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DNA Methylation in Colorectal Cancer: A brief Review.

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Abstract

In human tumors, epigenetic modifications, particularly DNA methylation in specific gene promoters, are recognized as common molecular alterations. In concert with other epigenetic mechanisms, DNA methylation acts to regulate gene expression and facilitate chromatin organization within cells. Substantial research has been done to determine the cause and role of aberrant DNA methylation ("epigenomic instability") in colon cancer. During carcinogenesis, epigenetic switching and 5'-methylcytosine reprogramming result in the hypermethylation of CpG islands, reducing epigenetic plasticity of critical developmental and tumor suppressor genes, rendering them unresponsive to normal stimuli. For early detection of cancer, quantitative approaches to identify DNA methylation differences between normal and cancer tissues could lead to the identification of a panel of highly specific methylated markers. Since it has been well established that genetic and epigenetic alterations influence the development of colorectal cancer (CRC), so to improve the current diagnosis, screening, prognosis and treatment prediction for the disease huge potential lies in the use of DNA methylation as a biomarker. Also, for therapy prediction, more studies should focus on finding markers for chemotherapeutic drugs as majority of the patients would be benefited.

Keywords: DNA methylation, CpG islands, CRC, prognosis, diagnosis.

I. INTRODUCTION

The complex eukaryotic genome has evolved to enable large amounts of DNA to be contained within the boundary of the nucleus.

Various genetic and epigenetic factors have been associated with the maintenance of DNA stability. The term 'epigenetic' refers to the study of heritable changes in the expression of genes or phenotype that are not due to changes in the genotype. DNA methylation is one of the key epigenetic factors involved in regulation of gene expression and genomic stability, and is biologically necessary for the maintenance of many cellular functions.

DNA METHYLATION

DNA methylation is a heritable epigenetic mark involved in the covalent transfer of a methyl group to the C-5' position of the cytosine ring of DNA by enzymes called DNA methyltransferases (DNMTs). (Robertson 2005). A family of DNMTs regulates DNA methylation: DNMT1, DNMT2, DNMT3A, DNMT3B, and DNMT3. DNA methylation is required for normal growth and development, in addition also plays an essential role in a number of key processes in mammals including X-chromosome inactivation, genomic imprinting, suppression of repetitive element transcription, transposition and carcinogenesis. (Gopalakrishnan et al., 2008). DNA methylation contributes to the regulatory mechanisms of tissue-specific gene expression in normal cells and is a mediator of long-term silencing as well. A normal cell is characterized by genome-wide methylation with the exception of CpG (cytosine-phosphateguanine) islands, which are normally unmethylated [11]. However, by virtue of various triggers in cancerous cells, certain events are set in motion which lead to the hypomethylation of entire genome with the exception of CpG island promoters, which undergo hypermethylation [Suzuki and Bird 2008; Jones and Baylin 2002].

II. DNA METHYLATION AND CANCER:

Cancer is the uncontrolled abnormal growth of body cells that grow out when they become malignant. Normally, cells in human body multiply as needed, and finally undergo genetically programmed cell death. Cancer appears to occur when the normal growth of cells in the body is out of control and cells divide too quickly or cells don't undergo apoptosis or cell death. Approximately 1,685,210 new cancer diagnoses and 595,690 cancer deaths were expected in 2016 in the United States. More than 20% of cancer cases are accounted for the behaviours such as poor diet choices, physical inactivity, excess alcohol consumption, and unhealthy body weight and therefore can be prevented with lifestyle modifications (America Cancer Society 2018). Many genetic and epigenetic alterations can lead to cancer and among

different epigenetic factors, DNA methylation is one of the most important factors that is thought to occur during the early stages of oncogenic transformation. Though, in mammalian genome DNA methylation which brings about heritable and reversible changes is one of the most commonly occurring epigenetic events taking place. These changes are making it a potential therapeutic target. The human genome contains unmethylated regions dispersed by methylated regions and so, is not uniformly methylated. In contrast to the rest of the genome, smaller regions of DNA ranging from 0.5 to 5 kb and occurring on average every 100 kb called CpG islands, have distinguishing properties. These regions being unmethylated have 60-70%GC rich, has a ratio of CpG to GpC of at least 0.6, and thus do not show any suppression of the frequency of the dinucleotide CpG (Cross et al., 1995). Approximately half of all protein-encoding genes in the human genome contain CG-rich regions or CpG islands in their promoters. In cancer, DNA methylation has become the topic of intensive investigation and is observed in many cancers including colorectal cancer.

In many types of human cancers aberrated DNA methylation patterns – hyper-methylation and hypo-methylation that differ from normal tissue have been discovered. [Timp & Feinberg 2013; Baylin, S. B. & Jones 2011]. DNA hypermethylation of CpG islands in the promoter region results in repression or gene inactivation of transcription in tumor suppressor genes [Zhang et al., 2011]. In general DNA hypomethylation, on the other hand, is linked to chromosomal instability and loss of imprinting [Daura et al., 2009]. Typically, tumor suppressor genes (TSGs) get hyper-methylated and oncogenes get hypomethylated. (Martha et al., 2011).

