Published OnlineFirst February 25, 2016; DOI: 10.1158/2159-8290.CD-RW2016-031

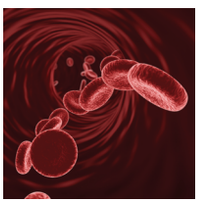
Myelodysplastic Syndrome

Major finding: *Rps14* haploinsufficiency promotes an S100A8-mediated p53-dependent erythroid differentiation block.

Concept: Heterozygous, hematopoietic deletion of *Rps14* phenocopies 5q deleted myelodysplastic syndrome.

Impact: *Rps14* deficiency links ribosomal dysfunction with innate immunity–driven defects in erythropoiesis.

Rps14 HAPLOINSUFFICIENCY PROMOTES ERYTHROID DIFFERENTIATION DEFECTS



The deletion 5q subtype of myelodysplastic syndrome is characterized by impaired erythropoiesis and is associated with ribosomal protein small subunit 14 (*RPS14*) haploinsufficiency and activation of p53. To study the effects of *Rps14* deficiency *in vivo*, Schneider and colleagues generated a mouse model with conditional haploinsufficiency of *Rps14* specifically in hematopoietic cells, which led to progressive anemia, fewer reticulocytes, and a p53-dependent terminal erythroid differentiation defect that induced apoptosis at the transition from polychromatic to orthochromatic erythroblasts. Older *Rps14*-haploinsufficient mice were characterized by increased long-term hematopoietic stem cell (HSC) and multipotent progenitor cell populations in the bone marrow due to quiescence exit. Transplantation of *Rps14*-haploinsufficient bone marrow led to an erythroid differentiation block, a progressive decrease in chimerism of *Rps14*-haploinsufficient cells among erythroid cells, and myeloid skewing, suggesting a link between *Rps14* haploinsufficiency and age-dependent loss of HSC function. Mechanistically, *Rps14* haploinsufficiency inhibited global protein synthesis in erythroid progenitor cells, but increased expression of innate immune proteins including S100A8 and S100A9. Increased expression of S100A8 was observed in the erythroid progenitor population, monocytes, and macrophages of *Rps14*-haploinsufficient mice and was dependent on p53. Upregulation of inflammatory targets downstream of S100A8 was also observed in *Rps14*-haploinsufficient cells, and cytokine profiling revealed an increase in inflammatory cytokines known to inhibit erythropoiesis. Similar to the phenotype of *Rps14*-haploinsufficent cells, the addition of exogenous S100A8 induced a differentiation block in wild-type erythroid cells, whereas genetic silencing of *S100a8* in *Rps14*-haploinsufficient mice rescued the p53-dependent erythroid differentiation defect and inhibited the inflammatory response in the bone marrow. The clinical relevance of these findings was supported by the high levels of S100A8 observed in bone marrow biopsies from patients with myelodysplastic syndrome and 5q deletion. Together, these results highlight how activation of an innate immune response by *Rps14* haploinsufficiency, including induction of S100A8 and S100A9, drives a p53-dependent erythroid differentiation block. ■

Schneider RK, Schenone M, Ferreira MV, Kramann R, Joyce CE, Hartigan C, et al. Rps14 haploinsufficiency causes a block in erythroid differentiation mediated by S100A8 and S100A9. Nat Med 2016;22:288–97.

Drug Resistance

Major finding: Dynamic tumor evolution promotes drug resistance and creates temporary sensitivity to other drugs.

Mechanism: A mutation in BCR–ABL1 confers collateral sensitivity to non-classic BCR–ABL1 inhibitors.

Impact: Temporal collateral sensitivities may be exploited to prevent tumor recurrences.

INTERMEDIATE STAGES IN TUMOR EVOLUTION CAN BE THERAPEUTICALLY TARGETED

Tumor cells may develop drug resistance through a dynamic clonal evolution. This evolution can create collateral sensitivities whereby the tumor cells become sensitive to drugs at the expense of sensitivity to other drugs. Previous studies have focused on determining the resistance mechanisms after relapse; however, the dynamic nature of clonal evolution may lead to temporary exploitable sensitivities during drug treatment. Zhao and colleagues explored this idea by identifying collateral sensitivities at intermediate stages of tumor evolution, termed "temporal collateral sensitivities." A mathematical model of step-wise clonal evolution simulated intermediate stages of drug selection and predicted a treatment window, or temporary collateral sensitivity, during which the cells might become sensitive to a different drug. This was tested in murine Ph^+ acute lymphoblastic leukemia cells, which are driven by the BCR–ABL1 fusion kinase, selected with the BCR–ABL1 inhibitor dasatinib to derive resistance. A pharmacologic screen discovered that resistant cells developed a collateral sensitivity to four other non-classic BCR–ABL1 kinase inhibitors. Mechanistically, the collateral sensitivity was determined to stem from preexisting BCR–ABL1 V299L mutations, which were selected for with dasatinib. However, as the V299L cells continued to evolve, compound mutations arose, which reduced the collateral sensitivity. Mathematical simulations suggested a therapeutic window of non-classic inhibitor sensitivity where BCR–ABL1 V299L cells predominated. The order in which the drugs were used affected the resistance mechanisms. For example, treatment with a non-classic inhibitor followed by dasatinib reduced the occurrence of V299L resistant subpopulations. Additional collateral sensitivities at intermediate-stage clonal evolution, as well as sensitivities at early- and late-stage evolution, were identified in a larger small-molecule screen. These findings were confirmed in mice, where non-classic inhibitors reduced dasatinib-resistant BCR–ABL1 V299L tumor burden. Together, these findings indicate that the development of tumor drug resistance is a dynamic process that creates temporal collateral drug sensitivities that may be exploitable for cancer therapy. ■

Zhao B, Sedlak JC, Srinivas R, Creixell P, Pritchard JR, Tidor B, et al. Exploiting temporal collateral sensitivity in tumor clonal evolution. Cell 2016 Feb 25 [Epub ahead of print].

Published OnlineFirst February 25, 2016; DOI: 10.1158/2159-8290.CD-RW2016-031

AACR American Association for Cancer Research

CANCER DISCOVERY

Rps14 Haploinsufficiency Promotes Erythroid Differentiation Defects

Cancer Discov 2016;6:341. Published OnlineFirst February 25, 2016.