Primary Cilia Respond To Nutrient Availability And Facilitate Glutamine Utilization Via Asparagine Synthetase

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Introduction

Shedding light on the still obscure function of primary cilia could provide relevant insights in their role both in physiological and in pathological contexts. Primary cilia dysfunction leads to a wide spectrum of disorders named ciliopathies. Among them, the most common one is Autosomal Dominant Polycystic Kidney Disease (ADPKD), which is characterized by renal cystogenesis leading to renal failure. Our group found that ADPKD shows a metabolic reprogramming which includes enhanced glycolysis, glutaminolysis, and fatty acid synthesis, and concomitant decreased oxidative phosphorylation and fatty acid oxidation. Given that ADPKD is a ciliopathy, we hypothesized that cilia might be involved in regulating bioenergetic pathways. Indeed, we revealed a new role of primary cilia as regulators of cellular metabolism.

Methods

Immunofluorescence staining for cilia was used to measure cilia length and frequency of ciliated cells and for ASNS localization. Cilium-deficient cells were generated by CRISPR-Cas9 technology. For metabolic profiling of cells upon different culture conditions, NMR and LC-MS metabolomics were employed. Mitochondrial respiration was measured by MitoStress Test.

Results

We found that primary cilia sense and respond to nutrient deprivation by elongating and that glutamine, but not glucose, promotes ciliary shortening through the glutamine capability to fuel the tricarboxylic acid (TCA) cycle upon nutrient deprived conditions. We revealed that the asparagine synthetase (ASNS) enzyme, which converts glutamine into glutamate (while converting aspartate to asparagine), plays a crucial role in this cilia-dependent function by facilitating fueling of the TCA cycle. We have found that the enzyme ASNS known to be cytosolic resident, is also a ciliary protein, as it can translocate to the base of the primary cilium.

Conclusions

We revealed that primary cilia regulate cellular metabolism by responding to glutamine via ASNS. Our findings shed light on the role of primary cilia and cellular metabolism in both physiological and pathological scenarios.