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Glutamine Skipping the Q into Mitochondria

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Abstract

Imported across the plasma membrane by SLC1A5, glutamine has emerged as a metabolic fuel that is catabolized by mitochondrial glutaminase to support tumor growth. The missing link between cytoplasmic and mitochondrial glutamine metabolism is now provided by Yoo *et al.*, identifying the mitochondrial glutamine importer as a variant of SLC1A5.

The mitochondrion is a primordial metabolic organelle, which emerged from its origin as a bacterium that was trapped in the cytoplasm of evolving eukaryotic cells. Major biosynthetic pathways and the respiratory chain that enables efficient production of ATP are compartmentalized in this special membrane-bound organelle. Nutrient exchange with the cytosol is essential for mitochondrial function, requiring nutrient import and export mechanisms, which have been uncovered over the years. However, the mechanism by which glutamine is imported into mitochondria has been elusive. Yoo *et al.* [1] now report their remarkable identification of a glutamine mitochondrial importer, adding to the growing list of mitochondrial metabolite transporters (Table 1) [1-5].

Cancer cells face microenvironments that are often depleted in nutrients and oxygen [6]. While Otto Warburg's observations of high levels of glucose metabolism in cancers were made almost a century ago, a role for mitochondrial glutamine metabolism in cancer cells has unfolded only recently [7].

Krebs found in the 1930s that the enzyme glutaminase, which converts glutamine to glutamate, was located in mitochondria. Eagle and colleagues showed in the 1950s that growth of cultured cancer cells was critically dependent on glutamine. Over the past 15 years, advances in the fields of cancer genetics and metabolism have uncovered links between oncogenes and glutamine dependence, resulting in glutaminase inhibitors entering the clinic [6,7]. However, despite all the progress in our understanding of the role of mitochondrial glutamine metabolism in cancer, how glutamine was imported into mitochondria remained unknown. Yoo *et al.* [1] discovered that the *SLC1A5* gene has alternative promoters, with one driving the expression of the well-studied cell surface transporter of glutamine SLC1A5 and another driving a variant (SLC1A5_var) that serves as the mitochondrial glutamine transporter. SLC1A5_var contains a mitochondrial targeting

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signal, which distinguishes it from the canonical cell surface SLC1A5 and directs mitochondrial localization. Intriguingly, they observed increased expression of this variant in cancer, although it is evolutionarily conserved and expressed at varying levels in normal human and mouse tissues.

Because our understanding is limited by technology for measuring metabolites in specific organelles, the effects of compartmentalization on controlling cellular function are only beginning to be understood. A well-studied example is acetyl-CoA compartmentation in distinct mitochondrial, cytoplasmic, and nuclear pools, which can control cellular metabolic and epigenetic state [8]. Similar to SLC1A5_var, a key player in the compartmentation of acetyl-CoA metabolism, the mitochondrial pyruvate carrier (MPC1 and MPC2) remained elusive for decades [5]. Glutamine metabolism also shows compartmentalization, with distinct cytoplasmic and mitochondrial processes [7]. Upon entering the cell, glutamine can play a variety of roles in the cytoplasm, where it can be exchanged for other amino acids and act as a nitrogen donor for the synthesis of nucleotides, hexosamine, and asparagine [7]. However, upon entering the mitochondria via SLC1A5_var, glutamine can be converted to glutamate by the mitochondrial enzyme glutaminase. Glutamate can then enter the TCA cycle following its conversion to alpha-ketoglutarate. Consistent with its role as a mitochondrial glutamine transporter, SLC1A5_-var specific knockdown, but not the knockdown of the cell surface form of SLC1A5, reduces contributions of isotopically labeled glutamine to the TCA cycle and levels of alpha-ketoglutarate. Importantly, SLC1A5_var knockdown cells showed impaired growth and ROS stress, consistent with the central role of glutamate in production of the antioxidant glutathione and TCA cycle control of cellular redox state through glutathione regenerating NADPH.

Many tumors contain poorly vascularized regions. The resulting low oxygen levels causes the stabilization of hypoxia inducible factors (HIF) 1alpha and 2alpha [6]. HIF-1alpha induces lactate dehydrogenase A and pyruvate dehydrogenase kinase, resulting in the shunting of glucose-derived pyruvate to lactate away from its conversion to acetyl-CoA by mitochondrial pyruvate dehydrogenase [6]. By contrast, glutamine has been shown to provide intermediates for the TCA cycle in hypoxic conditions as pyruvate is diverted away [7]. Intriguingly, Yoo *et al.* [1] show that hypoxia induces SLC1A5_var in a HIF-2alpha-dependent manner. Clustered regularly interspaced short palindromic repeats (CRISPR)-mediated disruption of the HIF response element in the SLC1A5_var alternative promoter causes reduced soft agar growth. Further, knockdown of SLC1A5_var diminishes *in vivo* tumor xenograft growth.

The identification of the glutamine transporter comes at an exciting time in understanding the transport of molecules across membranes. While older methods relied on relatively low throughput membrane reconstitution studies or genetic screens in yeast, the introduction of new techniques such as insertional mutagenesis allow for the identification of cell surface and mitochondrial transporters. Now, genome-wide CRISPR screens can be used to identify transporters for both nutrients and drugs [9,10]. While enrichment of sgRNAs targeting a drug’s transporter in a drug resistance screen is conceptually straightforward, designing the readout for identifying mitochondrial transporters can require complicated screening strategies. One recent report combined a CRISPR screen with the knockout of a

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cytoplasmic-specific enzyme and serine deprivation to identify a mitochondrial serine transporter [4]. As the use of alternative promoters to control transporter function is poorly understood, it would be interesting to determine if promoter-specific CRISPR interference-based screens could be used to deconvolute the role of alternative promoters in this regulation.

The discovery of a mitochondrial isoform of SLC1A5 raises a number of additional questions. It remains to be explored if SLC1A5_var has specific functions in normal tissues or tumor formation in transgenic models of tumorigenesis. Additionally, as tool compounds targeting SLC1A5 have been reported, it is as yet undetermined if these inhibitors can be optimized to selectively inhibit the mitochondrial form. Adding to potential clinical relevance, it is possible that high SLC1A5_-var expression will be predictive of glutamine dependence *in vivo* as glutamine metabolic inhibitors are being developed for cancer clinical trials.

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Table 1.

Selected Mitochondrial Nutrient Transporters

Mitochondrial transporter	**Substrate**
SLC1A5_var	Glutamine
SLC25A1	Citrate/malate
SLC25A2	Ornithine/citrulline
SLC25A10	Malate/phosphate
SLC25A11	Oxoglutarate/malate
SLC25A12	Aspartate/glutamate
SLC25A13	Aspartate/glutamate
SLC25A15	Citrulline/ornithine
SLC25A18	Glutamate
SLC25A20	Acyl-carnitine/carnitine
SLC25A22	Glutamate
SLC25A26	*S*-adenosylmethionine
SLC25A29	Basic amino acids
SLC25A32	Folate
SLC25A38	Glycine
SLC25A41	Coenzyme A
SFXN1	Serine
Mitochondrial pyruvate carrier	Pyruvate