Tailor antimetabolite therapy by targeting host nucleos(t)ide kinase and phosphohydrolase

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Nucleos(t)ide analogue (NA) drugs are cornerstone anticancer and antiviral therapies. Upon bioactivation via phosphorylation, they could mimic endogenous nucleotides and thereby induce catastrophic lesions during genome replication, ultimately deterring cell and/or viral replication. As the standard-of-care in clinics, personalization of NA therapies, to minimize dose-limiting toxicity whilst maximize efficacies, is highly warranted yet not fully achieved.

Previous studies by me and others have convincingly demonstrated that nucleos(t)ide kinases and phosphohydrolases could activate and inactivate critical NA drugs, respectively, and thereby dictate drug efficacy and ultimately constitute pharmacogenetic factors informing patient response (1-4).

Here, our comprehensive profiling pipeline against NA therapeutics integrating biochemical, biophysical, cellular, and in vivo readouts further identified additional enzyme-drug pairs as potential revenues for treatment personalization. First, we showed that nucleoside kinase uridine/cytidine kinase (UCK) is the first- and rate-limiting step governing bioactivation of anti-*SARS-CoV2 drug molnupiravir*. UCK phosphorylated molnupiravir with high catalytic efficiency in vitro, and ablation/inhibition of cellular UCK antagonized the anti-SARS efficacy of molnupiravir by 10-fold. Second, we identified that nucleotide pyrophosphatase NUDIX-type 15 (NUDT15) could directly hydrolyse and inactivate anti-leukemic agent *3'deazauridine*. Genetic ablation of NUDT15 aggravated 3'deazauridine-induced DNA damage and apoptosis in leukaemia cells, and ultimately tumour reduction in xenograft models, which is critically phenocopied by *bona fide* nanomolar NUDT15 inhibitors (4-5).

Collectively, study presented herein underscored nucleos(t)ide kinase and phosphohydrolase as targetable biomarkers against a broad spectrum of oncology and antiviral drugs, potentially indicating new avenues in personalizing routinely used NA therapy.

Reference

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