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The Emerging Role of ARID1A Expression and Its Promoter in Pathogenesis of Adenomyosis: a Narrative Review

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Abstract

Adenomyosis is a benign gynecological condition characterized by the presence of endometrial glands and stroma within the myometrium. It affects reproductive-aged women and causes significant morbidity. Recent evidence suggests that downregulation and mutation of ARID1A, a tumor suppressor gene and its epigenetic alteration that cause chromatin remodeling complexes, play crucial roles in adenomyosis pathogenesis. This narrative review aims to synthesize current evidence on the Role of ARID1A Expression and Its Promoter in adenomyosis pathogenesis. A comprehensive literature search was conducted in PubMed, Web of Science, and Scopus databases for studies published between 2015 and 2025. Search terms included "adenomyosis," "ARID1A," "oxidative stress," "DNA methylation," "chromatin remodeling," and "epigenetics." Studies investigating the molecular mechanisms underlying adenomyosis, particularly those examining ARID1A function, oxidative stress, and DNA methylation patterns, were included. We found that there are complex relationships among oxidative stress, ARID1A expression, and DNA methylation in the pathogenesis of adenomyosis. The interactions between oxidative damage, chromatin dysfunction, and genomic instability suggest that adenomyosis is an epigenetic disease driven by oxidative stress.

Keywords: adenomyosis, ARID1A protein, oxidative stress, DNA methylation, epigenetics

1. Introduction

Adenomyosis is a major gynecological condition that affects 20-30% of women of reproductive age and is defined by the presence of ectopic endometrial tissue within the muscle layer of the uterus. This non-cancerous condition leads to significant suffering due to symptoms such as painful periods, heavy menstrual flows, and infertility, greatly affecting overall quality of life. Although this condition is clinically important, the molecular mechanisms involved in the development of adenomyosis are not fully understood, highlighting the need for a thorough examination of the epigenetic and oxidative stress-related factors that play a role in the onset and progression of the disease [1].

The importance of understanding adenomyosis pathogenesis extends beyond clinical symptom management to potential prevention and targeted therapeutic interventions. Recent advances in molecular biology have revealed that adenomyosis shares pathogenic mechanisms with endometriosis and endometrial cancer, particularly involving chromatin remodeling dysfunction and aberrant DNA methylation patterns. These findings have shifted the conceptual framework from viewing adenomyosis as purely a structural abnormality to recognizing it as a complex epigenetic disorder [2].

ARID1A (AT-rich interactive domain 1A) has emerged as a critical tumor suppressor gene and chromatin remodeling factor that plays essential roles in transcriptional regulation, cell cycle control, and DNA repair [3, 4]. As a core component of the SWI/SNF (SWItch/Sucrose Non-Fermentable) chromatin remodeling complex, ARID1A facilitates nucleosome repositioning and chromatin accessibility, thereby regulating gene expression programs essential for normal cellular function. Mutations and altered expression of ARID1A have been identified in various malignancies, including endometriosis-associated ovarian cancers and endometrial carcinomas [5-7].

Oxidative stress, characterized by an imbalance between reactive oxygen species (ROS) production and antioxidant defense mechanisms, has been increasingly recognized as a fundamental pathogenic factor in adenomyosis. Chronic exposure to oxidative stress can induce DNA damage, alter gene expression through epigenetic modifications, and promote cellular transformation. In the context of adenomyosis, oxidative stress may arise from multiple sources, including chronic inflammation, iron accumulation from repetitive bleeding, and metabolic dysfunction [8, 9].

Through this narrative review, we aim to deepen our understanding for the possibility role of ARID1A expression patterns and functional significance in adenomyosis, analyze the role of oxidative stress in modulating ARID1A expression through promoter regulation and epigenetic mechanisms, Investigate the

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relationship between oxidative stress, DNA methylation patterns, and ARID1A function in adenomyosis pathogenesis.