III. DNA METHYLATION IN COLORECTAL CANCER

Colorectal cancer (CRC) arises as a consequence of the accumulation of genetic and epigenetic alterations in colonic epithelial cells during neoplastic transformation. (Myoung et al., 2010). Worldwide, colorectal cancer is the third most common malignant neoplasm and also one of the leading causes of cancer deaths in men and women in the United States. (Jemal et al., 2005) Each year colorectal cancer accounts for 610,000 mortalities worldwide and is the third and fourth most common cancer in females and males, respectively. The overall survival rate of patients with CRC at the time of diagnosis is highly dependent on the stage of the disease. For patients with stage I tumors, the estimated five year survival rates range from

85-90% and <5% for patients with stage IV cancer. (Tiago et al., 2013) However, to reduce mortality rate as well as CRC incidence early detection of colonic lesions is the most effective approach. A common event in the tumorigenesis of CRC is believed to be the association of global hypomethylation with discrete hypermethylation at the promoter regions of specific genes which are involved in cell cycle regulation, apoptosis, invasion, DNA repair, angiogenesis and adhesion. (Carmona and Esteller 2010) In sporadic microsatellite unstable colon cancers, gene inactivation of the mismatch repair gene MLH1 by promoter methylation is the molecular basis for microsatellite instability (Samowitz 2007). Margret (June 2011) performed DNA pyrosequencing to determine the status of promoter methylation of the mutL homolog 1 (MLH1) gene and it was found that approximately 15% of colorectal tumors displayed microsatellite instability, however only about 10% of those are due to hereditary causes, such as Lynch syndrome or hereditary non-polyposis colorectal cancer (HNPCC). The hypermethylation of the promoter region of hMLH1 gene was a strong indicator that the gene was silenced through epigenetic modifications, and not inactive due to a hereditary mutation of the gene. Aberrant promoter methylation of hMLH1 gene in Kashmiri population contributes to the process of carcinogenesis in colorectal cancer and is one of the commonest epigenetic changes in the development of CRC. (Mashooq et al., 2013) As methylation changes have been implicated in tumorigenesis, genetic disruption of both *DNMT1* and *DNMT3b* reduced DNA methylation in a colorectal cell line and resulted in the loss of insulin-like growth factor II imprinting, negation of silencing of the tumor suppressor gene $hMLH1^{INK4a}$, and growth suppression (Rhee et al., 2002). The hypermethylation of several gene promoters including APC, p16INK4a, TIMP3 in CRC has been reported. Hypermethylation of an increasing number of genes has been associated with human colorectal tumorigenesis, and the detection of CpG island hypermethylation in human DNA isolated from stool has been suggested as a promising application for noninvasive screening and early detection of colorectal neoplasia (Ahlquist 2012; Azuara et al., 2010; Osborn et al., 2005). Also, for the early detection of cancer epigenetic alterations (DNA methylation) of specific genes have recently emerged as potential candidate biomarkers.

IV. DNA METHYLATION AS A MARKER FOR CRC DIAGNOSIS AND PROGNOSIS

In the last few years, a colossal amount of knowledge has been reaped about altered methylation patterns in human cancers. Recent advancement in the methylation detection techniques includes potent tools such as cDNA (complementary DNA) microarray, CpG island microarrays, sodium bisulfite conversion and restriction landmark genomic scanning. Tumor specific changes of methylation pattern have been discovered and well documented in different genes and this is essential for the potential clinical application in diagnosis, prognosis, and cancer therapeutics. Regardless of the biological consequences of methylation-induced silencing of tumor suppressor genes, this epigenetic alteration constitutes a molecular signature that can serve as a promising biomarker for early detection of cancer. Several DNA methylation markers as early biomarkers have been proposed to be applicable for CRC detection. The identification of aberrant methylation of Vimentin in fecal DNA was introduced in CRC diagnosis with a high sensitivity and specificity (Chen et al., 2005). Earlier study by Tiago et al., 2013, using a quantitative real time PCR based technique; a group of five HM genes (RUNX3, PCDH10, SFRP5, IGF2 and Hnf1b) with the highest percentage of methylation were identified in CRC patients. As these genes were observed to have the highest potential for gene expression repression and, therefore, were the most promising biomarkers for the diagnosis of CRC. A total of 10 candidate hypermethylated (HM) and unmethylated (UM) genes were identified that may be useful epigenetic markers for non invasive CRC screening. (TIAGO DONIZETTI et al., 2013). Methylation of IGFBP3, mir148a and PTEN are found to be predictive markers for 5-FU and EGFR therapy respectively (Kevin et al., 2016).

V. CONCLUSION

Cancer development was generally considered to be a disease that is caused by genetic alterations like mutations and chromosomal abnormalities in tumor-suppressor genes and oncogenes, but now it is a well established fact that epigenetic alterations can lead to cancer. Epigenetics has become an emerging field due to the fundamental role of epigenetic modifications, including DNA methylation, specific histone modifications and noncoding RNAs (i.e., silencing RNA and microRNA), in the regulation of gene expression. Among different epigenetic factors, DNA methylation

is one of the most important factors that is thought to occur during the early stages of oncogenic transformation in colorectal cancer. DNA methylation-based tests appear to have a promising role in early CRC detection and screening. it is essential to search for novel biomarkers improving prognosis. DNA methylation-based tests appear to have a promising role in early CRC detection and screening promising.

