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ORIGINAL ARTICLE

The Underlying Influence of ARID1A Under Expression in The Pathogenesis of Colorectal Cancer

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OBJECTIVE

ARID1A has emerged as a pivotal tumour suppressor gene, essential to chromatin remodelling and gene regulation. In colorectal cancer (CRC), dysregulated ARID1A gene expression triggers uncontrolled cellular growth and chemoresistance. This study investigates the spectrum of ARID1A variants in exon-9, its mRNA expression in CRC tissues and potential correlations with clinicopathological parameters.

METHODS

The present study was a cross-sectional study conducted on 87 histopathologically confirmed CRC and their adjacent normal tissue samples, collected from patients attending SMHS Hospital in Kashmir, India. Sequence elucidation of Exon-9 was done by Di-deoxy Sequencing. mRNA expression of ARID1A gene was carried out using quantitative real-time PCR (qRT-PCR).

RESULTS

Genomic variants of ARID1A were identified in 19.5% of CRC cases, with a predominant heterozygous condition. In silico analysis of the Pro916His variant indicated a deleterious effect on protein function and stability. The mRNA expression of ARID1A was significantly reduced in 17.2% of CRC tissues compared to their adjacent normal tissue samples ($p<0.001$), with a 1.43-fold decrease observed.

CONCLUSION

Our study highlights the prevalence of ARID1A variants in CRC among Kashmiri population. This study proposes that ARID1A under-expression might be relevant in CRC development.

Keywords: ARID1A; colorectal cancer; Kashmir; m-RNA expression; variants.

INTRODUCTION

CRC is one of the most common cancers and ranks as the second leading cause of cancer-related deaths worldwide.[1] While CRC has historically been more common in individuals aged 50 and older, the incidence of early-onset CRC has been rising in both males and females. This shift in age distribution suggests that younger adults may be increasingly exposed to potential risk factors, leading to various genetic alterations.[2,3] CRC develops through a multistep process, beginning with the transformation of normal colorectal epithelium into an adenoma, and eventually progressing into an invasive and metastatic tumor.[4] Tumor suppressor genes (TSGs) play a crucial role in regulating key cellular functions, including DNA replication, repair, and tran-

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scription during cell division.[5] The loss of function in TSGs is a common mechanism that drives the initiation and progression of CRC.[6] ARID1A has emerged as a significant tumor suppressor, regulating the expression of multiple genes involved in cell division, DNA damage repair, and apoptosis.[7,8] It is typically expressed at low levels throughout the cell cycle and is degraded during mitosis, but it accumulates during the G0/G1 phase to induce cell cycle arrest.[9,10] Recent studies have revealed that ARID1A influences cancer-related signaling pathways by regulating the transcriptional activities of various proteins and nuclear hormone receptors.[11]

Mutations and genetic variants are key hallmarks of cancer, playing a pivotal role in cancer initiation and progression.[12] In 2010, two studies using next-generation sequencing revealed a high frequency of inactivating ARID1A variants in highly aggressive ovarian cancers, prompting further investigation into its function as a tumor suppressor gene across various cancers.[13,14] More than 97% of cancer-related ARID1A variants are inactivating, often resulting from nonsense or frameshift mutations that lead to partial or complete loss of functional ARID1A protein.[15] Most cancer-associated ARID1A variants are heterozygous and correlate with reduced protein expression, suggesting that haploinsufficiency may contribute to cancer development.[16] The reduction or loss of ARID1A expression has been linked to tumorigenesis in a wide range of cancers, including gastrointestinal carcinoma.[17] Significant efforts have been made to identify molecular markers that enable personalized therapeutic strategies to improve disease diagnosis and treatment. Recently, there has been growing interest in developing cancer therapies tailored to the ARID1A variant status. This study aims to explore the spectrum of ARID1A mutations in exon 9 and their expression in colorectal cancer (CRC). We shall also examine the potential relationship between decreased ARID1A expression and various clinicopathological characteristics.

