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Promoter Methylation Status Of Large Tumor Suppressor Gene Family (LATS1&2) And Its Significance As Therapeutic Target In Colorectal Cancer (CRC)

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Abstract

Background and Aim: Promoter methylation is an epigenetic modification that downregulates the expression of genes. Both LATS1&2 plays significant role as tumor suppressors. In this study promoter methylation of these genes and correlation with various clinico-pathological characters were studied.

Materials and methods: A total of 65 tumor and adjacent normal tissues were taken for the study. LATS 1 & LATS 2 methylation profiles were investigated using methylation specific PCR (MS-PCR).

Results: The promoter site of LATS 1 & LATS 2 genes were found to be hyper-methylated in 52.3% and 61.5% respectively of the CRC patients. Statistically a significant correlation was observed between LATS 1 & LATS 2 promoter hyper-methylation with Lymphnode metastasis (OR=2.24; 95% CI: 1.40-3.54, p=0.001);(OR=2.87;95% CI: 1.0-8.2, p=0.04).

Conclusion: LATS1/2 hypermethylation is a key step in the development of colorectal cancer and that it could be exploited as a diagnostic biomarker moreover these findings may provide useful insights for the development of CRC diagnoses and treatment.

Key words: Large tumor suppressor genes (LATS1,LATS2), Colorectal cancer, Promoter methylation.

Introduction

Colorectal Cancer (CRC) is globally known as one of the leading malignancies of gastro-intestinal tract (3rd position as far as incidence is concerned) with a major contribution to the worldwide cancer deathsmaking it 2nd in list (Cutsem 2016)(Cutsem 2016; Bray et al. 2018)(Bray et al. 2018). It is generally diagnosed in the advanced stages and exhibits an extremely poor prognosis.Despite advances in techniques like surgical resection and adjuvant chemotherapy or radiotherapy, the potential for this disease recurrence is still very high (Kankeu Fonkoua and Yee 2018). As a result, more diagnostic and prognostic biomarkers are required to improve clinical results in this malignancy.

The Large Tumor Suppressor (LATS) gene is one of the most evolutionarily conserved gene of the Hippo Lats pathway and has been reported to play an important role as tumor suppressor in Drosophila (Justice et al. 1995; Xu et al. 1995). Impairment in lats gene leads to uncontrolled cell proliferation and ultimately tumor in Drosophila (Xu et al. 1995). Mammalian counterparts of this gene are a family of two genes, LATS1 and LATS2 both of which serve as a tumor suppressors (St John et al. 1999; Huntoon et al. 2010) by regulating many cell cycle checkpoints, regulation through different signaling pathways like Hippo,Wnt, and p53 (Aylon et al. 2010; 2009; 2006; Visser and Yang 2010). Several studies have been reported regarding decrease in expression of both LATS1 and LATS2 in different human malignancies (Morinaga et al. 2000; Lin et al. 2014). Down-regulation of genes occurs in many ways like epigenetic modification, deletions, and loss of heterozygosity (Pérez-Sayáns et al. 2009).Gene silencing caused by promoter methylation contributes to cancer initation and progression.The covalent modifications of the cysteine residue within the CpG dinucleotides is directly linked to DNA methylation.Epigenetic changes occur early in the oncogenic process so DNA methylation indicators can be employed in cancer diagnostics for both disease classification and detection (Ehrlich 2019). Allelic failures, gene variants, and cryptic deletions are commonly known pathways for Tumor Suppressor Gene inactivation. Tumor suppressor genes are divided into two categories: those that directly limit tumour growth by suppressing cell proliferation or boosting cell death and those whose inactivation produces genetic diversity, which leads to mutations that promote tumour growth (Hisaoka, Tanaka, and Hashimoto 2002).Methylation-mediated down-regulation of LATS1 & LATS2 has been reported in a variety of human cancers. like Lung, Breast, andastrocytoma (Sasaki et al. 2010; Jiang et al. 2006; Takahashi et al. 2005).Based on the above mentioned evidences the goal of this study was to investigate the promoter hypermethylation status of LATS1 and LATS2 genes in Colorectal cancer patients and their relationship to clinicopathological aspects of the disease.

