Roles of ARID1A variations in colorectal cancer: a collaborative review

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Abstract
Colorectal cancer (CRC), a common malignancy, is one of the leading cause of cancer death in adults. AT-rich interaction domain 1A (ARID1A), a critical portion of the SWItch/sucrose non-fermentation (SWI/SNF) chromatin remodeling complexes, shows one of the most frequent mutant genes across different human cancer types. Deleterious variations of ARID1A has been recognized to be correlated the tumorigenesis and the poor prognosis of CRC. Here, we summarize recent advances in the clinical implications and molecular pathogenesis of ARID1A variations in CRC. According to independent data of 23 included studies, ARID1A is mutated in 3.6–66.7%. Consistently, all of the 23 relevant studies report that ARID1A functions as a specific tumor suppressor in CRC. Clinically, ARID1A variation status serves as a biomarker for survival prognosis and various therapies for CRC. Mechanistically, the pathophysiologic impacts of ARID1A variations on CRC may be associated with the co-occurrence variations of other genes (i.e., TP53, KRAS, APC, FBXW7, and PIK3CA) and the regulation of several signaling pathways being affected (i.e., WNT signaling, Akt signaling, and MEK/ERK pathway), leading to cell cycle arrest, chromatin remodeling, chromosome organization, and DNA hypermethylation of the cancer cells. The present review highlights ARID1A serving as a potent tumor suppressor and an important prognostic factor in CRC. ARID1A variations hint towards a promising tool for diagnostic tumor profiling and individualized therapeutic targets for CRC in the future.

Keywords: ARID1A variations, Colorectal cancer (CRC), Biomarker, Prognosis, Pathogenesis

Introduction
Colorectal cancer (CRC) is one of the top-common malignancies worldwide, nearly 1,850,000 incidences, and is the second leading cause of cancer deaths, with an approximate 881,000 fatalities (9.2% of all fatal cancer cases) in the world yearly (Bray et al. 2018). CRC with locoregional lymph node diffuse has a 5-year overall survival (OS) of 70% while disuse to distant organs carries a substantially worse prognosis with a 5-year OS of 12% (Siegel et al. 2018). Metastasis to the liver is the most common site of distant spread (Fong et al. 1997) while the peritoneal surface is the second most common site of metastasis, involving roughly 10% of patients with CRC at the very beginning of the presentation and the sole site of recurrence in as much as 25% of patients with CRC (Dawson et al. 1983; Russell et al. 1983). Peritoneal metastasis (PM) is associated with a poor prognosis, and the survival period for systemic chemotherapy alone is 5–7 months (Chu et al. 1989; Koppe et al. 2006). Compared to other site transfers, PM is associated with a greatly shorter progression-free survival (PFS) and OS (Franko et al. 2012). The molecular underlying mechanisms of CRC is driven by the continuous acquisition of epigenetic and genetic abnormalities, which is related to the repression of the tumor suppressor and the activation of pro-oncogenic factors (Lao and Grady 2011). The low effectiveness of conventional therapeutic interventions to...
prolong life span in CRC patients needs new and effective targeted therapies.

The heterogeneity of CRC tumor aggressiveness and prognosis might be prompted by differences in genetic variation. According to some reports, the gene encoding the SWI/sucrose non-fermenting (SWI/SNF) chromatin remodeling complex is one of the most common mutant genes in a variety of malignant tumors. SWI/SNF chromatin remodeling complex play role in the transcription and DNA reproduction and repair (Wilson and Roberts 2011). Among the family of the SWI/SNF genes, AT-rich interaction domain 1A (ARID1A) is a common-mutated gene in human cancers, which contributes to the binding of protein and DNA (Kadoch and Crabtree 2013; Guichard et al. 2012). ARID1A, a gene located on chromosome 1p36.11, is a core component of the mammalian SWI/SNF complex (Megaridis et al. 2018). ARID1A encodes a protein with nuclear/ cytosolic localization. Nuclear ARID1A is speedily degraded by the nuclear ubiquitin–proteasome system unstable due to the nuclear ARID1A is unstable (Mao and Shih 2013). In-frame deletions disrupting the nuclear export signal cause a decline of ARID1A expression, due to the nuclear retention of the protein and its subsequent degradation (Mao and Shih 2013; Guan et al. 2012). ARID1A exhibits its biological function by interacting with DNA and recruiting associated transcriptional co-activators, while ARID1A variation commonly cause the dysregulation of BAF complex-mediated chromatin remodeling (Chandler et al. 2013). ARID1A contains an ARID domain, which interacts with DNA in a sequence-nonspecific manner modulating cellular processes (e.g., proliferation and differentiation) (De and Dey 2019). Thus, ARID1A has been found to be contributed to the tumorigenesis of multiple cancers.