MATERIALS AND METHODS

This study received approval from the Institutional Ethics Committee of Government Medical College Srinagar (No: 66/ETH/GMC, Date: 30/03/2017) and conducted according to the Declaration of Helsinki.

Study Design

This cross-sectional study was conducted by the Department of Biochemistry and General Surgery, Shri Maharaja Hari Singh and Super Specialty Hospital, associated with Government Medical College Srinagar, North India.

Study Subjects and Sample Collection

The study included eighty-six (n=87) histopathologically diagnosed CRC patients.

Inclusion and Exclusion Criteria

All enrolled patients were newly diagnosed cases, and none had undergone chemotherapy or radiation. The individuals did not have any genetic disorder

Sample Collection

Colorectal tumor tissue samples and their neighboring normal tissue was taken from each CRC patient being operated upon in the Department of Surgery, Shri Maharaja Hari Singh (SMHS) and Superspeciality Hospital, Srinagar. The patients' clinicopathological data was supplied by the Medical Record Department. One aliquot of each tissue sample was immediately stored in RNA-later (Sigma-Aldrich, USA) at 4°C overnight to achieve full solution penetration before being frozen at -80°C for RNA extraction. Another aliquot was frozen immediately and kept at -80°C for DNA analysis.

DNA Isolation

Genomic DNA was extracted from tissue samples using the QIAamp DNA Mini Kit (Qiagen, Germany) in accordance with the protocol. The purity of the isolated DNA was validated using 1% agarose gel electrophoresis. The purity and concentration were evaluated using the NanoDrop 2000c spectrophotometer (Thermo Scientific, USA). DNA samples with high molecular mass, little fragmentation or shearing, and an A260/280 ratio of 1.7–1.9 were employed for molecular analysis.

Polymerase Chain Reaction (PCR)

The primers used to amplify the exon-9 of ARID1A gene were: Forward 5´-CACAGCACTATTTGGCTC-CAG-3´; reverse 5´-ATCATCTCTGGGCTGGCTG-3´ (Eurofins Genomics, Germany). The PCR reaction was performed in 50µl of reaction mixture containing 12.5µl of 2X PCR master mix (3B BlackBio, Biotech, India), 50–150 ng of genomic DNA, and 0.2 mM of each primer. The reaction cycle included an initial denaturation at 94°C for 5 minutes, followed by 35 cycles of denaturation at 94°C for 20 sec, annealing at 58°C for 30 sec, extension at 72°C for 30 sec, with a final extension at 72°C for 7 minutes. The 343 bp PCR product was run on 2.5% agarose gel and visualized using Omega Lum G Gel Documentation System (Aplegen).

DNA Sequencing

The PCR products were sequenced using the ABI prism 310 automated DNA sequencer (ThermoFisher Scientific, USA) using the Sangar dideoxy technique.

RNa Isolation Followed by cDNA Synthesis

Total RNA was extracted from tissue samples using the TRIzol reagent (ThermoFisher Scientific, USA) and quantified. The RNA purity and concentration were determined using a NanoDrop 2000c spectrophotometer (ThermoScientific, USA), and an A260/A280 ratio of 1.8–2.0 was judged suitable for further analysis. A 1.5% agarose gel revealed the presence of 28S, 18S, and 5S rRNA bands, confirming RNA integrity. cDNA was produced using the RevertAid First Strand cDNA Synthesis Kit (ThermoFisher Scientific, USA) according to the manufacturer's instructions, with the reactions incubated at 37°C for 60 minutes, followed by 10 minutes at 95°C.