2. Literature Search Methods

A systematic literature search was performed using PubMed, Web of Science, and Scopus databases for peer-reviewed articles published between January 2015 and December 2025. The search strategy employed both Medical Subject Headings (MeSH) terms and free-text keywords including: "adenomyosis," "ARID1A," "chromatin remodeling," "SWI/SNF complex," "oxidative stress," "reactive oxygen species," "DNA methylation," "epigenetics," "DNMT1," "DNMT3A," "DNMT3B," and "promoter methylation." Reference lists of relevant articles were manually searched to identify additional studies. Studies were included if they investigated molecular mechanisms of adenomyosis, examined ARID1A function or expression, explored oxidative stress pathways, or analyzed DNA methylation patterns in adenomyosis or related conditions. Both original research articles and review papers were considered, with emphasis on recent high-quality studies providing mechanistic insights.

2.1. ARID1A Expression and Function in Adenomyosis

2.1.1. ARID1A structure and chromatin remodeling function

ARID1A encodes a 270-kDa nuclear protein (BAF250a) that serves as a critical component of the BAF (BRG1-associated factor) chromatin remodeling complex, a mammalian homolog of the yeast SWI/SNF complex [4]. The protein contains several functional domains, including the ARID (AT-rich interactive domain) that mediates sequence-nonspecific DNA binding, and multiple protein-protein interaction domains that facilitate complex assembly and stability [10]. Through ATP-dependent nucleosome sliding and histone ejection mechanisms, ARID1A-containing SWI/SNF complexes regulate chromatin accessibility at promoters and enhancers, thereby controlling transcriptional programs essential for cell cycle regulation, differentiation, and DNA repair [11].

The functional significance of ARID1A in normal endometrial physiology includes regulation of hormone-responsive genes, particularly those involved in progesterone signaling and decidualization. ARID1A works in concert with transcriptional cofactors and hormone receptors to modulate the expression of genes critical for endometrial cycling, implantation, and pregnancy maintenance. Loss or dysfunction of ARID1A can therefore profoundly disrupt normal endometrial function and contribute to pathological conditions [12].

2.1.2. ARID1A alterations in adenomyosis

Recent genomic studies have identified ARID1A mutations in adenomyosis tissue, with frequencies ranging from 10-12% in adenomyotic epithelium. These mutations predominantly consist of frameshift that likely caused mRNA decay and loss of protein expression. Importantly, ARID1A mutations in adenomyosis often occur with high mutant allele frequencies (>0.25), suggesting clonal expansion of mutant cells and indicating that ARID1A loss may be an early driver event in adenomyosis pathogenesis [13, 14]. Protein expression studies have demonstrated reduced ARID1A immunoreactivity in endometriotic tissue compared to normal endometrium. This reduction in protein expression may result from multiple mechanisms, including genetic mutations, epigenetic silencing through promoter hypermethylation, or post-transcriptional regulation. The correlation between ARID1A loss and disease severity suggests that chromatin remodeling dysfunction plays a fundamental role in endometrial progression. Nonetheless, the expression of ARID1A in adenomyosis has not been studied, but possibly through oxidative stress and local inflammation that led to alteration of ARID1A expression. These events will cause increase angiogenesis, cell proliferation, the inhibition of apoptosis, production of ROS that enhances DNA damage, and mutation [9, 15].

2.1.3. Functional consequences of ARID1A loss

Loss of ARID1A function in adenomyosis appears to contribute to disease pathogenesis through several mechanisms. Cell cycle dysregulation represents a primary consequence, as ARID1A normally promotes G1/S checkpoint control through the regulation of p21 (CDKN1A) and other cell cycle inhibitors. In ARID1A-deficient cells, this checkpoint control is compromised, leading to increased proliferation and reduced apoptosis [3, 4].

Transcriptional reprogramming following ARID1A loss affects multiple pathways relevant to adenomyosis pathogenesis. Key downstream targets include SMAD3, which mediates TGF-β signaling and epithelial-mesenchymal transition, and various DNA repair genes that maintain genomic stability. The dysregulation of these pathways may contribute to the invasive characteristics of adenomyotic tissue and its resistance to normal growth controls [3].