Materials and methods

Tumor specimen and patients

Sixty-five (n=65) tumor tissues and their adjacent normals that were histologically verified as cancer-free were taken for this study collected from Surgery department. The males were comparatively higher [38 of 65 (58.5%)] in number as compared tofemales 27 of 65 (41.5%) with male to female ratio of 1.41:1. Age wise subjects with anage of more than or equal to 50 years were representing majority [42 out of 65 (64.6%)] ofcases as compared to less than 50 years [23 out of 65 (35.4%)] with a mean of 56.9 SD±16.3years. In the current study, Ca. colon and Ca. rectum presented with almost equal numbers with a percentage of 50.8% and 49.2 % respectively. In pathological stages, higher percentage (67.7% i.e., 44

out of 65) of subjects approached to hospital at I & II stages as compared to 32.3% (21 out of 65) of subjects with advanced stages (III & IV) of this malignancy. Patients who underwent any kind of therapy like chemo, radio or combination of both were excluded from this study. Approximately 50mg of tissue were taken in sterile tubes containing RNA later (Sigma Aldrich) and were kept at -80°C for future molecular analysis. The general demographic and clinical features of this study are given in **(Table 1).**

Ethics statement

All tissue samples were collected between September 2016 to October 2018 at Sher-e-Kashmir Institute of Medical Sciences Jammu and Kashmir (India). The ethics committee reviewed and approved this study via (SIMS 1 131/IEC-SKIMS/2018-190). From each patient written informed consent were taken for this study.

DNA isolation, Bisulfite modification

Almost 50-100 mg tissues were taken for DNA extraction by using the salt-out method. The quantity of DNA was measured in Nano-Drop 2000 (Thermo Scientific). The isolated genomic DNA (~3µg) were taken for bisulfite treatment by using methylation kit (Zymo Research, Irvine, California).

Methylation specific PCR of LATS1/2

Methylation-specific PCR (MS-PCR) was then performed on the modified DNA using primers targeting the promoter region of LATS1 & LATS2 gene **(Table 2).** All reactions were carried out in 0.2 ml PCR tube making a final volume of 25µl. Final concentrations of different reagents used in MS-PCR were, distilled Water 15.5µl, 10X Taq Pol Buffer without $MgCl_2$ 2.5µl, $Mgcl_2$ 1.5µl, Forward Primer 0.5µl, reverse Primer 0.5µl, dNTPs (10mM) 0.5µl, Bisulfite Modified DNA 2µl,Taq DNA Polymerase (1U/µl) 0.2µl.For the MS-PCR of LATS1 and LATS2, initial denaturation at 95 °C for 5 min, 40 cycles of amplification at 95 °C for 30 sec, 58 °C (methylated) & 50 °C (un-methylated) for 30 sec, 72 °C for 30 sec, and final extension at 72 °C for 10 min were performed. The PCR product LATS1 (M=138bp, UM=121bp) and LATS2 (M=148bp, UM=130bp) were detected by using 2% agarose gel, until being separated Figure 1.

Statistical Analysis

The independent t-test and paired t-test were used for continuous variables. Pearson's $\chi 2$test, Fisher's exact test, or $\chi 2$ test (trend) were used for discrete variables. The odds ratios (ORs) and 95 percent confidence intervals (CIs) were calculated using logistic regression analysis. Two-sided testing was used to calculate all P values.The significance level was taken at $P < 0.05$. STATA 14.1 software was used to perform the statistical tests (College station, Texas 77845 USA).