ARID1A has lately been recognized as a crucial tumor suppressor gene in diverse cancer types. Ovarian cancer, stomach cancer, and pancreatic cancer have the highest mutation (or variation) frequency (29–57%), while CRC (13%), liver cancer (10–17%), bladder cancer (13%), esophageal cancer (9%), breast cancer (3%) and childhood retinoblastoma (6%) have somewhat lower variation frequencies (Cornen et al. 2012; Dulak et al. 2013; Fujimoto et al. 2012; Gui et al. 2011; Guichard et al. 2012; Jones et al. 2012, 2010; Sausen et al. 2013; Shain et al. 2012; Wiegand et al. 2010). Also, Og iwara et al. (2019) summarized that ARID1A is mutated in about 46% of ovarian clear cell carcinomas, 43% of uterine corpus endometrial carcinomas, 33% of gastric carcinomas, 30% of ovarian endometrioid carcinomas, 28% of bladder carcinomas, 27% of cholangiocarcinomas, 15% of pancreatic carcinomas, 12% of lung adenocarcinomas, and 10% of CRC. The frequency of ARID1A variations in ovarian clear cell carcinomas is up to 60% in the US, Canada, and Japan, indicating that ARID1A deficiency may be a potential biomarker for precision medicine of ovarian cancer (Takahashi et al. 2021). It was reported that ARID1A variations was observed in up to 40% of low-grade endometrioid carcinomas (Toumpeki et al. 2019). The reported ARID1A mutant prevalence in gastric cancer among different studies was 8–27% (Wang et al. 2021). Dugas et al. (2019) demonstrated that ARID1A variation was observed in 3.6% of the non-muscle-invasive bladder cancer and 10% of the muscle-invasive bladder cancer. Zhao et al. showed that the variation rate of ARID1A in cholangiocarcinomas ranged from 5% to 68.2% (Zhao et al. 2021). Though ARID1A may be not the most highly mutated gene in the aforementioned malignancies, it can synergize with other mutant genes to promote the pathogenesis and the development of cancers.

Most of the ARID1A variations are inactive condition that result in the loss of the protein expression of ARID1A (Kishida et al. 2019). In current years, mounting evidence revealed that ARID1A variation is related to the clinicopathologic characteristics of CRC (Wei et al. 2014; Ye et al. 2014). At present, in different clinical studies, the specific role of ARID1A on the prognosis and clinicopathological features of CRC is widely debated. According to published data, most studies indicate that ARID1A serves as an important tumor suppressor gene. For example, Lee et al. (2016) demonstrated that no connection was evident between ARID1A expression and 5-year OS. However, a recent study conducted by Jiang et al. (2020) showed that disease-free or PFS of patients with ARID1A variations [DFS/PFS, HR = 0.74 (0.64–0.91), P = 0.0026]. The OS of patients with ARID1A variations was significantly prolonged by 28 months, compared with 18 months in those with wild-type ARID1A [HR = 0.73 (0.61–0.93), P = 0.0092]. The role of ARID1A in CRC is currently uncertain. In this narrative review, we aim to overview all the current evidence that ARID1A variation or expression is associated with the development of CRC, and reveal the potential molecular mechanisms.

**Searching strategy**

Four common data bases were searched to find the eligible studies prior to January 1, 2022. The searching strategy these databases was: (((((((((((((((((ARID1A) OR (B120) OR (BAF250) OR (BAF250a)) OR (BM029)) OR (C1orf4)) OR (CSS2)) OR (ELD)) OR (MRD14)) OR (OSA1)) OR (P270)) OR (SMARCF1)) OR (hELD)) OR (hOSA1)) AND ((((((“Colorectal Neoplasms”[Mesh]) OR (Colorectal Neoplasm)) OR (Neoplasm, Colorectal)) OR (Neoplasms, Colorectal)) OR (Colorectal Tumors)) OR (Colorectal Tumor)) OR (Tumor, Colorectal)) OR (Tumors, Colorectal)) OR
(Colorectal Cancer)) OR (Cancer, Colorectal)) OR (Cancers, Colorectal)) OR (Colorectal Carcinoma)) OR (Carcinoma, Colorectal)) OR (Carcinomas, Colorectal)) OR (Colorectal Carcinomas)) OR (Colon Cancer)) OR (Rectal Neoplasms)) OR (Rectum Cancer)). For identifying more eligible studies, we manually inspected the reference lists in the related articles. According to the data collection form, the following information in each study was extracted, including the first authors’ names, the publication year, study area, type of CRC, ARID1A variations in CRC, and some details of clinical and molecular aspects.