2.2. Oxidative Stress in Adenomyosis Pathogenesis

2.2.1. Sources and mechanisms of oxidative stress

Oxidative stress in adenomyosis arises from multiple interconnected sources that create a chronic pro-oxidant environment within the endometrium and myometrium. Iron accumulation from repetitive menstrual bleeding represents a major contributor, as free iron catalyzes the formation of highly reactive hydroxyl radicals through the Fenton reaction. This iron-mediated oxidative damage is particularly relevant in adenomyosis, where ectopic endometrial tissue undergoes cyclic bleeding within the myometrium, leading to sustained iron deposition and chronic oxidative stress exposure [16, 17].

Inflammatory mediates further amplify oxidative stress through activation of various cell types, including macrophages, neutrophils, and endometrial cells themselves. Pro-inflammatory cytokines such as TNF-α, IL-1β, and IL-6 stimulate NADPH oxidase and other ROS-generating enzymes, creating a positive feedback loop between inflammation and oxidative damage. Additionally, cyclooxygenase-2 (COX-2) upregulation in adenomyosis contributes to both inflammatory signaling and ROS production [16, 18].

2.2.2. Cellular responses to oxidative stress

Signaling pathway activation in response to oxidative stress involves multiple cellular mechanisms that can paradoxically promote both cell survival and pathological changes. The mitogen-activated protein kinase (MAPK) and extracellular signal-regulated kinase (ERK) pathways are activated by ROS, leading to increased cell proliferation and survival signaling. Additionally, the PI3K/AKT/mTOR pathway shows enhanced activation in adenomyotic tissues exposed to oxidative stress, contributing to increased cell growth and metabolic reprogramming [8].

Transcriptional changes induced by oxidative stress include upregulation of inflammatory genes, angiogenic factors, and cell cycle regulators. Nuclear factor κB (NF-κB) activation by ROS leads to increased expression of inflammatory cytokines and chemokines, perpetuating the inflammatory cycle. Hypoxia-inducible factor-1α (HIF-1α) stabilization under oxidative conditions promotes angiogenesis and metabolic adaptation, potentially facilitating the survival and growth of ectopic endometrial tissue [8].

2.2.3. Oxidative Stress and ARID1A Expression

2.2.3.1 Direct effects of ROS on ARID1A expression

Experimental evidence demonstrates that oxidative stress directly suppresses ARID1A expression in endometrial cells. In vitro studies using hydrogen peroxide (H2O2) as an oxidative stress inducer show dose-dependent reductions in ARID1A mRNA and protein levels in primary endometrial cells. This suppression occurs relatively rapidly, suggesting direct transcriptional or post-transcriptional mechanisms rather than solely genetic alterations. Mechanistic studies indicate that ROS-induced ARID1A downregulation involves multiple pathways. Oxidative stress can directly damage the ARID1A gene promoter region, leading to reduced transcriptional activity. Additionally, ROS can modify transcription factors and chromatin-modifying enzymes that normally promote ARID1A expression, thereby indirectly suppressing gene transcription. Concentration-dependent effects of oxidative stress on ARID1A expression have been characterized in detail. Low levels of ROS may initially trigger compensatory responses that maintain ARID1A expression, but sustained or high-level oxidative stress leads to progressive downregulation. This dose-response relationship suggests that chronic oxidative stress conditions, as occur in adenomyosis, would be particularly detrimental to ARID1A function. Fig. 1. [9, 19].

2.2.3.2. ROS-mediated transcriptional regulation

Promoter analysis of the ARID1A gene reveals multiple regulatory elements that are sensitive to oxidative stress. The ARID1A promoter contains binding sites for transcription factors that are known to be modified by ROS, including AP-1, NF-κB, and various hormone receptors. Oxidative modifications of these transcription factors can alter their DNA-binding affinity and transcriptional activity, leading to reduced ARID1A promoter activity [19]. Chromatin modifications at the ARID1A locus are significantly altered by oxidative stress exposure. ChIP-seq studies demonstrate that oxidative stress leads to recruitment of repressive chromatin modifiers, including DNA methyltransferases and histone deacetylases, to the ARID1A promoter region. These modifications create a repressive chromatin environment that persists even after the initial oxidative stimulus is removed, potentially explaining the sustained ARID1A downregulation observed in adenomyosis [20].

