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Authors
Parker, Seth J
Metallo, Christian M

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Chasing One-Carbon Units to Understand the Role of Serine in Epigenetics

Seth J. Parker[1] and Christian M. Metallo[1,2,*]
[1]Department of Bioengineering, University of California, San Diego, La Jolla, CA 92093, USA
[2]Moores Cancer Center, University of California, San Diego, La Jolla, California 92093, USA
*Correspondence: cmetallo@eng.ucsd.edu
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In this issue of *Molecular Cell*, Maddocks et al. (2016) use stable isotope tracing, mass spectrometry, and nutrient modulation in cancer cells to highlight the role of serine in supporting methylation through maintenance of nucleotide levels.

Beyond their contribution to protein synthesis, amino acids support numerous bioenergetic and biosynthetic processes in mammalian cells, including the production of precursors that influence epigenetics. Serine is a non-essential amino acid that can be synthesized via glycolysis, and deprivation of serine from media or chow can negatively impact tumor growth (Maddocks et al., 2013). However, the mechanisms through which serine deficiency impacts cell function are not completely clear. In this issue of *Molecular Cell*, using a combination of analytical chemistry and stable isotope tracing, Maddocks et al. (2016) explored how serine influences the methionine cycle.

The methionine cycle regenerates substrates for the methylation of DNA, RNA, and other molecules within the cell. Serine can supply one-carbon units to this process via a folate- and cobalamin-dependent metabolic pathway but also supports this cycle indirectly through nucleotide biosynthesis. While methionine provides the majority of one-carbon units for DNA and RNA methylation in proliferating cancer cells, serine deprivation decreased the contribution of methionine to 5-methylcytosine and *N*-6-methyl-adenine via *S*-adenosyl-methionine (SAM) at short time points (i.e., before compensation by serine synthesis). Further analysis of methionine, SAM, and nucleotide pools by Maddocks et al. (2016) indicated that serine deprivation most profoundly impacted de novo ATP synthesis rather than remethylation of homocysteine. Since the production of SAM from methionine is ATP dependent and serine is required for de novo purine synthesis, Maddocks et al. (2016) hypothesized that serine deprivation causes a reduction in ATP levels and thus SAM production. Indeed, serine deprivation caused a decrease in both AMP and ATP without activating AMP-activated protein kinase (AMPK) signaling, in contrast to glucose withdrawal. Methionine levels, on the other hand, increased significantly upon serine deprivation. Therefore, by tracing the utilization of serine and methionine in these interconnected pathways, Maddocks et al. (2016) determined that serine primarily supports the methionine cycle through de novo ATP synthesis rather than one-carbon unit transfer.

Serine lies at a critical pivot point within intermediary metabolism, linking biosynthetic flux from glycolysis to purine synthesis, folate-mediated one-carbon metabolism (FOCM), glutathione synthesis, and lipid metabolism (Figure 1) (Tibbetts and Appling, 2010). Each of these metabolic processes may influence a number of biological functions, including epigenetic regulation and cellular redox status. Not surprisingly, a growing number of studies have demonstrated the importance of this pathway in cancer. Genes encoding several enzymes along these pathways are amplified or overexpressed in tumors, including phosphohydroxyglycerate dehydrogenase (*PHGDH*) (Locasale et al., 2011) and methylene tetrahydrofolate dehydrogenase 2 (*MTHFD2*) (Nilsson et al., 2014). Furthermore, modulation of serine availability can impact in vivo tumor growth and the sensitivity to mitochondrial inhibitors (Gravel et al., 2014; Maddocks et al., 2013). Similar approaches to that conducted by Maddocks et al. (2016) in this issue have shed light on the impacts of serine on purine and NAD(P)H regeneration (Fan et al., 2014; Field et al., 2015; Lewis et al., 2014; Nilsson et al., 2014). An underappreciated role for serine in proliferating cells is its contribution to both signaling and structural lipids. Serine is the precursor for headgroups on a number of such biomolecules, including phosphatidylserine, phosphatidylethanolamine, and sphingolipids. Indeed, a significant fraction of lipids in mammalian tissues contain serine carbon and/or nitrogen. The impact of serine metabolism (e.g., deprivation, amplified enzyme expression) on polar lipid synthesis therefore warrants further investigation. Moving forward, continued exploration of this important pathway using a variety of isotope tracers will likely identify critical new mechanisms through which serine metabolism impacts cancer cell growth and survival.