Figure 1 showed the search flowchart. Finally, 23 eligible studies (16, 23–44) with a total of 15,580 subjects were included. The characteristics of the 23 eligible studies were listed in Table 1. According to the available
| Author and country | Publication year | Type of CRC | ARID1A variation (%) | ARID1A expression | Roles of ARID1A | Clinicopathologic features or biological effects of ARID1A | Antibodies of ARID1A | References |
|-------------------|-----------------|-------------|----------------------|-------------------|----------------|----------------------------------------------------------|----------------------|------------|
| Jones, USA        | 2012            | CRC         | 12/119, 10%          | Downregulated     | Suppressor     | ARID1A inactivation promoted CRC development             | NA                   | Jones et al. (2012) |
| Chou, Australia   | 2014            | CRC         | 110/1876, 5.9%       | Loss of expression| Suppressor     | No significant relationship between loss expression of ARID1A and the OS of CRC; Loss expression of ARID1A was associated with multiple clinical features, BRAPV600E variation and loss of mismatch repair protein expression (all P < 0.01) | Sigma 1: 100         | Chou et al. (2014) |
| Cajuso, Finland   | 2014            | CRC         | 18/46, 39%           | Downregulated     | Suppressor     | Exome sequencing showed that ARID1A play an important role in microsatellite-unstable CRC via DNA binding activity and transcription coactivator activity | Santa Clara          | Cajuso et al. (2014) |
| Xie, China        | 2014            | CRC         | 26/86, 30.2%         | Loss of expression| Suppressor     | Loss of ARID1A significantly associated with poor differentiation of CRC (P = 0.0009) | Rabbit antibodies Sigma 1:500 | Xie et al. (2014) |
| Ye, USA           | 2014            | CRC         | 22/257, 9%           | Loss of expression| Suppressor     | ARID1A loss was significantly associated with various clinicopathological features of CRC (all P < 0.05), and with a trend toward a worse OS (P > 0.05) | polyclonal antibody Sigma-1:100 | Ye et al. (2014) |
| Wei, China        | 2014            | CRC         | 54/209, 25.8%        | Loss of expression| Suppressor     | ARID1A loss was correlated to late TNM stage, distant metastasis, and poor pathological classification (all P < 0.05) | Santa Cruz Biotechnology | Wei et al. (2014) |
## Table 1 (continued)

| Author and country | Publication year | Type of CRC | ARID1A variation (%) | ARID1A expression | Roles of ARID1A | Clinicopathologic features or biological effects of ARID1A | Antibodies of ARID1A | References |
|--------------------|-----------------|-------------|----------------------|-------------------|----------------|----------------------------------------------------------|----------------------|------------|
| Lee, Korea         | 2015            | CRC         | 12/196, 6.1%         | Loss of expression | Suppressor     | Loss of ARID1A expression was significantly correlated with negative lymphatic invasion ($P = 0.003$) in CRC, and with expanding tumor border (CRC, $P = 0.010$) | Rabbit polyclonal, Sigma 1:100 | Lee et al. (2015) |
| Lee, USA           | 2016            | CRC         | 49/552, 8.9%         | Loss of expression | Suppressor     | ARID1A loss was associated with mismatch-repair protein deficiency, poor differentiation, lymphovascular invasion, and higher pT stage (all $P < 0.05$) | Rabbit polyclonal, Sigma, 1:300 | Lee et al. (2016) |
| Agaimy, Germany    | 2016            | Colon, small bowel, and stomach cancer | 2/13, 15.4%         | Loss of expression | Suppressor     | NA                                                      | Rabbit polyclonal, Abcam, 1:100 | Agaimy et al. (2016) |
| Fountzilas, USA    | 2018            | CRC         | 16/36, 44%           | Loss of expression | Suppressor     | ARID1A variations independently predicted for unfavorable DFS (HR = 1.99, 95%CI 1.11–3.54, $P = 0.020$) | NA                   | Fountzilas et al. (2018) |
| Wan, China         | 2018            | CRC         | 3/16, 18.8%          | Loss of expression | Suppressor     | NA                                                      | MygeneSeq technology | Wan et al. (2018) |
| Sen, USA           | 2019            | CRC         | 24/164, 14.6%        | Loss of expression | Suppressor     | The expression of ARID1A plays a key role in KRAS-mutated CRC cells | Cell Signaling, 1:500 | Sen et al. (2019) |
| Kishida, Japan     | 2019            | CRC         | 10/218, 4.6%         | Loss of expression | Suppressor     | Loss expression of ARID1A was significantly correlated to younger age, lymphatic invasion, and lymph node metastasis | Rabbit monoclonal, 1:500 | Kishida et al. (2019) |
| Author and country | Publication year | Type of CRC | ARID1A variation (%) | ARID1A expression | Roles of ARID1A | Clinicopathologic features or biological effects of ARID1A | Antibodies of ARID1A | References |
|--------------------|------------------|-------------|----------------------|-------------------|-----------------|-----------------------------------------------------------|---------------------|-----------|
| Xu, China          | 2020             | sCRC        | 1/28, 3.6%           | Frameshift variation | Suppressor     | ARID1A variations and the deficiency of its protein expression were significantly involved in advanced tumor depth, poor differentiation, lymphatic metastasis, BRAF V600E variation, MMR deficiency and MSI phenotype in tumors of CRC patients | NA                  | Xu et al. (2020) |
| Tokunaga-1, USA    | 2020             | CRC         | 468/5726, 8%         | Downregulated     | Suppressor     | ARID1A variations could regulate DNA repair pathways      | NA                  | Tokunaga et al. (2020) |
| Tokunaga-2, USA    | 2020             | CRC         | 50/619, 8%           | Downregulated     | Suppressor     | ARID1A variation was significantly associated with a favourable immune profile indicative of a higher likelihood of response to immune checkpoint inhibitors | NA                  | Tokunaga et al. (2020) |
| Tokunaga-3, USA    | 2020             | CRC         | 104/1099, 10%        | Downregulated     | Suppressor     | ARID1A variation was associated with right-sided primary tumor location and earlier tumor stage | NA                  | Tokunaga et al. (2020) |
| Tokunaga-4, USA    | 2020             | CRC         | 58/534, 11%          | Downregulated     | Suppressor     | ARID1A variations lead to strong immune activation in CRC | NA                  | (Tokunaga et al. 2020) |
| Erfani, Iran       | 2020             | CRC         | 12/18, 66.7%         | Loss or low expression | Suppressor     | No significant relationship was found between the loss of ARID1A and the OS or the clinicopathological features in CRC | Rabbit antibody Sigma 1:200 | Erfani et al. (2020) |
| Author and country | Publication year | Type of CRC | ARID1A variation (%) | ARID1A expression | Roles of ARID1A | Clinicopathologic features or biological effects of ARID1A | Antibodies of ARID1A | References |
|--------------------|------------------|-------------|----------------------|-------------------|----------------|----------------------------------------------------------|------------------|-----------|
| Villatoro, USA     | 2020             | Colorectal adenocarcinoma | 16/338, 4.7% | Deficiency | Suppressor | No difference in disease-specific or disease-free survival was found for ARID1A deficiency (all P > 0.05) | Abcam | Villatoro et al. (2020) |
| Stein, USA         | 2020             | pCRC PM | pCRC: 179/517, 29%, PM: 42/348, 12% | Variation | Suppressor | NA | NA | Stein et al. (2020) |
| Wang-1, China      | 2020             | CRC      | 76/156, 48.7% | Downregulated | Suppressor | NA | NA | Wang et al. (2020) |
| Wang-2, China      | 2020             | CRC      | 17/225, 7.6% | Downregulated | Suppressor | NA | NA | Wang et al. (2020) |
| Jiang, China       | 2020             | CRC      | 89/1234, 7.2% | Variation | Suppressor | CRC patients with ARID1A variation showed a significantly longer DFS/PFS (HR = 0.74, P = 0.0026) | NA | Jiang et al. (2020) |
| Huang, China       | 2021             | CRC      | 65/630, 10.3% | Variation | Suppressor | NA | The differences in survival were not statistically significant (HR = 0.58, 95% CI = 0.23–1.49, P = 0.257) | NA | (Huang et al. 2021) |
| Perna, Spain       | 2021             | HG-CRCs | 12/29, 41.4% | Loss of expression | Suppressor | NA | Polyclonal Sigma, 1:500 | Perna et al. (2021) |
| Kamori, Japan      | 2021             | CRC      | 20/201, 10% | Variation | Suppressor | Tumor histological grade was significantly correlated with ARID1A variation status in those patients with right-sided CRC | Rabbit polyclonal, | Kamori et al. (2021) |

