Uncovering metabolic bottlenecks in KEAP1 mutant lung cancer

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Abstract

During tumorigenesis, cancer cells continuously encounter metabolic bottlenecks as a result of accelerated growth, overall increased metabolic demand and increased oxidative stress due to the formation of reactive oxygen species (ROS). Lung cancer, the leading cause of cancer-related deaths worldwide, is the most common cancer type to acquire mutually exclusive gain-of-function mutations in the anti-oxidant transcription factor Nrf2 or loss-of-function mutations in its negative regulator KEAP1. Loss of Keap1 activates Nrf2, increases antioxidant production and dramatically accelerates KRAS-driven lung cancer.

We observe that the ability of KEAP1 mutant tumors to divert their metabolism towards antioxidant production comes with a cost, generating multiple metabolic vulnerabilities1,2, including a dependency on glutamine metabolism that can be therapeutically exploited using DRP-104, a novel broad acting glutamine antagonist. DON (6-Diazoo-5-oxo-L-norleucine) is the active moiety of DRP-104 that irreversibly inhibits all known enzymes in glutamine metabolism. Glutamine pathway inhibition by DON affects multiple pathways critical for tumor growth and survival (schematic). Broad inhibition of glutamine metabolism may provide a more effective therapeutic for glutamine addicted cancers and reduce the development of resistance.

Here we show DRP-104 is potent in reducing KEAP1 mutant tumor growth in both murine and patient derived LUAD and squamous tumor models. Our data suggests that DRP-104 is a promising therapy to treat KEAP1 mutant lung cancers and may offer further therapeutic potential when combined with standard of care or other novel metabolic strategies.

Results

DRP-104 reduces growth of Keap1 mutant murine LUAD

Activation of Nrf2 induces sensitivity to DRP-104

Figure 2: Tumor growth of murine LUAD cell line (KrasG12D/+;Keap1-/-) expressing an empty vector (A) or an Nrf2 gain of function construct (B) in immunocompetent animals. Cells were injected subcutaneously into the flanks of Nude mice. Animals were dosed subcutaneously in the opposite flank with either vehicle or DRP-104 daily for five days and then received a two day drug holiday.

DRP-104 reduces growth of KEAP1 mutant patient derived xenografts

Figure 3: Relative tumor growth of patient derived KEAP1 mutant LUAD in immunocompromised animals. Tumors were implanted subcutaneously into the flanks of NSG mice. Animals were dosed subcutaneously in the opposite flank with either vehicle or DRP-104 daily for five days and then received a two day drug holiday. CTG743 was treated until day 53 and then drug was removed.

Conclusions

- DRP-104 effectively inhibits tumor growth in Keap1 mutant murine LUAD tumor model
- Activation of Nrf2, which enhances glutamine dependence of tumor cells, sensitizes tumors to DRP-104
- DRP-104 effectively inhibits tumor growth in multiple Keap1 mutant LUAD and squamous PDxS, often resulting in tumor stasis or regression
- DRP-104 is more effective in slowing tumor growth than selective glutaminase 1 (GLS1) inhibitors in PDx models
- DRP-104 reduces carbon flux into the TCA cycle.

References