

## Genetic and Epigenetic Interaction in the Development of Colorectal Cancers

Tomomitsu Tahara<sup>1\*</sup> and Tomiyasu Arisawa<sup>2</sup>

<sup>1</sup>Department of Gastroenterology, Fujita Health University School of Medicine, Toyoake, 1-98 Dengakugakubo Kutsukake-cho, Toyoake, Aichi, 470-1192, Japan

<sup>2</sup>Department of Gastroenterology, Kanazawa Medical University, 1-1, Daigaku, Uchinada-machi, Ishikawa, 920-0293, Japan

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Colorectal cancer (CRC) is one of the most common malignancies, representing the third most common cancer worldwide [1]. Approximately 75% of all CRCs are sporadic and characterized by genetic lesions, most commonly mutations on *TP53*, *KRAS* and *APC* genes [2,3]. In addition, epigenetic defect in CRCs are also well reported mainly regarding DNA methylation. DNA methylation anomalies define distinct subgroups of CRC, termed CpG island methylator phenotype (CIMP). The existence of a CIMP and its correlation with clinicopathologic features have been confirmed [4,5]. CIMP-positive CRCs display distinct clinical features, such as greater age, proximal location, and mucinous and poorly-differentiated histopathology. Recent studies have shown that sessile serrated adenomas, mainly observed in the proximal colon are associated with CIMP [6], suggesting the precursor origin of CIMP-positive CRCs is also different from that of CIMP-negative CRCs. Importantly, CIMP-positive CRCs are usually associated with better prognosis [7]; however, patients with CIMP-positive CRCs do not benefit from 5-FU-based adjuvant chemotherapy [8].

It has been thought that epigenetic change is an alternative mechanism in cancer development, however, current knowledge also suggest that most of cancer has mixture of both genetics and epigenetic defects, it would be easy to expect there is also an interaction between genetics and epigenetics in the development of CRCs. Previous researches combining the genetic mutation and CIMP status have identified that there are distinct link between DNA methylation and genetic alterations in CRCs [4]. Consequent study has divided CIMP-positive cases into two different categories (CIMP1 or CIMP-high, and CIMP2 or CIMP-low) suggesting the possibility that CRCs arose from distinct and different genetic and epigenetic abnormalities. CIMP1 cases present intense methylation of multiple genes and are associated with microsatellite instability (MSI) through the epigenetic silencing of a mismatch repair gene (*MLH1*) as well as *BRAF* mutation [9]. CIMP2 is characterized by the methylation of a limited group of genes and mutation in *KRAS*. CIMP-negative cases have less frequent methylation changes and very frequent *TP53* mutation and chromosomal instability [5,9]. The result is a good example of genetic and epigenetic interaction in the development of cancer and the discovery of CIMP in CRCs is the rand mark for research in the combining of genetic mutation and methylation profiling of carcinomas in order to understand the individual heterogeneity of tumors, which may be useful for a better understanding of the pathogenesis of individual tumors. The concept of genetic and epigenetic interaction in the development of cancers can be well applied for other malignancies such as gastric cancer and glioblastoma. High level CIMP (CIMP-H) gastric cancers with MSI are lacking *TP53* or *KRAS* mutation [10]. Another study in gastric cancer has also revealed an association between the CIMP and oncogenic mutations including *CTNNB1*, *ERBB2*, *KRAS*, and *PIK3CA* [11]. A comprehensive methylation profiling in glioblastoma suggested the existence of a glioma-CpG island methylator phenotype (G-CIMP),

displaying distinct copynumber alterations, and are tightly associated with somatic mutations in *IDH1* gene [12].

Recent study in CRCs tried to catalogue both genetics and epigenetics of this cancer type by genome-scale [13]. The result revealed a subset of CRCs which was found to be hypermutated: three-quarters of these had the high MSI, hypermethylation and *MLH1* silencing, with completely different landscape of mutated genes as shown in non-hypermethylated tumors. The result provide a framework for understanding oncogenesis in tumors, highlighting the importance of genomic and epigenomic interactions in human cancers. Although the mechanisms causing methylation phenotypes is remain unclear, revealing the causes of epigenetic instability will help us understand the biology of methylation-positive tumors and may reveal new therapeutic targets.

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\*Corresponding author: Tomomitsu Tahara, Department of Gastroenterology, Fujita Health University School of Medicine, Toyoake, 1-98 Dengakugakubo Kutsukake-cho, Toyoake, Aichi, 470-1192, Japan, Tel: +81-562-939240; Fax: +81 562 93 8300; E-mail: [tomomiccyu@yahoo.co.jp](mailto:tomomiccyu@yahoo.co.jp)

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