ARID1A AT-rich interactive domain 1A, CRC colorectal cancer, HR Hazard ratio, OR odds ratio, OS overall survival, DFS disease-free survival, HG-CRC high grade colorectal carcinomas, RCC right-sided colorectal cancer, LCC left-sided colorectal cancer, pCRC primary colorectal cancer, NA not available, PFS progression-free survival, RFS recurrence-free survival
Since the variation rate, clinical significance, and biological function of ARID1A are different in 23 qualified studies, we have therefore conducted an in-depth review of these eligible studies as follows.

**ARID1A expression and variations in CRC**

**Variation rate of ARID1A in CRC among different studies**

Comprehensive genome analysis is one useful tool to identify variations of various oncogenes and tumor-suppressor genes, particularly in those genes that code for chromatin remodeling factors (Centore et al. 2020; Goswami et al. 2020; Mao et al. 2013; Mathur 2018; Wei et al. 2014; Ye et al. 2014) One of such genes is ARID1A. However, the variation rate of ARID1A in CRC is low, Jones et al. (Jones et al. 2012) reported 10%, and Kim et al. (49) did not find variations. Based on this evidence, the effect of ARID1A loss in CRC is still underestimated. Wei et al. (2014) found that the ARID1A protein loss caused by immunohistochemistry occurred in 25.8% of primary CRC tumors, and the proportion was higher in stage IV CRC, which was 35.2%, suggesting that ARID1A protein loss is not very common in CRC.

**Fig. 2** Variation rate of ARID1A in CRC among different studies
In this narrative review, the evidence related to the \textit{ARID1A} variants in CRC was comprehensively summarized. According to the data of 23 eligible studies, great differences have been identified on the \textit{ARID1A} variation rate varies greatly. As shown in Fig. 2, \textit{ARID1A} variation in pCRC, PM-CRC, and HG-CRC was recorded at 29%, 12%, and 41.4%, respectively. Based on the previous publications, the highest variation rate of \textit{ARID1A} in ovarian clear cell carcinoma, which is as high as 46–57% (Yoshino et al. 2020). But CRC did not make any comments or conclusions.