2.2.3.3. Post-transcriptional Regulation

MicroRNA involvement in oxidative stress-mediated ARID1A suppression has been identified through expression profiling studies. Several microRNAs, including miR-146a and miR-200c, are upregulated by oxidative stress and can directly target ARID1A mRNA for degradation. These microRNAs are also elevated in adenomyosis tissue, suggesting that they may contribute to the reduced ARID1A expression observed in this condition. Protein stability of ARID1A is also affected by oxidative stress through post-translational modifications. ROS can induce oxidative modifications of ARID1A protein, including carbonylation and nitrosylation, which can affect protein stability, subcellular localization, and functional activity. These modifications may contribute to the functional impairment of ARID1A even when protein levels are not dramatically reduced [10].

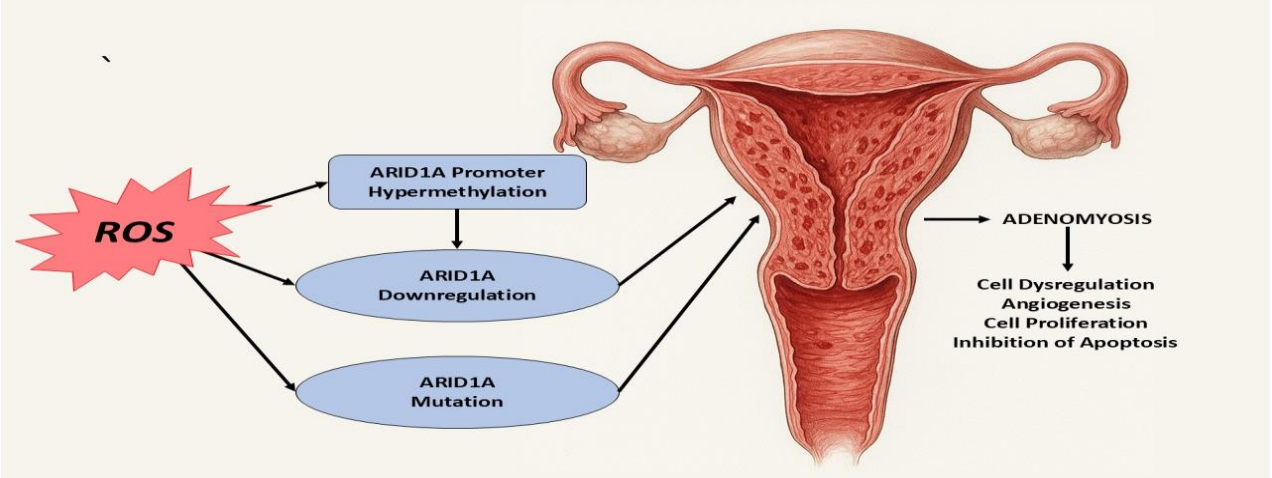

Figure 1: Role of ARID1A expression influenced by ROS microenvironment in the pathogenesis and development of adenomyosis.

2.3. DNA Methylation and ARID1A Promoter Regulation

2.3.1. ARID1A promoter methylation in adenomyosis

Promoter hypermethylation of ARID1A represents a key mechanism for gene silencing in adenomyosis. Methylation-specific PCR analysis and bisulfite sequencing studies have consistently demonstrated increased CpG methylation within the ARID1A promoter region in adenomyotic tissues compared to normal endometrium. This hypermethylation is particularly prominent in CpG islands located within 2 kb of the transcriptional start site, regions that are normally unmethylated in healthy tissues [4, 19].

Quantitative analysis reveals that approximately 86% of endometriosis cases with low ARID1A expression exhibit promoter hypermethylation. This strong correlation suggests that DNA methylation is a primary mechanism for ARID1A silencing in endometriosis, potentially more important than genetic mutations in most cases. The frequency of promoter methylation is significantly higher in endometriosis tissues than in normal endometrium, where ARID1A promoter methylation is rarely observed [4, 19].