Quantitative real-time PCR for (qRT-PCR) for relative mRNA expression of ARID1A

The relative mRNA expression of ARID1A in colorectal tumor tissue samples and their adjacent normal tissues was measured by using qRT PCR (7500 Real-Time PCR system (ThermoFisher Scientific, USA). Each sample was analyzed in triplicate and expression levels were normalized using GAPDH as an internal control. The primers used were as follows: Forward 5´-CTTCAACCTCAGTCAGCTCCCA-3´ reverse: 5´GGTCACCCACCTCATACTCCTTT-3´; and GAPDH forward 5´-TTTGGCTACAGCAACAGGGT-3´ and GAPDH reverse 5´-TCCTCTTGTGCTCTTGCTGG-3´. The PCR reaction mixture consists of 10µl of KAPA SYBR®FAST master mix (Sigma-Aldrich, USA), 0.4µl of cDNA from each sample, 0.2µM of each forward and reverse primers, in a total volume of 20µl. The PCR condition included an initial 10-minute preheat at 95°C, followed by 40 cycles of denaturation at 95°C for 30 sec, annealing at 60°C for 1 minute, extension at 72°C for 35 sec, and a final extension at 72°C for 10 minutes. Specificity of the PCR was confirmed using melting curve analysis (58–95°C). ARID1A mRNA was quantified based on the cycle threshold (Ct) value. Relative expression was calculated using the $2^{-\Delta\Delta Ct}$ method.[18] The fold change in expression between tumor and adjacent normal tissue was determined as $2^{-\Delta\Delta Ct}$.

Statistical Analysis

The data was analyzed using SPSS software version 23.0 (SPSS Inc., Chicago, IL, USA). Continuous variables were analyzed using independent and paired t-tests, whilst categorical/dichotomous variables were tested using Pearson's χ^2 test, Fisher's exact test, or χ^2 test. Logistic regression was used to compute odds ratios (ORs) and 95% confidence intervals (CIs). Statistical significance was assessed using a two-sided p-value<0.05.

Table 1 Demographic and clinicopathological parameters of the study subjects

Variables	CRC cases (n=87)	%
Gender		
Male	56	64.3
Female	31	35.6
Age (years)		
≥50	55	63.2
<50	32	36.8
Dwelling		
Rural	59	67.8
Urban	28	32.2
Smoking status		
Never	39	44.8
Ever	48	55.1
BMI (kg/m^2)		
Normal	38	43.6
Underweight	06	7.0
Preobese	31	35.6
Obese class I	09	10.3
Obese class II	03	3.4
Family history		
Yes	13	15.0
No	74	85.0
Stage		
I & II	55	63.2
III & IV	32	36.8
Grade		
WD	58	66.6
PD	29	33.3
Tumor site		
Colon	53	60.9
Rectum	34	39.1

Body mass index (BMI) (<18.5=underweight, 18.5-24.99=normal, 25-29.99=preobese, 30-34.99=obesity class I, 35-39.99=obese class II); well differentiated (WD); moderately differentiated (MD) and poorly differentiated (PD).

RESULTS

Patient Characteristics

In this study, histologically confirmed colorectal cancer (CRC) cases (n=87) and their adjacent normal tissues were analyzed for ARID1A variants and mRNA expression. The mean age of CRC patients was 52.7±12.2 years. CRC was more prevalent in males (64.3%) than in females (35.6%). Notably, 56.3% of