CRCs have two genetic and clinically distinct subtypes: chromosomal instability tumors (CIN) and microsatellite instability tumors (MSI). Most tumors show CIN, and about 15% are MSI. In MSI tumors, the mismatch repair (MMR) system is defective, which can usually correct a large number of errors that occur during DNA replication. This leads to a large number of small insertions and deletions in the repetitive regions surrounding the genome, especially in the short tandem repeat regions called microsatellites. The overall variation rate of MSI-CRC is estimated to be about 10 times that of microsatellite stable (MSS)-CRC (2012; Vogelstein et al. 2013). Tokunaga et al. (2020) compared the relationship between \textit{ARID1A} variations and the molecular characteristics in CRC by using the next-generation sequencing, RNA sequencing, and the immunohistochemistry methods. They found that \textit{ARID1A} variations were more common in primary and early age tumors on the right site of CRC. \textit{ARID1A} mutant tumors mainly have gene variations related to chromatin modification, DNA repair, WNT signaling pathway, and EGFR inhibitor resistance pathway at the same time, and \textit{ARID1A} variations have a strong regulatory effect on DNA repair pathways. CMS1, one of the consensus molecular subtypes of the CRC classification system, plays an essential role in immune response (Guinney et al. 2015). It was reported that \textit{ARID1A} mutant samples proved a higher prevalence of CMS1 than \textit{ARID1A} wild-type samples, which indicates \textit{ARID1A} variation could result in strong immune activation (Tokunaga et al. 2020).

The data from the 23 eligible studies showed that the \textit{ARID1A} variation rates and expression levels were different among different studies. These discrepancies might be related to various factors, e.g., different demographic features (i.e., sample size and race), CRC stage (early or advanced), different antibodies of anti-\textit{ARID1A}, the assessments of the \textit{ARID1A} protein expression (i.e., IHC, western blot, targeted sequencing analysis, qRT-PCR, tissue microarrays, and chromatin immunoprecipitation), and multifarious co-present or targeted genes being affected.

All studies indicate that \textit{ARID1A} is low or absent in CRC, and \textit{ARID1A} acts as a tumor suppressor, which is consistent with the function of \textit{ARID1A} in other types of cancer (Wu and Roberts 2013). According to the current evidence, \textit{ARID1A} variants are only expected to play a tumor suppressor effect CRC development.

\textbf{Clinical significance of \textit{ARID1A} in CRC}

Although the high frequency of \textit{ARID1A} variants has been observed in CRC, the prognostic value of \textit{ARID1A} in CRC is still controversial. Jiang et al. (2020) found that DFS or PFS of patients with variations in \textit{ARID1A} was significantly prolonged (HR = 0.74, 95%CI: 0.64–0.91, \(P = 0.0026\)). The OS of patients with \textit{ARID1A} variation was significantly prolonged than those with wild-type (28 months vs. 18 months, \(P = 0.0092\)). In other words, \textit{ARID1A} deletion predicts superior OS in stage IV CRC. Wei et al. (2014) analyzed 209 primary CRC tumor samples by IHC and discovered that \textit{ARID1A} loss was detected in fifty-four (25.8%) primary CRC tumors. Moreover, the authors also observed that the distant metastasis rate was higher in patients with \textit{ARID1A} loss than those without \textit{ARID1A} loss (46.3% vs. 29.7%). In addition, Wei et al. further observed that \textit{ARID1A} loss was related to the late TNM stage (\(P = 0.020\)) and poor pathological classification (\(P = 0.035\)). However, this study highlighted that positive \textit{ARID1A} was associated with worse OS as compared to those with negative \textit{ARID1A} in stage IV CRC (HR = 2.49, 95% CI: 1.13–5.51), indicating that \textit{ARID1A} loss predicted superior OS in stage IV CRC. Largely consistent with Wei et al.’s findings, (Ye et al. 2014) found that \textit{ARID1A} was related to tumor staging, lymphatic invasion, and tumor recurrence of CRC. \textit{ARID1A}-deficient CRC has a higher proportion of lymph node and distant metastasis, and the overall 5-year survival rate shows a downward trend. Kishida et al. (2019) proved that lymphatic invasion is independently related to \textit{ARID1A} expression. The above studies confirmed that the prognostic value of \textit{ARID1A} variants in CRC is related to \textit{ARID1A} defect or low expression. Tokunaga et al. (2020) believed that the \textit{ARID1A} variation was related to the location of the primary tumor on the right side and the stage of the early tumor. The above data suggest that both low and high expression of \textit{ARID1A} variants are related to the prognostic significance of CRC.

