic approaches to prevent or eliminate t-MN.

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MIR300 Impairs NK Cells and Promotes CML Progenitor Cell Quiescence

• BCR-ABL downregulates MIR300 in CML stem cell (CML-SC) blasts, boosting their proliferation and clonogenic potential
• TUG1 IncRNA opposes MIR300 proapoptotic but not antiproliferative activity in quiescent CML-SCs
• MIR300 is induced by hypoxia and bone marrow mesenchymal cell exosomes and impairs anti-leukemic NK cell cytotoxicity

Kinase inhibitors eliminate the bulk of chronic myeloid leukemia (CML) cells but are less effective against quiescent leukemic stem cells, which remain a major obstacle to CML eradication. Investigating the mechanisms of quiescence as a proxy of therapy resistance, Silvestri and colleagues find that MIR300 expression in dividing CML stem and progenitor cells (CML-SC) was much lower than in quiescent CML-SC or in normal progenitors, regardless of proliferation state. By loss- and gain-of-function experiments, the authors establish that MIR300 promotes apoptosis in CML-SC blasts (through a PP2A inhibitor SET); cell cycle arrest in quiescent leukemic cells (through downregulation of CCND2/CDK6); and impairs cytotoxic function of NK cells (through both pathways). The differential effect on quiescent CML-SC is linked to TUG1 IncRNA, which selectively suppresses MIR300 PP2A-dependent pro-apoptotic but not anti-proliferative activity. Blocking MIR300-TUG1 interaction improves NK cytotoxicity and eliminates drug-resistant quiescent LSCs in a PDX myeloid leukemia model. MIR300 expression is induced by hypoxia and exosomes derived from mesenchymal stem cells, suggesting that bone marrow niche signals may promote quiescence and immune tolerance, at least in part, by inducing MIR300 expression in leukemic and NK cells. Collectively, these findings reveal a new mechanism of CML-LS quiescence and immune escape, and identify MIR300 as a potential therapeutic key to overcoming quiescence-mediated therapy resistance.

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Loss of MIR15A/MIR16-1 Instigates Multiple Myeloma

- Monoallelic loss of Mir15a/Mir16-1 promotes monoclonal gammopathy in wild-type mice
- Loss of one Mir15a/Mir16-1 allele accelerates progression to multiple myeloma in Vk*MYC mice
- Mir15a/Mir16-1 loss is a major contributor to myelomagenesis driven by chromosome 13 deletions

While chromosome 13 (chr13) is common in multiple myeloma (MM), it is unclear which of its resident genes are relevant to the disease. Here, Chesi and colleagues dissect the role of candidate genes using Vk*MYC mice, which recapitulate the key features of human multiple myeloma. Vk*MYC plasma cells frequently lose a region homologous to human chr13 containing Dis3, Rb1 and the Mir15a/16-1 cluster. In this model, monoallelic deletion of Mir15a/16-1 accelerated both disease initiation and progression. No additional fragments of this chromosomal region occurred during disease progression, suggesting that other resident genes including Dis3 and Rb1 have no critical role in myelomagenesis. Indeed, monoallelic inactivation of Rb1 on Vk*MYC background did not speed up the disease. Accordingly, del(13) frequency is similar in monoclonal gammopathy of undetermined significance (MGUS) and multiple myeloma patient groups, which is consistent with del(13) being an early event in myelomagenesis. In this dataset, MIR15A/16-1 inactivation is one of the most frequent alterations within chr13. Offering cues into the oncogenic mechanism, the authors correlate MIR15A/16-1 copy number to the expression of CCND2 and other proliferation-related genes. Together, these findings identify the cluster as a MIR15A/16-1 as a major haploinsufficient tumor suppressor in multiple myeloma.

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MEF2D-fusion B-ALL Core Transcriptional Circuits Converge On Pre-BCR

- MEF2D-fusion promotes growth and survival by direct transcriptional activation of pre-BCR signaling
- MEF2D-fusion forms feed-forward circuits with SREBF1, FOS, EGR1, and BCL6, which also activate pre-BCR genes
- Lipid metabolism and pre-BCR are targetable nodes in fusion-driven B-ALL

