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FAM134B, a new player in human colorectal cancer pathogenesis

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Abstract

Background: FAM134B (family with sequence similarity 134, member B) is a relatively new player in many human diseases including cancers. In colorectal carcinomas, FAM134B plays important role in the pathogenesis and associated with biological aggressiveness of the disease. However, expression pattern, the frequency of mutations, methylation status in colon cancer cells and tissue samples has never been studied. Also, the functional roles of FAM134B in cell have never been studied in colorectal cancer.
Objectives: To investigate FAM134B promoter methylation, mutations in tissues samples from patients with colorectal cancer and cell lines. Also, promoter methylation, expression and functional roles of FAM134B in colon cancer were studied.

Methods: Methylation and mutations in FAM134B sequence in cancer tissues (n=126) and matched non-cancer samples was studied by high-resolution melt curve analysis followed by Sanger sequencing. FAM134B expression was studied and quantified in cell lines and cancer tissues samples using immunofluorescence, immunocytochemistry, Western blot and real time PCR. In vitro functional assays and mouse xenotransplantation model were performed to unveil the molecular roles of FAM134B in colon cancer pathogenesis followed by shRNA-mediated silencing in cells.

Results: We noted that 46.5% (41/88) patients with colorectal cancer were identified as FAM134B mutations positive. Thirty-one novel pathogenic mutations were detected and these mutations were associated with gender of the patients, presence of metachronous cancer, size, T staging, presence of distant metastases and positivity of microsatellite instability (MSI) in the cancer ($p < 0.05$). Majority of cancer tissues had shown promoter hyper-methylation and were correlated with reduced mRNA and protein expression in both cancer samples and cells. FAM134B expression in cancer cells derived from advanced stages (stage III; SW48 and stage IV; HCT116) of colon cancer was significantly ($p<0.01$) reduced when compared to non-neoplastic colon cells (FHC) and cancer cells derived from stage II colon cancer (SW480). Expression of FAM134B mRNA in cancer tissues was noted significantly ($p<0.001$) downregulated when compared to that of non-cancer tissues samples. FAM134B suppression significantly ($p<0.05$) increased the proliferation of colon cancer cells, remarkably increased (3452% ; $p<0.05$) the clonogenic, migration capacity, and increases the proportion of cells in S phase of cell cycle ($p<0.01$). Xenotransplantation model showed that larger and higher grade tumors were formed in mice treated with FAM134B knockdown cells.

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Conclusion: Reduced expression in cancer samples, in vitro and in vivo functional studies implied that FAM134B acts as a cancer inhibitor in colon cancer play important roles in colorectal carcinogenesis.

Keywords

FAM134B, Colorectal cancer, Tumor suppressor, Cancer genetics, JK1

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References

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