However, other studies did not support a positive association between the \textit{ARID1A} variant or expression level and the prognosis of the disease in the CRC. Chou et al. (2014) found that there is a strong correlation between \textit{ARID1A} expression loss and older age, right-sided tumors, larger tumor size, medullary morphology, high histological grade, BRAFV600E variation, and
loss of mismatch repair protein expression (all $P<0.01$), however, no significant association was found between loss of ARID1A expression and overall survival. Similarly, Lee et al. (2015) have also found that the loss of ARID1A expression was significantly related to the negative lymphatic invasion of CRC ($P=0.003$), and tumor boundary expansion (CRC, $P=0.010$). But there is no obvious correlation between ARID1A expression and 5-year OS. Lee et al. (2016) suggested that at a median follow-up of 49 months, ARID1A deletion was not associated with the OS, disease-specific survival, or recurrence-free survival in CRC patients.

Based on these studies, there is no significant correlation between ARID1A variants and the survival of CRC. One potential explanation for this observation may be due to the low number of CRC cases in some studies. For instance, the study by Erfani et al. (2020) reported that the ARID1A variation rate in CRC was as high as 66.7%. The authors found that among the 18 CRC tumors studied, 7 cases (38.8%) and 5 cases (27.7%) had no or low ARID1A expression, respectively. The limited number of patients may limit the study’s results. Conversely, studies involving a relative large number of patients are more likely to determine the poor prognostic significance of ARID1A variants in CRC (Fountzilas et al. 2018; Jiang et al. 2020; Xie et al. 2014). Certainly, various anti-ARID1A antibodies being used in every study conducted by IHC (e.g., antibody’s clone, manufacturer, dilution rate, IHC score, and cut-off value). These factors may be the underlying reasons behind the different results obtained in each study.

In summary, ARID1A variants may be predictive of metastasis, recurrence, and death of CRC patients, which indicates that ARID1A may play a crucial role in the development of CRC. It is worth noting that because some studies do not support the prognostic value of ARID1A, further studies are needed to verify the prognostic significance of ARID1A variants in CRC.

Molecular mechanisms of ARID1A variations on CRC

Since the causal association between ARID1A variation and CRC has been observed in multiple clinical studies, an exhaustive comprehension of the molecular functions of ARID1A is of great significance to researchers. ARID1A is a driver gene that encodes the DNA binding subunit of the SWI/SNF chromatin-remodeling complex. ARID1A provides specificity for the SWI/SNF complex and promotes protein–protein or protein-DNA molecular interactions. ARID1A inactivation may activate the cell cycle process, resulting in uncontrolled cell proliferation of cancer cells, indicating that ARID1A is a potential tumor suppressor function and the correlation between ARID1A deletion and tumorigenesis (Nagl et al. 2005). ARID1A might exert its biological functions and pathological impact on CRC by interacting with multiple mutated genes, affected signaling pathways, and some other factors.

ARID1A variation was associated with the co-occurrence variation of TP53 and some other genes

Some authors believe that there is a link between ARID1A and TP53 variations. TP53 (also named P53) is one of the most common genetic variants in human cancers and plays an important role in the regulation of the apoptosis, cell cycle, and DNA repair (Pinto et al. 2020). The variation of TP53 has become a critical biomarker of cancer prognosis due to its cancerous biological function. Guan et al. (2011) proposed the theory that ARID1A and p53 inhibit tumor growth synergistically at the molecular level. Other researchers suggested that ARID1A and TP53 variations are reciprocally exclusive and in charge of alternative pathways of tumorigenesis (Jones et al. 2012; Wang et al. 2011). In gastric cancer and gynecological cancer, ARID1A variation or loss of ARID1A protein expression is closely related to microsatellite instability, and negatively related to the variation of TP53 (Bosse et al. 2013). Tokunaga et al. (2020) reported that among the 20 genes assessed in the CRC cohort, only TP53 variations and ARID1A variations were reciprocally exclusive. ARID1A variation cause defects in cell cycle control point activation and TP53 variation in answer to DNA damage (Watanabe et al. 2014). ARID1A and TP53 jointly prevent tumorigenesis by inhibiting the transcriptional activation of genes downstream of tumors. As a result, the prognostic significance and biological effects of ARID1A in CRC may partly depend on the variation of TP53.