References

1) Ahlquist DA, Zou H, Domanico M, Mahoney DW, Yab TC, Taylor WR, et al. Next-generation stool DNA test accurately detects colorectal cancer and large adenomas. Gastroenterology 2012;142:248–56; quiz e25-6.

2) America Cancer Society. Cancer facts & figures 2016. Atlanta, GA: American Cancer Society; 2016.

3) Azuara D, Rodriguez-Moranta F, de Oca J, Soriano-Izquierdo A, Mora J, Guardiola J, et al. Novel methylation panel for the early detection of colorectal tumors in stool DNA. Clin Colorectal Cancer 2010;9:168–76.

4) Baylin, S. B. & Jones, P. A. A decade of exploring the cancer epigenome - biological and translational implications. Nat Rev Cancer 11, 726–734 (2011).

5) Carmona FJ and Esteller M: Epigenomics of human colon cancer. Mutat Res 693: 53-60, 2010.

6) Chen WD, Han ZJ, Skoletsky J, Olson J, Sah J, et al. Detection in fecal DNA of colon cancer specific methylation of the nonexpressed vimentin gene. J Natl Cancer Inst. 2005; 97:1124–1132.

7) Suzuki M. M. and Bird A., "DNA methylation landscapes: provocative insights from epigenomics," Nature Reviews Genetics, vol. 9, no. 6, pp. 465–476, 2008.

8) Jones P. A. and Baylin S. B., " Thee fundamental role of epigenetic events in cancer," Nature Reviews Genetics,vol.3,no. 6, pp.415– 428, 2002.

9) Cross SH, Bird AP: CpG islands and genes. CurrOpin Genet Dev 5:309-314, 1995.

10) Daura-Oller E, Cabre M, Montero MA, Paternain JL, Romeu A (2009) Specific gene hypomethylation and cancer: new insights into coding region feature trends. Bioinformation 3: 340-343.

11) Jemal, A., Murray, T., Ward, E., Samuels, A., Tiwari, R. C., Ghafoor, A., et al. (2005). Cancer statistics, 2005. CA: A Cancer Journal for Clinicians, 55(1), 10–30.

12) Kevin Lam, Kathy Pan, Janneke Fiona Linnekamp, Jan Paul Medema, Raju Kandimalla. DNA methylation based biomarkers in colorectal cancer: A systematic

review. Biochimica et Biophysica Acta 1866 (2016) 106–120.

13) Martha L. Slattery, and Wade S. Samowitz.CpG Island Methylation in Colorectal Cancer: Past, Present and Future Karen Curtin Pathology Research International. 2011. doi:10.4061/2011/902674.

14) Mashooq A Dar, Showkat A Bhat, Ahmad Arif, Hilal Ahmad Wani, Khalid B Dar, Rouf Maqbool, Suhail Anees Manzoor R Mir. Methylation Status of hMLH1 Gene in Colorectal Cancer Patients in Ethnic Population of Kashmir Valley. International journal of medical research (IJMR) 2013(1);4.

15) Robertson KD. DNA methylation and human disease. Nat Rev Genet. 2005;6(8):597-610.

16) Gopalakrishnan S, Van Emburgh BO, Robertson KD. DNA methylation in development and human disease. Mutat Res. 2008;647(1-2):30-8.

17) Myoung Sook Kim & Juna Lee & David Sidransky DNA methylation markers in colorectal cancer. Cancer Metastasis Rev (2010) 29:181–206 DOI 10.1007/s10555-010-9207-6.

18) Osborn NK, Ahlquist DA. Stool screening for colorectal cancer: molecular approaches. Gastroenterology 2005;128:192–206.

19) Rhee I, Bachman KE, Park BH, et al: DNMT1 and DNMT3b cooperate to silence genes in human cancer cells. Nature 416:552-556, 2002.

20) Samowitz W. S., "The CpG island methylator phenotype in colorectal cancer," Journal of Molecular Diagnostics, vol. 9, no. 3, pp. 281–283, 2007.

21) Tiago Donizetti Silva, Veronica Marques Vidigal, Aledson Vitor Felipe, Jacqueline Miranda De Lima, Ricardo Artigiani Neto, Sarhan Sidney Saad and Nora Manoukian Forones. DNA methylation as an epigenetic biomarker in colorectal cancer. ONCOLOGY LETTERS 6: 1687-1692, 2013.

22) Timp, W. & Feinberg, A. P. Cancer as a dysregulated epigenome allowing cellular growth advantage at the expense of the host. Nat Rev Cancer 13, 497–510 (2013).

23) Zhang FF, Cardarelli R, Carroll J, Zhang S, Fulda KG, et al. (2011) Physical activity and global genomic DNA methylation in a cancer-free population. Epigenetics 6: 293-299.