Low expression of gamma-glutamyl hydrolase mRNA in primary colorectal cancer with the CpG island methylator phenotype.

Kawakami K, Ooyama A, Ruszkiewicz A, Jin M, Watanabe G, Moore J, Oka T, Iacopetta B, Minamoto T.

The CpG island methylator phenotype (CIMP+) in colorectal cancer (CRC) is defined as concomitant and frequent hypermethylation of CpG islands within gene promoter regions. We previously demonstrated that CIMP+ was associated with elevated concentrations of folate intermediates in tumour tissues. In the present study, we investigated whether CIMP+ was associated with a specific mRNA expression pattern for folate- and nucleotide-metabolising enzymes. An exploratory study was conducted on 114 CRC samples from Australia. mRNA levels for 17 genes involved in folate and nucleotide metabolism were measured by real-time RT-PCR. CIMP+ was determined by real-time methylation-specific PCR and compared to mRNA expression. Candidate genes showing association with CIMP+ were further investigated in a replication cohort of 150 CRC samples from Japan. In the exploratory study, low expression of gamma-glutamyl hydrolase (GGH) was strongly associated with CIMP+ and CIMP+-related clinicopathological and molecular features. Trends for inverse association between GGH expression and the concentration of folate intermediates were also observed. Analysis of the replication cohort confirmed that GGH expression was significantly lower in CIMP+ CRC. Promoter hypermethylation of GGH was observed in only 5.6% (1 out of 18) CIMP+ tumours and could not account for the low expression level of this gene. CIMP+ CRC is associated with low expression of GGH, suggesting involvement of the folate pathway in the development and/or progression of this phenotype. Further studies of folate metabolism in CIMP+ CRC may help to elucidate the aetiology of these tumours and to predict their response to anti-folates and 5-fluorouracil/leucovorin.

[Reference]

Kawakami K, Ooyama A, Ruszkiewicz A, Jin M, Watanabe G, Moore J, Oka T, Iacopetta B, Minamoto T. Low expression of gamma-glutamyl hydrolase mRNA in primary colorectal cancer with the CpG island methylator phenotype. Br J Cancer. 2008 May 6;98(9):1555-1561.