SMAD4 Promoter Hypermethylation in Kashmiri Colorectal Cancer Cases

Sir,

Colorectal cancer (CRC) is the fourth most common cancer in men and the third most common cancer in women and a major cause of mortality and morbidity worldwide. In Kashmir valley CRC represents the third most common GIT cancer after esophageal and gastric.[1]

During the last decade, epigenetic changes have been reported in many cancers and they are now recognized to be at least as common as genetic changes.[2] Aberrant methylation of cytosine located within the dinucleotide CpG in the promoter region is by far the best categorized epigenetic change. A CpG island methylator phenotype (CIMP+) has been described in colorectal cancer (CRC) and is characterized by simultaneous methylation of multiple genes such as the cell cycle (*RB*, *p15INK4b*, *p16INK4a*), the *TP53* pathway (*p14ARF*), the WNT signalling pathway (*APC*, *E-cadherin*), DNA repair (*MGMT*, *hMLH1*, *BRCA1*), apoptosis (*DAPK*), and the metastasizing process (*E-cadherin*, *TIMP3*).[3]

Inactivation of tumor suppressor genes by promoter hypermethylation has been recognized to be at least as common as gene disruption by mutation in tumorigenesis. A number of studies on colorectal cancer around the globe have demonstrated the role of promoter hypermethylation of number of different genes in development and progression of colorectal carcinoma. Likewise, we carried out this study to know the status of *SMAD4* promoter methylation in Kashmiri Colorectal Cancer cases. We carried out the study on 86 colorectal cancer cases who attended Department of General Surgery for resective surgery treatment. The *SMAD4* promoter lacks typical TATA boxes and CpG islands, but contains some TATA-like structures (TAAAAT) as well as some binding sites for transcription factors. We used the previously described protocol for promoter hypermethylation detection using the two restriction enzymes *HpaII* and *MspI* for differential digestion.[4] This protocol utilizes the ability of the *HpaII* restriction enzyme to distinguish CpG sites that are methylated versus those that are non-methylated. If the restriction sites are methylated, the methylation-sensitive *HpaII* does not cleave the DNA if its restriction sites are methylated but *MspI* is capable of cleaving the methylated restriction sites located well with the CpG islands of the promoter region [Figure 1]. Our results showed that none of the CRC cases had hypermethylation in the *SMAD4* promoter region. These results were in tune with the previous study.[4] Hence, we conclude that hypermethylation is not the foremost aberration in *SMAD4* gene and hence does not play any role in CRC tumorigenesis in Kashmiri population.

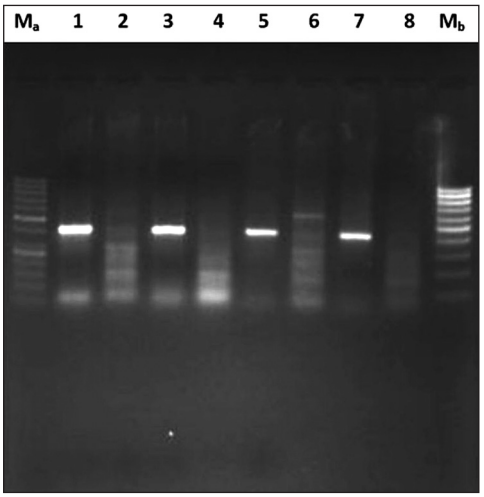

Figure 1: Representative picture showing the hypermethylation status of the SMAD4 promoter Lane Ma: 50bp molecular marker; Lane Mb: 100bp molecular marker; Lane 1,3,5 and 7: Amplicon of the undigested template; Lane 2,4,6 and 8: Amplicon of the HpaII

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