Results

MS-PCR analysis of LATS1 and correlation with various clinico-pathological characteristics

The promoter site of LATS1 gene were found to be hyper-methylated in 52.3% (34/65) among CRC patients**.** On correlation of promoter hypermethylation of LATS1 gene with variousdemographic and clinico-pathological characteristics, statistically, a significantcorrelation was found only with Lymphnode metastasis with a relative risk of (OR=2.24; 95% CI: 1.40-3.54, p=0.001)**Table 3**

MS-PCR analysis of LATS2 and correlation with various clinico-pathological characteristics

The promoter site of LATS2 genes were found to be hyper-methylated 61.5% (40/65) of the CRC patients respectively**.** On correlation of promoter hypermethylation of LATS2 with variousdemographic and clinico-pathological characteristics, statistically, a significantcorrelation was found only with Lymphnode metastasis with a relative risk OR=2.87;95% CI: 1.0-8.2, p=0.04) in case of LATS2 **Table 4**.

Discussion and Conclusion

Promoter methylation is a significant epigenetic modification that plays a significant role in the down-regulation of genes as studied in many tumor suppressor genes (Esteller et al. 2001; Clark and Melki 2002; Jones and Baylin 2002). Both LATS1 &LATS2 are tumour suppressors that are key components of the hippo lats pathway, which plays significant impact on cell fate and tumorigenesis in normal cells.Promoter hypermethylation status of LATS1 and LATS2 has been studied in different human malignancies (Sasaki et al. 2010; Jiang et al. 2006; Takahashi et al. 2005). In the current study, we observed promoter regions of LATS1&2 were hypermethylated in 52.3% and 61.5% of CRC tumors respectively. The observed results in the current study were completely in concordance with the studies conducted in different malignancies including Breast, astrocytoma and lung (Sasaki et al. 2010; Takahashi et al. 2005; Wierzbicki et al. 2013). Together these genes could not show any hypermethylated promoter region in any of the adjacent normal CRC tissues among the study subjects, showing that there is the possibility of LATS1&2 hypermethylation involved in the pathogenesis of CRC. We observed a strong metastatic potency of both LATS1 and LATS2 genes and these findings are completely in agreement with previously published reports (Sasaki et al. 2010; Jiang et al. 2006; Takahashi et al. 2005; Wierzbicki et al. 2013). However, a single study has reported contradictory results with an increased expression of LATS1 genes in its hypermethylated form (Bianchini et al. 2006), this interesting discrepancy could be a result of differences in employed experimental methods.Promoter methylation is a significant element in colorectal carcinogenesis.DNA methylation studies are valuable approach for assessing the biological properties of colorectal malignancies and could be used as a diagnostic biomarker.As a result, the goal of this study was to look into the methylation status of the LATS1/2 genes and to statistically link the methylation status of these genes with the risk of colorectal cancer.This demonstrates that LATS1/2 hypermethylation is a key step in the development of colorectal cancer in the Kashmiri population and that it could be exploited as a diagnostic biomarker. Moreover, some drugs showed reversal of promoter methylation and induction of apoptosis which strongly supports our study that methylation status of LATS1&2 could play a role as prognostic factors in CRC as well.This research is significant since it is the first to look at the methylation status of LATS1/2 genes in colorectal cancer in Kashmiri population. This research is significant since it is the first to look at the methylation status of these genes in CRC in the Kashmiri population(Northern India)

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Conflict of Interest: -The authors have no conflicts of interest to state regarding this study

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Table 1: Epidemiological and Clinico-pathological variables of study subjects

Characteristics	Number n(%age)
Age	
≥50years	23 (35.4)
<50years	42 (64.6)
Mean age	56.9±16.3
Gender	
Male	38 (58.5)
Female	27 (41.5)

Smoking status	
Smoker	27 (41.5)
Non-smoker	38 (58.5)
Dwelling	
Rural	45 (69.2)
Urban	20 (30.8)
Socio economic status	
Upper class	08 (12.3)
Lower/lower middle class	57 (87.7)
Physical activity/Lifestyle	
Active	57 (87.7)
Sedentary	08 (12.3)
Body mass	
Lean	37 (56.9)
Normal	25 (38.5)
Obese	03 (04.6)
Salted Tea consumption	
Yes	59 (90.8)
No	06 (09.2)
Pesticide exposure	
Yes	27 (41.5)
No	38 (58.5)
FHC	
Yes	12 (18.5)
No	53 (81.5)
Site of cancer	
Colon	33 (50.8)
Rectum	32 (49.2)
Grading	
WD	24 (38.7)
MD	27 (43.6)
PD	11 (17.7)
Staging	
I &II	44 (67.7)
III&IV	21 (32.3)
LN Metastasis	
Yes	27 (41.5)
No	38 (58.5)