Transcriptional regulator fusion proteins are major drivers of pre-B acute lymphoblastic leukemia (B-ALL). Tsuzuki and colleagues hypothesized that fusion proteins establish and maintain B-ALL through autoregulatory transcriptional loops. By ChIPseq and gene expression characterization of a B-ALL cell line with a tagged allele of MEF2D-HNRNPUL1, the authors map direct transcriptional targets of the fusion protein. Prominent among them are several pre-BCR components and signaling partners, often regulated by superenhancers. The expression of pre-BCR components is sustained by self-reinforcing transcriptional activation between MEF2D-fusion and each of the transcription factors SREBF1, FOS, EGR1, and BCL6. These factors are also directly involved in transcriptional activation of pre-BCR genes. The importance of this core transcriptional circuit is demonstrated by functional interrogation of each component through genetic and pharmacological inhibition. SREBF1 or pre-BCR signaling inhibitors show activity against MEF2C-fusion positive leukemia. This work offers first insights into genome-wide mechanisms of reprogramming a lymphocyte precursor into leukemic transcriptional state. It also demonstrates that disrupting the core feed-forward signaling loops is a viable therapeutic strategy in leukemia driven by fusion proteins, for many of which no direct pharmacological inhibitors exist.

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Plasmablastic lymphoma (PBL) pathogenesis is associated with immunodeficiency, HIV and EBV infection and MYC translocations. In a first large-scale analysis of somatic mutations in HIV-associated PBL, Liu and colleagues reveal additional genomic aberrations in a cohort of 110 South African patients. Within this cohort, 15 patients are characterized by whole exome sequencing, based on which 34 selected genes are assayed by targeted sequencing in additional 95 cases. These results are complemented with transcriptomic data from 20 cases, and copy number analysis of 46 cases. These findings point to constitutive activation of JAK-STAT, which is confirmed by phosphoprotein assays. Mutations in CD44 as well as in RAS-MAPK and Notch pathways are each found in approximately one third of patients. Collectively, alterations in these pathways are sufficient to distinguish PBL from multiple myeloma or diffuse large B-cell lymphoma. In particular, STAT3 mutations are found in 42% of PBL but are rare in the comparators. By characterization of the genomic and transcriptomic landscape of HIV-associated PBL, this study provides the genetic evidence for unique pathogenesis of this disease and offers insights into its potential therapeutic vulnerabilities.

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Nearly 90% of pediatric B-ALL respond to therapy by long-term remission, but relapsing disease is highly resistant to pharmacological therapies and is associated with dismal prognosis. Waanders, Gu Dobson, Antić and colleagues investigate mechanisms of relapse in a large cohort of pediatric ALL. Performing multifaceted, high-resolution genomics on samples taken at diagnosis and upon relapse, the authors trace mutations prevalent at relapse to a subclone already present at diagnosis. Although taken from treatment-naive patients, these subclones carry mutations in genes functionally related to therapy resistant. Indeed, these subclones display drug resistance when xenografted in mice. Repeated relapses are associated with accelerated mutagenesis: leukemia cells from patients who experienced more than one relapse display hypermutation. Increased frequency of putative neoantigens in these clones is suggestive of increased immunogenicity. Collectively, these findings provide mechanistic understanding of selective pressures shaping clonal evolution following therapy. Importantly, they offer hope that that detection of drug-resistant subclones at diagnosis may inform treatment choices with minimized risk of relapse.

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Relapse Is Seeded in Drug-Resistant Subclones in Treatment-Naïve Pediatric B-ALL

HIV-Associated Plasmablastic Lymphoma Reveals Unique Genomic Features

Plasmablastic lymphoma (PBL) pathogenesis is associated with immunodeficiency, HIV and EBV infection and MYC translocations. In a first large-scale analysis of somatic mutations in HIV-associated PBL, Liu and colleagues reveal additional genomic aberrations in a cohort of 110 South African patients. Within this cohort, 15 patients are characterized by whole exome sequencing, based on which 34 selected genes are assayed by targeted sequencing in additional 95 cases. These results are complemented with transcriptomic data from 20 cases, and copy number analysis of 46 cases. These findings point to constitutive activation of JAK-STAT, which is confirmed by phosphoprotein assays. Mutations in CD44 as well as in RAS-MAPK and Notch pathways are each found in approximately one third of patients. Collectively, alterations in these pathways are sufficient to distinguish PBL from multiple myeloma or diffuse large B-cell lymphoma. In particular, STAT3 mutations are found in 42% of PBL but are rare in the comparators. By characterization of the genomic and transcriptomic landscape of HIV-associated PBL, this study provides the genetic evidence for unique pathogenesis of this disease and offers insights into its potential therapeutic vulnerabilities.

See article, p. 112.