TP53 and ARID1A are considered to be the most common mutant genes in CRC (Stein et al. 2020). In addition to TP53, ARID1A variations can also occur simultaneously and may interact with some other genes (such as APC, FBXW7, PIK3CA, PD-L1, and KRAS), which may be involved in the development of CRC. Numerous studies have shown that ARID1A variations are often accompanied by Adenomatous polyposis coli (APC) variations in CRC. It was reported that the APC tumor suppressor is mutated in 27–71.7% of the CRC cases (Ashktorab et al. 2019; Huang et al. 2021). ARID1A and APC variations could increase the proliferation and survival of the CRC cells (Sen et al. 2019). It was reported that FBXW7 was one of the most frequently mutated genes of Chinese CRC patients (Liu et al. 2018). ARID1A variations are frequently accompanied by FBXW7 variations. Huang et al. (2021) found that both FBXW7 (17.5%) and ARID1A (10.3%) were the most common mutated genes in CRC patients via a genomic alteration analysis. Wang et al.
PIK3CA is 6% (7/121) in CRC, and both two genes contribute to the carcinogenic process of CRC. The significant association between ARID1A variation associated with MMR deficiency and hypermethylation might also contribute to the tumorigenesis mechanisms of CRC, and act collectively with ARID1A variations. It was described ARID1A as belonging to the ARID domain-containing gene family (Cajuso et al. 2014). ARID1B (13%, 6/46), ARID2 (13%, 6/46), ARID4A (20%, 9/46) and ARID1A (39%, 18/46) was reported to frequently have variations in tumors. The results show that besides ARID1A, other members of the ARID gene family might also play a part in MSI CRC. Jones et al. (2012) evaluated 759 malignant tumors, including pancreas, breast, colon, stomach, lung, prostate, brain, and blood (leukemia). And truncated variations were found in 6% of the tumors studied; non-truncated cell variations were found in another 0.4% of tumors. Variations are most common in gastrointestinal samples, and 12 of 119 (10%) colon samples have ARID1A variations. The majority of the mutant colorectal tumors show microsatellite instability (MSI). The variations in these tumors are insertions or deletions of single nucleotide repeats outside the frame.

Roles of the affected signaling pathways
The pro-oncogenic roles of ARID1A variation on CRC development may also associate with its regulation on the activity of several affected signaling pathways. Some investigators even believe that variations in some tumor pathways are involved in the first step of progress from normal to CRC (Suleiman et al. 2015). Crosstalk between ARID1A and PI3K/Akt pathway has been detected in multiple cancers (Sun et al. 2021). Xie et al. (2014) believed that ARID1A depletion could promote CRC cell proliferation, enhance chemoresistance, and inhibit cell apoptosis by regulating the activity of the Akt signaling pathway. MTT experiments showed that overexpression of ARID1A in SW620 cells led to decreased cell proliferation, and deletion of ARID1A could increase cell growth rate. Sen et al. (2019) found that ARID1A has a previously unknown background-dependent tumor support function in CRC downstream of the KRAS signal and MEK/ERK pathway, showing that the absence of ARID1A enhances the proliferation of CRC cells. In addition, at the transcriptional level, the authors also detected a strong colocalization of ARID1A and TCF7L2, a downstream effector of the Wnt pathway. Aurora kinase A (AURKA) commonly functions in mitosis and non-mitotic biological processes. Wu et al. (Wu et al. 2018) demonstrated that ARID1A loss contributed to the growth and survival of the CRC cells via negatively regulating AURKA-mediated signaling and the downstream genes, such as PLK1 and CDC25C. A gene set enrichment analysis conducted by Tokunaga et al. showed that ARID1A mutant status was closely correlated to the DNA repair pathway, mediating chemotherapy/radiotherapy sensitivity of CRC (Tokunaga et al. 2020). Since intestinal deletion of ARID1A was tightly associated with CRC development, Hiramatsu et al. believed the underlying molecular mechanisms might be related to the disruption of the intestinal homeostasis, and pointed out that the Wnt signaling pathway crucially involved this action.

ARID1A variation associated with MMR deficiency
MMR deficiency is one of the important prognostic factors in CRC. The significant association between ARID1A...
deletion and MMR defect in CRC has been fully demonstrated in the literature, showing that loss ARID1A expression in 15–25% of MMR-deficient versus 4–6% of MMR-intact CRC cases, respectively (Agaimy et al. 2016). Lee et al. (Lee et al. 2016) reported that ARID1A loss was significantly more prevalent in the MMR-deficient CRC cases than in the MMR-proficient CRC cases (18.7% vs 6.3%, P < 0.001). A previous study (Ye et al. 2014) indicated that ARID1A variations were associated with a worse outcome among the MMR-abnormal CRC cases. This study also demonstrated that the main mechanism of MMR deficiency in ARID1A-deficient tumors was hypermethylation of the mutL homolog 1 (MLH1) gene promoter (Ye et al. 2014). BRAF V600E variations are frequently shown in these MMR-deficient tumors with ARID1A deletion. By comparison, MMR defects due to germline variations (i.e., Lynch syndrome) appear to occur mainly in ARID1A-preserving cases (Chou et al. 2014; Ye et al. 2014). The association between ARID1A deletion and MMR defect co-exists in the early CRC. In addition, most of these MMR-deficient ARID1A deletion tumors do show simultaneous deletion of MLH1 and PMS2, and this pattern is expected in tumors where the MLH1 promoter is methylated (Lee et al. 2016). Chou et al. (Chou et al. 2014) believe that, considering these associations, ARID1A may be used as a marker of somatic hypermethylation for the classification genetic testing of Lynch syndrome. It is worth noting that the MMR defect pattern that suggests Lynch syndrome can also occur in tumors with ARID1A deletion. Promoter hypermethylation is one of the main reasons for ARID1A variations. ARID1A loss leads to epigenetic alterations by a deficient SWI/SNF complex with subsequent MLH1 promoter methylation. Chou et al. reported that a low level of ARID1A was closely associated with larger tumor size, right-sided tumors, and high histological grade of CRC, which were features of somatic hypermethylation (Chou et al. 2014). Erfani et al. (Erfani et al. 2020) found that promoter DNA hypermethylation significantly promoted the silencing or down-regulation of ARID1A in CRC cell lines. The authors also suggested that ARID1A might be an effective tumor suppressor gene in certain subtypes of CRCs because it affects many genes through its role in chromatin remodeling expression (Erfani et al. 2020). Based on the above evidence, promoter hypermethylation may serve as a down-regulation mechanism of ARID1A in CRC.