FHC: Family history of Cancer, WD: Well differentiated, MD: Moderately differentiated

PD: Poorly differentiated, LN: Lymph node metastasis

Table 2: Primers used for LATS1 & LATS2 in MS-PCR

Gene	Methylated Primers	Un-methylated primers
LATS1 (F)	5'GGAGTTTCGTTTTGTC3'	5'TAGGTTGGAGTGTGGTGGT3'
(R)	3'CGACGTAATAACGCCTA5'	3'CCCAACATAATAACAAACACCT5'
LATS2 (F)	5'ATTTCGGTTTATTGTAATTTC3'	5'TTTGTTTTTTGGGTTTAAAGT3'
(R)	3'AACCAACATAATAAAACCCCG5'	3'CCAACATAATAAAACCCCA5'

LATS1: Large tumor suppressor 1; F: Forward primer; R: Reverse primer

LATS2: Large tumor suppressor 2; F: Forward primer; R: Reverse primer

Table 3: Relationship between LATS1 promoter hypermethylation with various clinico-pathological characteristics

Variable	Hyper-methylated n (%age)	Un- methylated n (%age)	OR (95% CI)	P value
Age				
<50 years	11 (32.3)	12 (38.7)	0.75 (0.27-2.09)	0.6
>50 years	23 (67.7)	19 (61.3)		
Gender				
Male	20 (58.8)	18 (58.1)	1.03 (0.38-2.77)	1.0
Female	14 (41.2)	13 (41.9)		
FHC				
Yes	05 (14.7)	07 (22.6)	0.59 (0.16-2.10)	0.52
No	29 (85.3)	24 (77.4)		
Smoking				
Yes	15 (44.11)	12 (38.70)	1.25 (0.46-3.36)	0.80
No	19 (55.88)	19 (61.29)		
Site				
Colon	21 (63.63)	13 (40.62)	2.55 (0.94-6.95)	0.08
Rectum	12 (36.36)	19 (59.37)		
Histopathological grading				

PD	07 (21.87)	04 (13.33)	1.82 (0.47-6.98)	0.51
MD/WD	25 (78.12)	26 (86.66)		
Stage				
I & II	20 (58.8)	24 (77.4)	0.41 (0.145-1.23)	0.122
III & IV	14 (41.2)	07 (22.6)		
LN metastasis				
Yes	21(61.76)	10(32.26)	**3.39 (1.22-9.43)**	**0.025**
No	13 (38.24)	21 (67.74)		

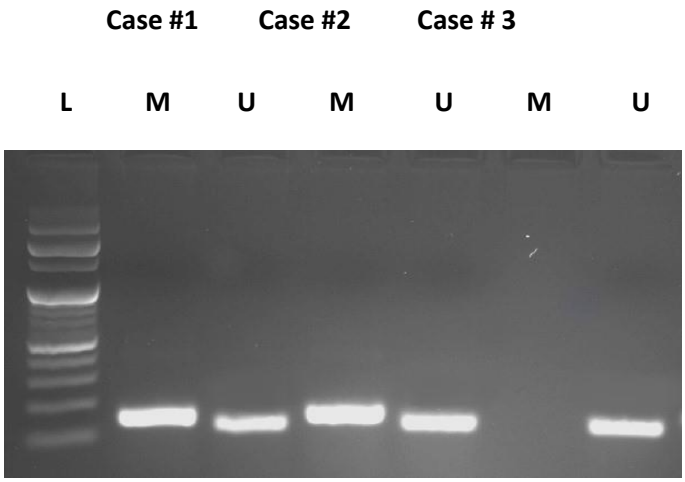
FHC; Family history of cancer, PD; Poorly differentiated, MD; Moderately differentiated, WD; Well differentiated, LN; Lymph node metastasis