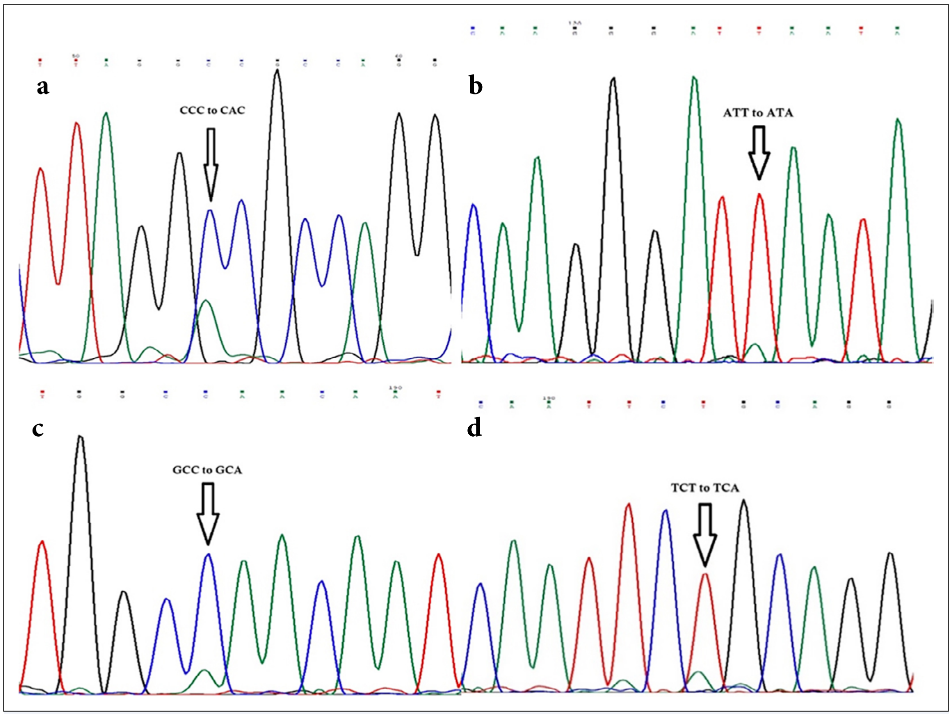

Fig. 1. Partial electrophoretograms (forward) of ARID1A variations at exon-9 in CRC patients, demonstrating changed sequences. (a) Electrophoretogram of the C-to-A substitution (proline to histidine) at amino acid position 916. (b) Electrophoretogram demonstrating a T-to-A substitution at amino acid position 934. (c) Electrophoretogram revealing the C-to-A substitution at amino acid position 955. (d)Electrophoretogram demonstrating a T-to-A substitution at amino acid position 958.

Table 2 ARID1A variants at exon-9 of colorectal tumor tissue samples

S.no.	Amino acid change	Amino acid position	Codon change	Type of substitution	Base pair substitution	Frequency (%)
1	Pro to His	916	CCC to CAC	Nonsynonymous (missense)	Transversion	11 (12.6)
2	Ile to Ile	934	ATT to ATA	Synonymous	Transversion	7 (8.0)
3	Ala to Ala	955	GCC to GCA	Synonymous	Transversion	3 (3.4)
4	Ser to Ser	958	TCT to TCA	Synonymous	Transversion	6 (7.0)

patients had BMI out of the normal range. 15.5% of CRC patients had a positive family history of gastrointestinal cancer. Table 1 provides a detailed breakdown of the socio-demographic and clinicopathological characteristics of enrolled CRC cases.

Analysis of ARID1A Variants

The CRC samples were screened for the presence of ARID1A variants at exon-9 of the ARID1A gene. Partial electrophoretograms (forward) of ARID1A exon-9 in CRC patients is shown in Figure 1 (a-d). The detected variants were present in 17 cases (19.5%). Out of 17 cases, 9 (53.0%) were mutually exclusive (only one variant) whereas, 6 (35.3%) harboured at least two variants and 2 (11.7%) of them carried three variants. The heterozygous condition was predominant. The nonsynonymous variants were rare than synonymous type (Table 2). The high frequency of variants (70.3%) was observed in the age group of ≥50 years.

In Silico Analysis of Pro916His

The nonsynonymous missense Pro916His was submitted to SIFT and PROVEN computational tools to predict the effect of amino acid substitution on

Table 3 Comparison of mRNA expression of ARID1A gene between CRC tumor tissues and adjacent normal tissue

Gene	CRC tumor tissue ΔCt (mean±SD)	Adjacent normal tissue ΔCt (mean±SD)	Average fold change (2−ΔΔCt)	p
ARID1A	0.8615±0.44	0.5364±0.31	1.43 ↓	<0.001

mRNA; Messenger RNA; ARID1A; AT-rich interaction domain 1A; CRC; Colorectal Cancer; SD: Standard deviation

