Title: PARPi selectively kills spliceosome mutant leukemias through R-loop-associated genomic instability

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Somatic mutations in genes encoding for RNA splicing factors (SF) SRSF2, U2AF1, and SF3B1 are frequently mutated in patients with hematologic malignancies. These mutations represent attractive genetic vulnerabilities for targeted therapy. Here, we report a surprising finding from our focused drug screen that SF-mutant cells are sensitive to five different PARP inhibitors (PARPi), four of which are FDA-approved to treat solid tumors.
Mechanistically, both SRSF2P95H and U2AF1S34F cells exhibited higher poly-ADP-ribose polymerase 1 (PARP1) association and activity directly at R loops by Proximity Ligation Assay (PLA), and upon PARPi treatment, exhibited higher DNA damage level and cell death in a R-loop dependent manner. Furthermore, PARPi treatment also induced more R loop accumulation in SRSF2P95H cells, which led to more transcription-replication collisions and ATR activation. Combined PARPi+ATRi led to synergistic effect in SF-mutant cell lines, primary patient samples, and patient derived xenografts (PDX). Importantly, the level of PARP1 activity at R loops and the level of transcription-replication collision by PLA in the primary patient samples correlated well with their mutational status. Collectively, our results suggest that SF-mutant cells induce R-loop accumulation and elicit a PARP1 response critical for cell survival. Our findings highlight a new genetic vulnerability between SF mutations and PARP1 inhibition, and provide a pre-clinical rationale that PARP1 modulation could potentially represent a new therapeutic strategy in patients harboring SF mutations.