Table 4: Relationship between LATS2 promoter methylation with various clinico-pathological characteristics

Variable	Hyper-methylated n (%age)	Un-methylated n (%age)	OR(CI 95%)	P value
Age				
<50 years	13 (32.5)	10 (40)	0.72 (0.25-2.03)	0.59
>50 years	27 (67.5)	15 (60)		
Gender				
Male	21 (52.5)	17 (68)	0.52 (0.18-1.47)	0.30
Female	19 (47.5)	08 (32)		
FHC				
Yes	09 (22.5)	03 (12)	3.14 (0.74-13.22)	0.18
No	31 (77.5)	22 (88)		
Smoking				
Yes	17 (42.5)	10 (40)	1.10 (0.40-3.06)	1.0
No	23 (57.5)	15 (60)		
Site				
Colon	21 (52.5)	12 (48)	1.19 (0.44-3.25)	0.80
Rectum	19 (47.5)	13 (52)		
Histopathological grading				
PD	09 (24.32)	02 (8)	3.69 (0.72-18.8)	0.174
MD/WD	28 (75.67)	23 (92)		
Stage				
I & II	24 (60)	20 (80)	0.37 (0.11-1.20)	0.11
III & IV	16 (40)	05 (20)		
LN metastasis				
Yes	23(57.5)	8 (32)	**2.87 (1.0-8.2)**	**0.04**
No	17 (42.5)	17 (68)		

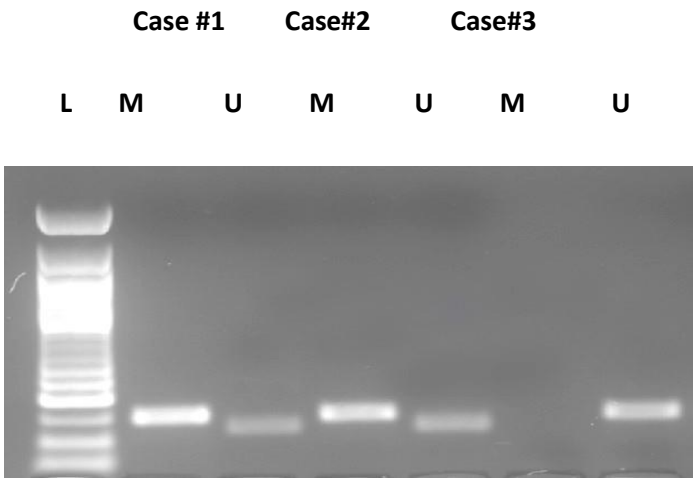
FHC; Family history of cancer, PD; Poorly differentiated, MD; Moderately differentiated, WD; Well differentiated, LN; Lymph node metastasis

Figure 1



Representative results of LATS 1promoter hypermethylation of CRC tissue samples by MS-PCR (3% agarose gel). Lane L represents 100bp ladder, lane M (138bp) indicates methylated LATS 1 and lane U (121bp) indicates the presence of un-methylated LATS1.

Figure 2



Representative picture of LATS 2promoter hypermethylation of CRC tissue samples by MS-PCR (3% agarose gel)
Lane L represents 50bp ladder, lane M (148 bp) indicates methylated LATS 2 and lane U (130bp) indicates the presence of un-methylated LATS 2.

Highlights

- ✓ Incidence of Colorectal Cancer (CRC) is alarmingly increase in Kashmir Valley with unknown etiology.
- ✓ Hippo pathway deregulation has been associated with a wide range of Human malignancies. One of its core components is Large Tumour Suppressor (LATS) genes that has been established as tumour growth regulator.
- ✓ Molecular events regulating such process are quite limited.
- ✓ The current study was aimed to identify the association of LATS1/2 in the genesis of CRC by subjecting them to their status in cancer and their adjacent normal tissues.
- ✓ LATS1/2 hypermethylation is a key step in the development of colorectal cancer and that it could be exploited as a diagnostic biomarker moreover these findings may provide useful insights for the development of CRC diagnoses and treatment