The work from Maddocks et al. (2016) highlights the interconnected nature of biochemical pathways, and the insights that can be provided by detailed metabolic tracing. A single metabolite or nutrient (in this case serine) can influence the function of numerous biological pathways. By exploiting the availability of specifically labeled isotope tracers and mass spectrometry-mediated analytical chemistry, one can trace how nutrients (or the individual atoms of a compound) are used by cells. Since metabolism impacts virtually every cellular process, including epigenetics, such detailed analyses can provide mechanistic insights into the pathways responsible for a phenotypic observation (in this case, the impact of serine deprivation on methylation dynamics). Without the

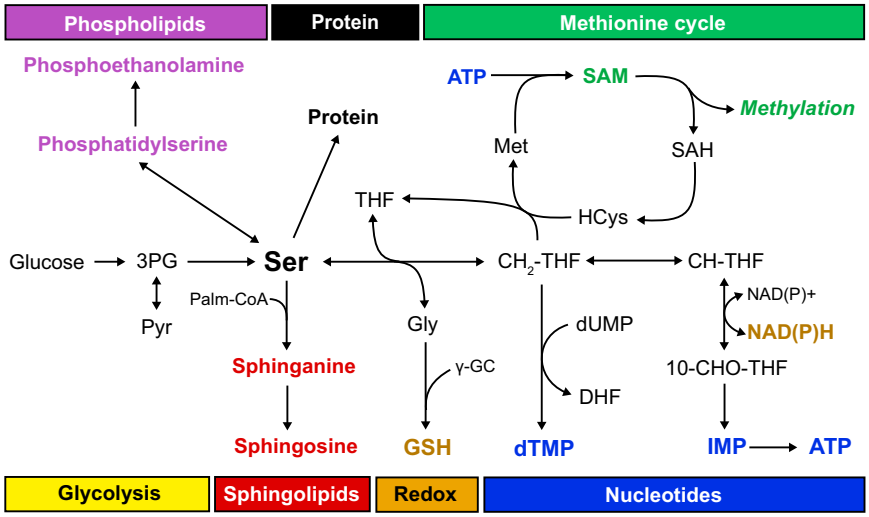

Figure 1. Simplified Representation of Metabolic Pathways Involving Serine

Serine lies at a critical juncture in metabolism supplying precursors for nucleotide and lipid biosynthesis, one-carbon units for DNA/RNA and histone methylation, and pyridine nucleotides for redox homeostasis and reductive biosynthesis. 10-CHO-THF, 10-formyl-tetrahydrofolate; 3PG, 3-phosphoglycerate; ATP, adenosine triphosphate; CH_2-THF, 5,10-methylenetetrahydrofolate; CH-THF, 5,10-methenyltetrahydrofolate; DHF, dihydrofolate; dTMP, thymidine monophosphate; dUMP, uridine monophosphate; Gly, glycine; GSH, glutathione; HCys, homocysteine; IMP, inosine monophosphate; Met, methionine; Pyr, pyruvate; SAH, S-adenosyl-homocysteine; SAM, S-adenosyl-methionine; Ser, serine; THF, tetrahydrofolate.

employment of metabolic tracers, the *association* of serine, one-carbon metabolism, and epigenetics was clear but the specific pathway responsible for this dysregulation could not have reliably been uncovered.

The detailed tracing studies conducted here also provide a roadmap for analyzing the dynamics of global DNA, RNA, and/or histone methylation. By quantifying the kinetics of labeling in 5-methylcytosine, 5-hydroxymethylcytosine, *N*-6-methyl-adenine, or other metabolites, one can reliably observe de novo methylation and its turnover in a number of systems. Such data would provide quantitative insights into the crosstalk between serine metabolism and the proteins that regulate methylation (e.g., α-ketoglutarate-dependent dioxygenases, LSD1, methyltransferases).

One caveat to consider in this and related studies is the context in which metabolic pathways are investigated. The nutritional environment is a critical factor influencing substrate utilization both in vivo and in vitro. While serine did not contribute one-carbon units to the SAM pool under the conditions studied here, homocysteine levels and methionine regeneration are profoundly impacted by cobalamin deficiency in patients (Carmel et al., 2003). As such, the specific impact of serine deprivation may be influenced by the cellular environment and in particular extracellular nucleotide and cofactor availability. These issues pose additional challenges to interpretation of metabolomic data and further highlight the importance of detailed metabolic tracing studies (both in vivo and in vitro) such as those executed here.

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