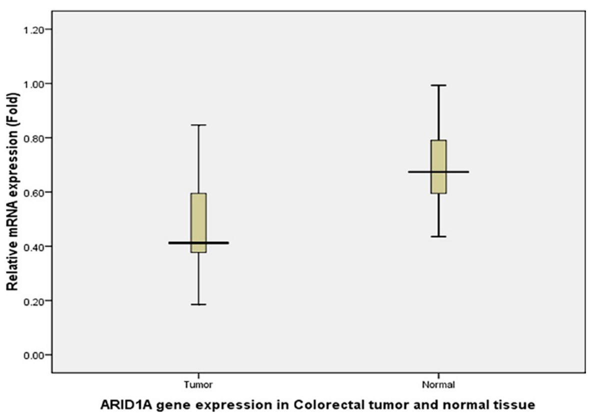

Fig. 2. A box and whisker plot demonstrating ARID1A mRNA expression in CRC patients and controls (adjacent normal). The experiment was carried out in triplets. Colorectal tumor tissue samples showed considerably lower mRNA expression of ARID1A compared to non-tumorous tissues ($p<0.001$). Data was given as mean±SD.

protein function. Both software tool predicted the deleterious effect with the Sift score of ≤0.05 and PROVEN score of -3.839. The disease-associated impact of histidine substitution was analyzed by MutPred2 & GO software. The amino acid substitution was predicted as neutral by both tools (score>0.5). I-mutant 2.0 and MU pro were used to examine the effect of ARID1A variant on the structural stability of proteins. I-mutant 2.0 detected decreased protein stability with reliability index 5, whereas the MU pro predicted decreased protein stability with $\Delta\Delta G=-0.5$. Furthermore, to study the effect of the variant on protein structure, the Hope project revealed substitution of proline to histidine disturbs the backbone conformation of the resultant protein.

Relative mRNA Expression of ARID1A Gene

We used qRT-PCR to examine the expression of ARID1A mRNA in 87 CRC tumor tissues and surrounding normal tissue samples. Among the 87 CRC patients, 17.2% (15/87) exhibited under-expression of ARID1A mRNA compared to adjacent normal tissues. The average fold change ($2^{-\Delta\Delta Ct}$) found to be 0.70 exhibited a statistically significant decrease of 1.43-fold (1/0.70) in mRNA levels of the ARID1A gene (Table 3).

Figure 2 shows a box and whisker plot of relative mRNA expression. The melt curve studies revealed no production of any non-specific product. Table 4 shows the association between ARID1A expression and other clinicopathological characteristics. The data revealed that there was no significant association between the decreased mRNA expression of the ARID1A with any of the socio-demographic and clinicopathological characteristics of CRC cases (p>0.05).

DISCUSSION

CRC is one of the leading causes of cancer-related mortality in the world. The global trends of CRC are also heterogeneous, as it is manifested in differences in incidence and mortality rates influenced by factors such as age, gender, and ethnicity.[19]

The underlying molecular mechanism of CRC is driven by the continuous acquisition of genetic and environmental risk factors, related to the suppression of tumor suppressor genes (TSGs).[6] ARID1A has emerged as a potent TSG due to its association with various types of cancer, including CRC.[20] ARID1A is an important subunit of the SWI/SNF chromatin remodelling complex, which plays a pivotal role in regulating gene expression and maintaining cellular homeostasis. Therefore, ARID1A is essential for a broad spectrum of cellular processes including proliferation, differentiation, DNA damage repair, and genomic stability.[8] Genetic variations leading to altered gene expression, disrupt these processes resulting in uncontrolled cell division and tumor formation.[4] Several studies have demonstrated that genetic variations in ARID1A often leads to haploinsufficiency in various types of cancers, which are linked to more aggressive characteristics and poor clinical outcome.[21] In the present study, we identified that 19.5% of the patients have variations in the ARID1A gene. This prevalence emphasizes the role

Table 4 Correlation between ARID1A expression and clinicopathological variables of CRC