In summary, ARID1A variants seem to play an important role in the occurrence and progression of CRC tumors. As illustrated in Fig. 3, this schematic diagram summarizes the multi-factor mechanisms that may be involved in the development of ARID1A-driven CRC, including cell cycle arrest, chromatin remodeling and chromosome organization, and DNA hypermethylation. The interactions of multiple genes (i.e., TP53, APC, FBXW7, PIK3CA, PD-L1, and KRAS) and the affected signaling pathways (i.e., PI3K/Akt, MEK/ERK pathway, Wnt pathway, AURKA-mediated signaling, and DNA repair pathway) enhance the process of cell proliferation and anti-apoptosis. Nevertheless, further relevant studies are still needed to better clarify the potential mechanism of ARID1A variations that trigger the development of CRC.

Limitations and perspectives
This is the first study to comprehensively review ARID1A variations associated specifically with CRC from the clinical through the molecular level. However, several drawbacks in the present study should be acknowledged. First, though ARID1A variation is closely associated with the clinicopathologic features of CRC (i.e., TNM stage, tumor location, and histological grade), its role on the prognostic significance of CRC remains controversial among the 23 eligible studies, especially on the survival. Second, large differences in the variation rate of ARID1A in CRC were observed among different included studies, ranging between 3.6 and 66.7%. This heterogeneity might be partly due to various geographic populations, study design, sample size, different tumor staging, gender, age, and the assessments for the expression level of ARID1A. Third, the biomarker role, the potential antitumor effect, and the underlying biological mechanisms for the participation of ARID1A variants in the tumorigenesis of CRC, development, prediction, and therapy need to be further studied.

Conclusions
In the present review, all of the 23 included studies consistently suggest that ARID1A is a tumor suppressor in CRC. The loss of ARID1A expression may represent the ARID1A-driven carcinogenesis in CRC. However, the rate of ARID1A variation in CRC cases is diverse across different studies, ranging from 3.6 to 66.7%. Though ARID1A variation status has several clinical impacts on CRC, such as serving as a biomarker for survival prognosis and various therapies, no significant differences were observed between the variation and wild type of ARID1A in a few studies. The biological functions and pathologic impacts of ARID1A variations on CRC might be correlated to the co-occurrence variation of other genes (i.e., TP53 and KRAS) and the regulation of signaling pathways (i.e., Akt signaling and WNT signaling). Upon further validation with the clinical and biological features of ARID1A variations in CRC by future studies, ARID1A has the potential to serve as an important prognostic factor and individualized therapeutic target for CRC.
Fig. 3 The mechanism by which the ARID1A variation contributes to the pathogenesis of CRCs. ARID1A, a subunit of the chromatin remodeling protein SWI/SNF, is considered to be associated with the tumorigenesis and the progression of CRCs. The process is initiated by the mutation of multiple genes (i.e., TP53, ARID domain-containing gene family, APC, FBXW7, PIK3CA, PD-L1, and KRAS), the dysregulation of several signaling pathways (i.e., PI3K/Akt signaling, MEK/ERK pathway, WNT pathway, AURKA-mediated signaling, and DNA repair pathways), chromatin remodeling, mismatch repair deficiency, and DNA hypermethylation, leading to the cell cycle arrest, proliferation, and survival of the CRC cells. ARID1A AT-rich interaction domain 1A, APC adenomatous polyposis coli, FBXW7 F-Box and WD repeat domain containing 7, PIK3CA phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit α, SWI/SNF SWItch/Sucrose non-fermenting, PD-L1 programmed death ligand 1, KRAS Kirsten rat sarcoma viral oncogene homolog, AURKA aurora kinase A.
Author contributions
RL and WW wrote the manuscript. XW summarized the table. ZJ and TF designed the figures. ZS, DL, and XW participated in the revision of manuscript. All authors read and approved the final manuscript.

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Availability of data and materials
Not applicable.

Declarations

Ethics approval and consent to participate
Declarations

Consent for publication
All authors approved for the publication.

Competing interests
Shankun Zhao, Weizhou Wu, Zufu Jiang, Lingzhi Ding, Weifang Xu, and Libin Ruan declare that they have no competing interests.

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