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Carbon metabolic kinetics in human disease models

En-Pei Isabel Chiang
National Chung Hsing University, Taiwan

Abstract

Folate-mediated one-carbon metabolism has been the target of many therapies in diseases involving cell proliferation, as folate is essential in purine and thymidylate biosynthesis. We have been interested in studying how genetic variation in folate metabolic genes may affect human disease risk and clinically used antifolate drug sensitivity. The homozygous mutation (677TT) in the methylenetetrahydrofolate reductase (MTHFR) gene reduces enzyme activity and alters cellular folate composition. Previous epidemiological studies reported a potential protective effect of MTHFR677C --> T against acute lymphocytic leukemia and malignant lymphoma, but the mechanism remains to be determined. We investigated the biochemical impacts of MTHFR677C --> T on cellular S-adenosyl methionine (adoMet) synthesis, global DNA methylation, and *de novo* purine synthesis, all of which are potential regulatory pathways involved in tumorigenesis. Metabolic fluxes of homocysteine remethylation and *de novo* purine synthesis were compared between Epstein-Barr virus-transformed lymphoblasts expressing MTHFR 677C and MTHFR 677T using stable isotopic tracers and GCMS. MTHFR TT genotype significantly reduced folate-dependent remethylation under folate restriction, reflecting limited methylated folates under folate restriction. Data also suggested increased formylated folate pool and increased purine synthesis when folate is adequate. The impacts of MTHFR 677T polymorphism appeared closely related to folate status, and such alterations may modulate metabolic pathways involved in cancer onset/progression. The advantage of *de novo* purine synthesis found in the MTHFR TT genotype may account for the protective effect of MTHFR in hematological malignancies. Using different cell models we further discovered that methotrexate and MTHFRC677T have distinctive impacts on 1-carbon metabolic pathways in different target tissues that may account for the increased tissue sensitivity of homozygous MTHFRC677T individuals. These studies shed lights on the interactions between folate pathway genetic variation and anti-folate therapies. These model systems are feasible for studying the consequences of human genetic variation on disease occurrence, progression, and antifolate immunoregulatory drugs in the future.

Biography

En-Pei Isabel Chiang received her Ph.D. in Biochemical and Molecular Nutrition from Tufts University in 2000. She then received the post-doctoral training at UC Berkeley from 2000-2003 in Folate Metabolism. She became a faculty member in the Dept. of Food Science & Biotechnology at National Chung Hsing University in 2003, Associate Professor in 2007, and became a Professor in 2011. Her laboratory mostly investigates the relationships between human diseases and nutritional factors at the cellular and molecular level. Human, animal and cell studies are being conducted to better understand the role of nutrition in human diseases. Specific cell and transgenic mouse models are utilized to investigate how genetic variations in the folate metabolic pathways may affect chronic disease progression. Metabolic kinetics of drugs-nutrient interactions are also under investigation. She published her work in significant journals such as Leukemia, J Clin Endocr Metab, BMC Med, J Nutr and others. Throughout the years she has received numerous academic honors including awards from the American Association of Cancer Research (AACR Scholar-In Training Award, USA), Arthritis Foundation (Doctoral Dissertation Award, USA), from National Science Council (Junior Research Investigator Awards, Taiwan), the Nutrition Society of Taiwan (JSC Memorial Award for Young Scholar), and Taiwan Association for Food Science and Technology (CHLJ Memorial Award for Junior Scholar). She was also elected as one of the ten outstanding young females of Taiwan in the year of 2009.