Variables	Cases n=87 (%)	Normal expression 72 (82.7%)	Reduced expression 15 (17.2%)	OR (95% CI)	p
Gender					0.70
Male	56 (64.3)	47 (65.3)	09 (60.0)	1.00	
Female	31 (35.6)	25 (34.7)	06 (40.0)	1.2 (0.37-4.0)	
Age (years)					0.52
<50	55 (63.2)	49 (68.0)	06 (40.0)	1.00	
≥50	32 (36.8)	23 (32.0)	09 (60.0)	3.1 (1.0-10.6)	
Dwelling					0.64
Rural	59 (67.8)	48 (66.7)	11 (73.3)	1.00	
Urban	28 (32.2)	24 (33.3)	04 (26.6)	0.73 (0.2-2.5)	
Smoking status					0.48
Never	39 (44.8)	31 (43.0)	08 (53.3)	1.00	
Ever	48 (55.1)	41 (57.0)	07 (46.7)	0.66 (0.2-2.1)	
BMI (kg/m^2)					0.39
Normal	38 (43.6)	33 (45.8)	05 (33.3)	1.00	
Underweight	6 (7.0)	04 (5.5)	02 (13.3)	3.2 (0.3-23.5)	
Preobese	31 (35.6)	27 (37.5)	04 (26.7)	1.0 (0.21-4.2)	
Obese class I	09 (10.3)	06 (8.3)	03 (20.0)	3.2 (0.5-18.0)	
Obese class II	03 (3.4)	02 (2.7)	01 (6.7)	3.1 (0.1-48.7)	
Family history					0.90
No	74 (85.0)	61 (84.7)	13 (86.7)	1.00	
Yes	13 (15.0)	11 (15.3)	02 (13.3)	0.8 (0.11-4.0)	
CEA levels					0.26
Normal	63 (72.4)	54 (75.0)	09 (60.0)	1.00	
Elevated	24 (27.6)	18 (25.0)	06 (40.0)	2.0 (0.58-6.4)	
Stage					0.40
I & II	55 (63.2)	44 (61.1)	11 (73.3)	1.00	
III & IV	32 (36.8)	28 (38.9)	04 (26.7)	0.6 (0.14-2.0)	
Grade					0.25
WD	58 (66.6)	50 (69.4)	08 (53.3)	1.00	
PD	29 (33.3)	22 (30.5)	07 (46.7)	2.0 (0.6-6.3)	
Tumor site					0.80
Rectum	34 (39.1)	27 (37.5)	07 (46.7)	1.00	
Colon	53 (60.9)	45 (62.5)	08 (53.3)	1.2 (0.36-4.2)	

BMI: Body mass index (<18.5=underweight, 18.5-24.99=normal, 25-29.99=preobese, 30-34.99=obesity class I, 35-39.99=obese class II); WD: Well differentiated; MD: Moderately differentiated; PD: Poorly differentiated

of ARID1A in the molecular context of CRC. Majority of these variations were heterozygous as it was expected because earlier studies suggested that the haploinsufficiency of ARID1A is sufficient to cause tumorigenesis by disrupting normal chromatin remodelling structure and gene expression.[8] Therefore, ARID1A haploinsufficiency is associated with increased genomic instability. The Pro916His variation was predicted to be deleterious by the in-silico tools because it is a nonsynonymous missense variant that may affect the protein function and stability. This variation was demonstrated to change the protein's secondary structure which could alter the protein's ability to correctly interact with the SWI/SNF complex possibly causing abnormal cell division and defective DNA repair mechanism.

Furthermore, according to the published data the loss or low expression of ARID1A has a significant role in the development and progression of CRC.[22] The reduced ARID1A could alter the antigen presentation of tumor, potentially leading to strong immune response in CRC. However, this can also prompt the tumor to develop mechanism to evade immune detection.[23]

Spontaneous or mutation-induced reduction in ARID1A expression can act as a tumorigenic trigger, contributing to both the initiation and progression of cancer. ARID1A serves a dual role: As a “gatekeeper” controlling cell proliferation, and as a “caretaker” tumour suppressor that preserves genomic integrity by preventing sequence mutations and chromosomal aberrations.[16] Studies by Wei et al.[24] and Erfani et al.[25] have demonstrated that decreased or lost ARID1A expression is significantly associated with distant metastasis, lymph node invasion, and consequently, poor prognosis in CRC.

