Leukemia

Major Finding: *IDH2* mutations, causing DNA hypermethylation, cooperate with splicing-factor mutations in leukemia.

Mechanism: Missplicing of the Integrator-component gene *INTS3* led to transcriptional dysregulation.

Impact: This study elucidates a mechanism—which may be targetable—involved in driving leukemogenesis.

MUTATIONS AFFECTING SPLICING AND EPIGENETICS PROMOTE LEUKEMOGENESIS

Mutations that affect the regulation of transcription or RNA splicing are common in leukemia; often, mutations affecting both processes are found in the same patients. In an analysis of RNA sequencing (RNA-seq) data from patients with acute myeloid leukemia (AML), Yoshimi, Lin, Wiseman, and colleagues found evidence of mutations in the splicing-factor gene *SRSF2* in several patients. Of patients with mutated *SRSF2*, 47% also had mutated *IDH2*, encoding the mitochondrial enzyme isocitrate dehydrogenase 2, mutations in which often result in DNA hypermethylation. Experiments in mice transplanted with bone marrow overexpressing mutant human *IDH2* with or without expression of mutant *Srsf2* demonstrated a cooperative effect between mutations in the two genes in promoting leukemogenesis. RNA-seq data from patients with AML indicated that cells bearing mutations in both *SRSF2* and *IDH2* had increased splicing errors compared with cells bearing mutations in *SRSF2* alone. Reverse-transcriptase PCR experiments using primary AML samples revealed aberrant splicing of *INTS3*, encoding a component of the transcription-regulating Integrator complex. Chromatin immunoprecipitation with DNA sequencing experiments using SRSF2-mutant cell lines as well as primary samples from patients with AML implied dysfunction of the entire Integrator complex in *SRSF2*-mutant cells and suggested a connection between increased DNA methylation and stalling of RNA polymerase II in *SRSF2* and *IDH2* double-mutant AML cells. Further, loss of INTS3 associated with splicing errors caused by mutant IDH2 or SRSF2 was shown to contribute to leukemogenesis in mice. Notably, in patient AML samples, incorrect splicing of *INTS3* was present not only in *IDH2*- and *SRSF2*-mutant cases, but also in other cases—but not in healthy blood cells. Together, these findings provide mechanistic insight into the role of aberrant splicing and transcriptional misregulation in leukemogenesis and, especially given that approximately half of patients with leukemia have mutations in *IDH2*, suggest that therapies that modulate splicing may be worth exploring. ■

Yoshimi A, Lin KT, Wiseman DH, Rahman MA, Pastore A, Wang B, et al. Coordinated alterations in RNA splicing and epigenetic regulation drive leukaemogenesis. Nature 2019;574:273–7.

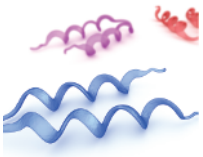
Structural Biology

Major Finding: Structures of components of cancer-associated mTORC1 bound to regulators reveal mechanisms.

Mechanism: Rag heterodimers interact with mTORC1 component RAPTOR to localize mTORC1 to lysosomal membranes.

Impact: These structures will enable basic and translational studies, possibly including drug development.

STRUCTURES OF mTORC1 AND ASSOCIATED PROTEINS YIELD MECHANISTIC INSIGHT



The serine/threonine protein-kinase complex mTORC1 is a major regulator of cellular and organismal growth, and its deregulation is associated with several cancers. Small GTPases called Rags, which form heterodimers, are required for mTORC1 activation, but much about how they interact with mTORC1 is unknown. To investigate this, Anandapadamanaban and colleagues used cryo-electron microscopy (cryo-EM) and X-ray crystallography to determine the structures of mTORC1 bound to RagA–RagC heterodimers and RagA–RagC heterodimers alone. Binding to RagA–RagC did not cause a conformational change in mTORC1, implying that the function of Rag-heterodimer binding may be to localize mTORC1 to the lysosomal surface (where mTORC1 can be activated) through the Rags' interaction with the Ragulator complex. Combining these results with those of previous structural studies suggests that mTORC1 can associate with the required activator RHEB on the lysosomal surface while keeping the mTOR active sites facing the cytosol, allowing mTOR to phosphorylate its cytosolic targets. In a separate study, Rogala and colleagues used cryo-EM to determine the structure of mTORC1's RAPTOR subunit bound to the Rag–Ragulator complex. This structure supports a model in which transient interactions between RAPTOR and GTP-bound RagA along with weak interactions between RAPTOR and RagC together promote a stronger interaction between RAPTOR and the Rag heterodimer only once RagC is bound to GDP. Knowledge of this structure along with the results of prior structural studies enabled modeling of mTORC1 docked on the lysosomal surface. Further, the characterization of the interface between RAPTOR and the RagA–RagC heterodimer provides insight that may be valuable in developing small molecules targeting mTORC1 signaling with greater specificity than that of currently available drugs. Together, these two structural studies have led to a much more detailed understanding of mTORC1 regulation than was previously available, providing a basis for continued work on this important complex. ■

Anandapadamanaban M, Masson GR, Perisic O, Berndt A, Kaufman J, Johnson CM, et al. Architecture of human Rag GTPase heterodimers and their complex with mTORC1. Science 2019;366:203–10.

Rogala KB, Gu X, Kedir JF, Abu-Remaileh M, Bianchi LF, Bottino AMS, et al. Structural basis for the docking of mTORC1 on the lysosomal surface. Science 2019;366:203–10.