Chemotherapy

Major finding: IRBIT inhibits ribonucleotide reductase (RNR) by stabilizing dATP binding to the RNR activity site.

Concept: Depletion of IRBIT in cancer cells perturbs intracellular dNTP levels and alters cell cycle progression.

Impact: Understanding mechanisms of RNR inhibition may lead to less toxic inhibitors of DNA synthesis.

IRBIT PROMOTES ALLOSTERIC INHIBITION OF RIBONUCLEOTIDE REDUCTASE

Some chemotherapeutic agents in clinical use are inhibitors of ribonucleotide reductase (RNR), which supplies the building blocks necessary for DNA synthesis and repair by converting ribonucleotide diphosphates to deoxynucleotide diphosphates, immediate precursors of deoxynucleotide triphosphates (dNTP). However, given that most of these compounds are nucleoside analogs that bind other nucleotide-binding proteins in addition to RNR, off-target interactions may contribute to the toxicity of these compounds. Arnaoutov and Dasso found that inositol-1,4,5-trisphosphate receptor-binding protein (IRBIT; also known as adenosylhomocysteinase-like 1, or AHCYL1) directly interacts with the R1 subunit of RNR in a deoxyadenosine triphosphate (dATP)–dependent manner. dATP is an allosteric regulator of RNR that either inhibits RNR by binding R1 at its low-affinity activity site (A-site) or promotes RNR catalytic activity by binding R1 at its specificity site (S-site). The authors showed that IRBIT binding to RNR inhibited the dissociation of dATP from the A-site of R1, thus stabilizing RNR in its inactive state and significantly inhibiting RNR activity *in vitro*. This inhibitory potential of IRBIT was modulated by phosphorylation, as a nonphosphorylatable IRBIT mutant had a reduced capacity to stabilize the dATP–R1 interaction. Depletion of IRBIT in asynchronously growing HeLa cells led to imbalanced dNTP levels; the imbalance was particularly pronounced during mitosis, when IRBIT was found to bind R1 more strongly compared with G_1. Knockdown of IRBIT also led to interphase length variability and accelerated mitotic progression, but the nonphosphorylatable IRBIT mutant was unable to rescue this phenotype, suggesting that IRBIT controls cell-cycle progression and that IRBIT phosphorylation is necessary for this role. These findings raise the possibility that regulation of RNR by IRBIT controls genomic stability and ensures proper cell-cycle progression by maintaining balanced intracellular dNTP pools and provide a framework for the development of RNR-selective inhibitors that may be less toxic than RNR inhibitors currently in use. ■

Arnaoutov A, Dasso M. IRBIT is a novel regulator of ribonucleotide reductase in higher eukaryotes. Science 2014;345:1512–5.

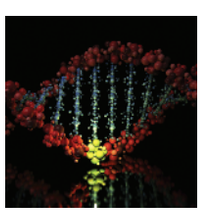
Genomics

Major finding: Salivary gland polymorphous low-grade adenocarcinomas commonly harbor activating *PRKD1* mutations.

Concept: Expression of the hotspot *PRKD1* mutation increases epithelial cell viability but reduces invasion.

Impact: *PRKD1* mutation may distinguish polymorphous low-grade adenocarcinomas from more aggressive tumors.

PRKD1 MUTATIONS CHARACTERIZE SALIVARY GLAND POLYMORPHOUS LOW-GRADE ADENOCARCINOMA



Polymorphous low-grade adenocarcinoma (PLGA) is a relatively indolent malignant salivary tumor that metastasizes to the lymph nodes in approximately 29% of patients but rarely metastasizes to distant sites. PLGAs are histologically heterogeneous and thus are difficult to distinguish from more aggressive salivary gland cancer subtypes. To identify characteristic molecular features of salivary gland PLGA that may aid in diagnosis, Weinreb, Piscuoglio, Martelotto, Waggott, and colleagues performed whole-transcriptome and whole-exome sequencing of 3 PLGAs and whole-exome sequencing of an additional 3 tumors and identified a protein kinase D1 (*PRKD1*) mutation resulting in an E710D amino acid substitution in 5 of 6 samples. Screening of an additional 53 salivary gland PLGAs revealed that this hotspot mutation occurred in 43 of 59 (73%) PLGAs overall. Although *PRKD1* was found to be mutated in 2% of samples in published cancer genome datasets, none of the tumors had the E710D hotspot mutation, suggesting that this might be a distinguishing feature of PLGA. Indeed, in an analysis of 311 benign and malignant salivary gland tumors, this *PRKD1* mutation was found only in PLGAs. The E710D mutation, which lies within the catalytic loop of the PRKD1 kinase domain, led to significantly increased kinase activity compared with wild-type PRKD1 in an *in vitro* kinase assay, suggesting that this mutation activates PRKD1. Interestingly, forced expression of the E710D mutant promoted proliferation and altered the glandular architecture of epithelial cells *in vitro*, further suggesting that this mutation confers a growth advantage to cells, but expression of the mutant protein reduced cellular migration. Consistent with these findings, the presence of the *PRKD1* hotspot mutation was significantly associated with metastasis-free survival. Collectively, these findings indicate that *PRKD1* mutations may have diagnostic and prognostic utility and distinguish indolent PLGA from more aggressive salivary gland tumors. ■

Weinreb I, Piscuoglio S, Martelotto LG, Waggott D, Ng CK, Perez-Ordonez B, et al. Hotspot activating PRKD1 somatic mutations in polymorphous low-grade adenocarcinomas of the salivary glands. Nat Genet 2014 Sep 21 [Epub ahead of print].

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