Report

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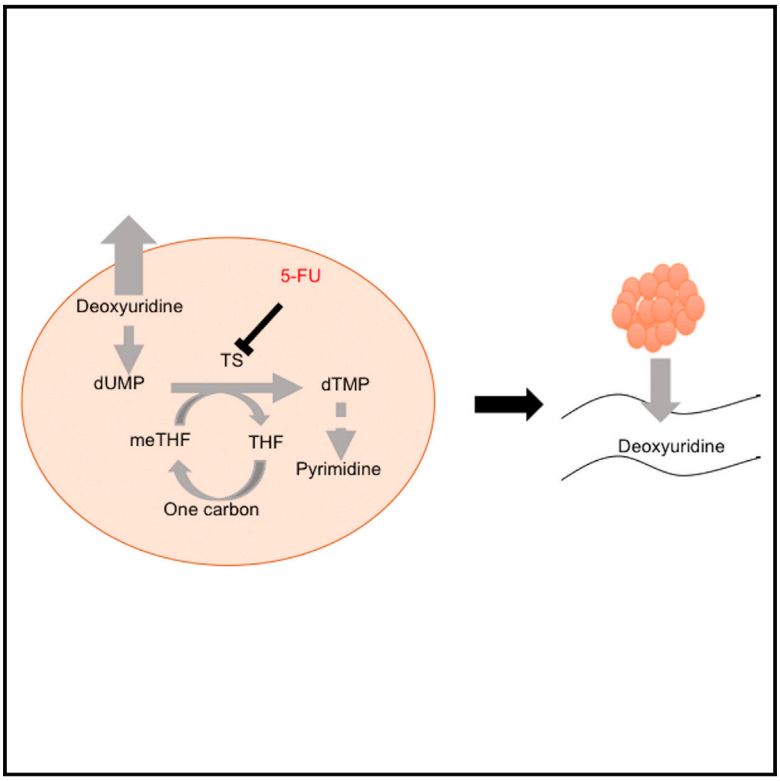
Targeting One Carbon Metabolism with an Antimetabolite Disrupts Pyrimidine Homeostasis and Induces Nucleotide Overflow

Graphical Abstract



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In Brief

Ser et al. show that 5-fluorouracil, a commonly used antimetabolite in chemotherapy, disrupts thymidylate synthase activity, causing nucleotide imbalance and the induction of overflow metabolism in cells and in the serum of mice bearing colorectal tumors.

Highlights

- One carbon metabolism fluxes correlate with 5-fluorouracil (5-FU) sensitivity
- 5-FU causes nucleotide imbalance by inhibiting thymidylate synthase
- 5-FU induces overflow metabolism in pyrimidine synthesis
- Alterations in overflow metabolism from colorectal tumors can be measured in serum

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SUMMARY

Antimetabolites that affect nucleotide metabolism are frontline chemotherapy agents in several cancers and often successfully target one carbon metabolism. However, the precise mechanisms and resulting determinants of their therapeutic value are unknown. We show that 5-fluorouracil (5-FU), a commonly used antimetabolite therapeutic with varying efficacy, induces specific alterations to nucleotide metabolism by disrupting pyrimidine homeostasis. An integrative metabolomics analysis of the cellular response to 5-FU reveals intracellular uracil accumulation, whereas deoxyuridine levels exhibited increased flux into the extracellular space, resulting in an induction of overflow metabolism. Subsequent analysis from mice bearing colorectal tumors treated with 5-FU show specific secretion of metabolites in tumor-bearing mice into serum that results from alterations in nucleotide flux and reduction in overflow metabolism. Together, these findings identify a determinant of an antimetabolite response that may be exploited to more precisely define the tumors that could respond to targeting cancer metabolism.

INTRODUCTION

Antimetabolite chemotherapy is one of the most-successful therapeutic strategies for the treatment of neoplastic disease (Kaye, 1998). It is also highly toxic while exhibiting variable efficacy. Thus, identifying the precise situations where it might be effective as a medicine is a pressing biomedical need. One commonly prescribed example is 5-fluorouracil (5-FU), which remains a frontline chemotherapy for multiple advanced stage cancers, notably colorectal cancer (CRC) (Longley et al., 2003). However, there lacks a comprehensive and mechanistic understanding of its effects on metabolism that could have prognostic value clinically (Locasale, 2013). This agent and other antimetabolite compounds are thought to target metabolic enzymes that are either involved in nucleotide metabolism or the folate cycle—directly affecting nucleotide biosynthesis and indirectly affecting other metabolic processes that are coupled to the flux into the nucleotide pool and one carbon metabolism. Therefore, we reasoned its direct effects on metabolism might encode information that could lead to biomarker identification for cytotoxic response that would improve the precision of its indication. If successful, this endeavor would bring precision medicine to a set of agents that have historically been thought to lack specificity.

Many of the current chemotherapies target a metabolic network known as one carbon metabolism. The serine, glycine, and one carbon (SGOC) metabolic network involving the folate and methionine cycles integrates nutritional status from amino acids, glucose, and vitamins and generates diverse outputs, such as the biosynthesis of lipids, nucleotides, and proteins; the maintenance of redox status; and the substrates for methylation reactions. Recently, multiple studies have found newfound roles of genes in this pathway in tumorigenesis (Locasale, 2013; Mehrmohamadi et al., 2014). Examples include the presence of cancer-driving genes, such as *PHGDH*, whose product diverts glucose metabolism into one carbon metabolism (Locasale et al., 2011; Possemato et al., 2011). Furthermore, in an analysis of uptake and excretion rates measured across population of cancer cells, glycine uptake was found to most strongly correlate with cell proliferation (Jain et al., 2012). Serine has also been found to be essential for cell proliferation (Labuschagne et al., 2014; Maddocks et al., 2013, 2016), and *SHMT2*, which encodes a mitochondrial serine hydroxymethyltransferase, was shown to provide context-dependent susceptible liabilities for tumor maintenance (Kim et al., 2015; Ye et al., 2014). Together, these newfound roles for genes in this network in cancer provide further rationale for targeting the pathway in cancer in a specific manner.