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## Distinct and overlapping roles of ARID3A and ARID3B in regulating E2F-dependent transcription via direct binding to E2F target genes

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INTERNATIONAL JOURNAL OF ONCOLOGY

Volume: 58 Issue: 4

Article Number: 12

DOI: 10.3892/ijco.2021.5192

Published: APR 2021

Document Type: Article

[View Journal Impact](#)

### Abstract

The AT-rich interacting domain (ARID) family of DNA-binding proteins is involved in various biological processes, including the regulation of gene expression during cell proliferation, differentiation and development. ARID3A and ARID3B are involved in chromatin remodeling and can bind to E2F1 and retinoblastoma tumor suppressor protein (RB), respectively. However, their role in regulating E2F target gene expression remains poorly understood. E2F transcription factors are critical regulators of cell cycle progression and are modulated by RB. Herein, putative ARID3-binding sites (BSs) in E2F target genes were identified, including Cdc2, cyclin E1 and p107, and it was found that ARID3A and ARID3B bound to these BSs in living cells. The mutation of ARID3 BSs reduced Cdc2 promoter activity, while ARID3A and ARID3B overexpression increased the promoter activity, depending on both ARID3 and E2F BSs. ARID3B knockdown blocked the transcription of Cdc2, cyclin E1 and p107 in normal human dermal fibroblasts (NHDFs), whereas the effects of ARID3A knockdown varied depending on the target genes. ARID3B overexpression, but not that of ARID3A, upregulated the transcription of E2F target genes, and activated cyclin E1 transcription and induced cell death with E2F1 assistance. Finally, ARID3A and ARID3B knockdown attenuated the cell cycle progression of NHDFs and T98G cells, and suppressed tumor cell growth. On the whole, these results indicate that ARID3A and ARID3B play distinct and overlapping roles in E2F-dependent transcription by directly binding to the E2F target genes. The present study provides novel insight into the mechanisms underlying the E2F dysregulation caused by ARID3A and ARID3B overexpression, which may have a significant influence on the progression of tumorigenesis.

### Keywords

**Author Keywords:** AT-rich interacting domain; ARID3A; ARID3B; E2F; transcriptional regulation; E2F target genes; cell proliferation; tumorigenesis

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### Funding

| Funding Agency   | Show details | Grant Number |
|--|--------------|--------------|
| Ministry of Education, Culture, Sports, Science and Technology, Japan (MEXT) |              | JP21390502   |
| Japan Society for the Promotion of Science                                   |              | JP24659870   |
| Grants-in-Aid for Scientific Research (KAKENHI)                              |              | JP19K10259   |

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