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Myc induces expression of glutamine synthetase through promoter demethylation

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The proto-oncoprotein Myc is known to promote glutamine usage by up-regulating glutaminase (GLS), which converts glutamine to glutamate that is catabolized in the tricarboxylic acid (TCA) cycle. Here we report that in a number of human and murine cells and cancers, Myc overexpression leads to elevated expression of glutamate-ammonia ligase (GLUL), also termed glutamine synthetase (GS), which catalyzes the de novo synthesis of glutamine from glutamate and ammonia. Elevated expression of GS promotes cell survival under glutamine limitation, while silencing of GS leads to decreased cell proliferation and xenograft tumor growth. Stable isotope based metabolite tracing shows that GS overexpression increases glutamine synthesis, cataplerotic flux at the α-ketoglutarate (αKG) step of the TCA cycle, and contributes to nucleotide synthesis and amino acid transport. Mechanistically, Myc binds to the promoter of thymine DNA glycosylase (TDG) and upregulates its expression, which leads to active demethylation of the GS promoter and its increased expression. These results demonstrate an unexpected role of Myc in promoting glutamine synthesis, and suggest a previously uncovered molecular connection between DNA demethylation and glutamine metabolism in Myc-driven cancers.

Biography

I-Chen Peng is an Assistant Professor of Department of Life Sciences at National Cheng Kung University, Taiwan. She received her PhD in the Biochemistry and Molecular Biology Graduate Program from University of California at Riverside, USA, and Postdoctoral training in the Department of Molecular Genetics & Microbiology at Stony Brook University in New York, USA. She has published several papers in reputed journals. She joined the faculty in the Department of Life Sciences at National Cheng Kung University in 2014. Her research focuses on targeting lipid and glutamine metabolism to treat obesity and obesity-related diseases.

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