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Clinical Significance of Loss of ARID1A Expression in Colorectal and Small Intestinal Carcinoma

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AT-rich interactive domain containing protein 1A (*ARID1A*), a subunit of the chromatin remodeling complex, has been established as a tumor suppressor gene. Its inactivation has been reported to drive mutation in carcinogenesis of different tumor types, most notably ovarian clear cell carcinoma.[1] Loss of ARID1A expression has also been associated with endometrial carcinoma cases with sporadic microsatellite instability (MSI), secondary to hypermethylation of the MutL Homolog 1 (*MLH1*) gene.[2] Recently, there has been an increasing interest in the clinical importance of abnormal ARID1A expression in gastrointestinal malignancies with mismatch repair (MMR) deficiency. In this mini-review, we highlighted the key findings of recent publications evaluating the significance of ARID1A expression in colorectal carcinoma (CRC) and small intestinal carcinoma (SIC).

A pilot study from the Memorial Sloan-Kettering Cancer Center evaluated ARID1A expression in 257 CRC patients who underwent Lynch syndrome screening.[3] The CRC cases were further stratified by the expression of DNA MMR proteins and *MLH1* promoter methylation. *ARID1A* expression in each case was evaluated using immunohistochemistry and abnormal expression was defined as complete loss of nuclear staining in the tumor. The study revealed that about 9% of the cases showed abnormal ARID1A expression. Furthermore, loss of ARID1A expression was more frequently seen in MMR-deficient CRC cases, predominantly sporadic cases with *MLH1* promoter methylation.

These results confirmed the results from an earlier study with a larger number of cases. Chou *et al.*[4] reported that 5.9% of 1,876 CRC cases in their cohort had a loss of nuclear staining for ARID1A. Moreover, they correlated the abnormal ARID1A expression with MMR status and V-Raf Murine Sarcoma Viral Oncogene Homolog B (*BRAF)* V600E mutation. In MMR-deficient CRC cases, *BRAF* mutation has been suggested as a surrogate marker for *MLH1* promoter methylation. More than half of the CRC patients with abnormal ARID1A expression in the study were MMR-deficient cases with *BRAF* V600E mutation.

Both studies reported that loss of ARID1A expression was seen in a small subset of CRC, strongly associated with sporadic MSI cases. The prevalence of CRC with loss of ARID1A expression was slightly higher in the study conducted by Ye *et al.*[3] because their patient population only included CRC patients with increased risk for MSI. Furthermore, clinical and histological characteristics of CRC cases with loss of ARID1A expression were consistent with sporadic MSI tumor phenotypes. This subset of CRC was associated with older patients, larger tumor size, medullary morphology, and high-grade differentiation. These patients were also at a higher risk for nodal and distant metastasis.[3] However, loss of ARID1A expression was not proven to be a strong predictor of overall survival in CRC patients.

Earlier this year, another study evaluated the clinicopathologic correlation and prognostic significance of ARID1A and p53 expression in primary SIC.[5] Loss of and low ARID1A expression was observed in 20.2% and 33.7% of 178 SIC cases, respectively. Reduced ARID1A expression (loss of and low expression), irrespective of p53 expression, was associated with signet ring cell carcinoma and undifferentiated carcinoma, high-grade differentiation, and higher pathologic tumor stages. Poorer overall survival was also seen in cases with loss of ARID1A expression. In addition, the authors discussed the association between loss of ARID1A expression and MMR protein deficiency. They reported that ARID1A loss was more frequently seen in SIC cases with loss of MLH1 and MutS Homolog 2/MSH2 expression.

Several potential problems in evaluating ARID1A immunohistochemistry include observer variability and tumor heterogeneity. In their study, Kim *et al.*[5] utilized a four-tier scoring system, which is prone to interobserver and intraobserver variability. A consistent method to interpret ARID1A staining among studies is necessary to obtain meaningful and reliable results. Furthermore, a small percentage of cases in one of the studies showed heterogeneous staining with distinct areas of positive and negative staining.[4] Thus, loss of ARID1A expression might be missed if immunohistochemical evaluation is only performed in a limited number of biopsy specimens. Alternative methods such as next-generation sequencing and exome sequencing have been reported to be reliable in detecting *ARID1A* mutation.[6,7] These molecular techniques allow a better understanding of the role of the ARID1A mutation in the carcinogenesis of different tumor types. Nonsense and frameshift mutations have been shown to be the most common types of *ARID1A* mutation, and in-frame insertions or deletions (indel) that involve a small stretch of peptides comprise 5% of *ARID1A* mutations. These mutations are associated with loss of tumor suppressor function to inhibit cell

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proliferation and to activate cyclin-dependent kinase inhibitor 1A (*CDKN1A*) transcription, supporting the idea that *ARID1A* is a cancer-driving gene.[5,8]

How do we use this information in our clinical practice? Currently, the presence of *BRAF* V600E mutation is helpful in distinguishing sporadic from Lynch syndrome-associated MMR-deficient CRC cases. However, only two-thirds of the sporadic *MLH1* promoter methylated cases show *BRAF* V600E mutation.[4] ARID1A immunohistochemistry could potentially be used as an additional tool to exclude Lynch syndrome-associated CRC. Further studies looking at ARID1A expression in Lynch syndrome patients and the validity of this method in addition to reflex *BRAF* mutation testing in *MLH1*-deficient tumors are necessary to determine the utility of this testing. The prognostic information on different tumor types from recent published studies has been based on a limited number of cases with loss of ARID1A expression.[3,5,7] Additional data are required to support the reported prognostic significance of ARID1A expression loss in CRC and SIC patients. Finally, a recent study reported Enhancer of Zeste Homolog 2/*EZH2* as a potential therapeutic target in *ARID1A*-mutated cancers.[9] *ARID1A* mutational status will become important information for CRC and SIC patients when targeted therapies become available in the future.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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