Although statistically insignificant, the frequency of CRC among older individuals (≥50 years) was higher compared to younger individuals. The CRC risk increases significantly with age due to the combined effects of several risk factors, with over 70% of CRC patients being over 55 years old.[1] Nevertheless, early exposure to many of the recognized risk factors increases the likelihood of developing early-onset of CRC (EOCRC), which is a considerable cancer concern among young individuals.[3,26] The causes of EOCRC are not yet fully understood; however, factors such obesity, physical inactivity and diet have been linked to its development.[2]

Obesity is a well-established risk factor for colorectal cancer across all age groups. Elevated BMI, especially abdominal obesity, is closely associated with chronic low-grade inflammation and insulin resistance, both of which may contribute to the formation of neoplastic lesions in colorectal tissue.[27] In line with these findings, our study observed a higher incidence of CRC in patients with abnormal BMI compared to the control group, although the difference was not statistically significant ($p<0.001$).

As per previous studies, the significant loss of ARID1A expression in CRC patients has been recorded compared to controls.[25,28] Consistent with the above studies, Quantitative real-time PCR (qRT-PCR) analysis revealed significant under-expression of ARID1A mRNA in 17.2% of the CRC cases compared to adjacent normal tissues. This reduction in mRNA levels indicates a potential loss of functional protein, corroborating the variational analysis. The fold change analysis exhibited a 1.43-fold decrease in ARID1A expression, suggesting that even partial loss of ARID1A function can contribute to CRC pathogenesis. Several studies have reported that the ARID1A variations and reduced expression levels were significantly correlated with tumor histological grade, advanced tumor depth, poor differentiation, lymphatic metastasis, primary tumor location and early tumor stage.[29] Notably, the study failed to establish any correlation of ARID1A mRNA expression with clinicopathological characteristics such as age, gender, and tumour stage. This fact indicates that ARID1A variation and altered expression can be involved in CRC development without consideration of other characteristics of patients.

The discovery of the presence of ARID1A variations and their effects on the function of the protein provides new possibilities of targeted treatment of CRC. Understanding the link between the ARID1A loss and immune activation can help to shape the development of effective therapies, such as tumors with different ARID1A variations might respond differently to the immunotherapies such as checkpoint inhibitors. By targeting the altered immune pathways or harnessing the increased immune activation found in ARID1A-deficient tumors, novel treatment approach can be developed to boost anti-tumor immunity and improve patient outcome. Furthermore, therapies that can either reverse the loss of ARID1A function or at least supply for it might be new treatment strategies for CRC patients. For example, drugs that act on epigenetic changes or those that boost DNA repair mechanisms could be used in combination with the ARID1A status to enhance the effectiveness of the treatment. The results obtained are in line with the prior literature that has established the involvement of ARID1A in several cancers such as ovarian, gastric, and endometrial cancers.[9]

Limitation of the Study

Considerable number of patients in this region were diagnosed with advanced stage CRC and were in-operable. For that reason, the tumor tissue could not be collected from those very patients. Therefore, studies are warranted to validate the results, especially in case of CRC, due to relatively modest sample size.

CONCLUSION

In conclusion, the present study confirmed a high frequency of ARID1A variations and down-regulation of ARID1A protein in CRC tissues compared to the normal adjacent tissues. Our research has shown that ARID1A plays a significant role in colorectal tumorigenesis and may be used as a biomarker for CRC. Subsequent research with more participants and deeper assessment of the ARID1A-associated molecular processes are required to enhance the understanding of the gene’s function in CRC and to evaluate the possibility of using it as a biomarker for individualized treatment.

Ethics Committee Approval: The study was approved by the Institutional Ethics Committee of Government Medical College Srinagar (no: 66/ETH/GMC, date: 30/03/2017).

Informed Consent: Informed consent was obtained from all participants.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

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