Regional specificity of methylation within the ARID1A promoter shows distinct patterns that correlate with transcriptional activity. The most critical CpG sites for transcriptional regulation are located within the core promoter region and the first exon, where methylation directly interferes with transcription factor binding and RNA polymerase II recruitment. Additional methylation sites in upstream regulatory regions may affect enhancer activity and long-range chromatin interactions [4].

2.3.2. DNA methyltransferase expression in adenomyosis

DNMT1 upregulation is consistently observed in adenomyotic tissues, particularly in response to oxidative stress. Immunohistochemical analysis reveals significantly higher DNMT1 expression in both eutopic and ectopic endometrial tissues from adenomyosis patients compared to controls. This upregulation correlates with the extent of ARID1A promoter methylation and the severity of clinical symptoms, suggesting a direct pathogenic role [21].

DNMT3A and DNMT3B expression patterns in adenomyosis show complex regulation that differs between eutopic and ectopic tissues. DNMT3A expression is generally reduced in adenomyotic tissues, which may seem counterintuitive given the hypermethylation phenotype. However, this reduction may reflect a cellular response to excessive methylation or may indicate that DNMT1, rather than de novo methyltransferases, is primarily responsible for ARID1A promoter methylation maintenance [21, 22].

Subcellular localization of DNMTs is altered in adenomyotic cells, with increased nuclear accumulation observed in response to oxidative stress. This nuclear enrichment facilitates access to chromatin and promotes targeted methylation of gene promoters, including ARID1A. The altered localization patterns correlate with disease severity and may serve as a biomarker for epigenetic dysfunction in adenomyosis [21].

2.3.3. Oxidative stress-induced methylation

Mechanistic linkage between oxidative stress and DNA methylation involves multiple interconnected pathways. Oxidative stress can directly recruit DNMT1 to damaged chromatin through formation of protein complexes that include members of the Polycomb Repressive Complex 4 (PRC4). This recruitment specifically targets CpG-rich regions, including gene promoters, for de novo methylation [19, 20].

SIRT1 involvement in oxidative stress-induced methylation has been demonstrated through chromatin immunoprecipitation studies. SIRT1, a histone deacetylase that is activated by oxidative stress, can facilitate the recruitment of DNMTs to target gene promoters. The formation of SIRT1-DNMT complexes at the ARID1A promoter correlates with both oxidative stress markers and promoter hypermethylation [20].

Temporal dynamics of oxidative stress-induced methylation show that initial ROS exposure leads to rapid recruitment of methylation machinery, followed by progressive accumulation of methyl marks over time. This process may explain why chronic oxidative stress conditions, such as those present in adenomyosis, lead to stable epigenetic silencing of tumor suppressor genes like ARID1A [20].

2.3.4. Chromatin context and methylation

Histone modifications accompanying ARID1A promoter methylation include loss of active marks (H3K4me3, H3K27ac) and gain of repressive marks (H3K27me3, H3K9me3). This chromatin remodeling creates a stable repressive environment that maintains gene silencing even in the absence of continued oxidative stress. The combination of DNA methylation and repressive histone modifications represents a particularly robust mechanism for long-term gene silencing. Chromatin accessibility at the ARID1A locus is significantly reduced in adenomyotic tissues with promoter hypermethylation. ATAC-seq analysis demonstrates decreased chromatin accessibility across the ARID1A gene body and regulatory regions, consistent with the formation of repressive chromatin domains. This reduced accessibility limits the binding of transcriptional activators and RNA polymerase II, contributing to sustained gene silencing [23].

2.4. Interplay Between Oxidative Stress, DNA Methylation, and ARID1A

2.4.1. Mechanistic integration

A multistep process characterizes the relationship between oxidative stress, DNA methylation, and ARID1A dysfunction in adenomyosis. Initial oxidative stress exposure leads to direct recruitment of DNA methyltransferases to the ARID1A promoter, facilitated by protein complexes that include PRC4 components and SIRT1. This recruitment results in targeted CpG methylation that initiates transcriptional repression. Feed-forward mechanisms amplify the initial oxidative damage through several pathways. Reduced ARID1A expression compromises chromatin remodeling capacity, leading to dysregulated gene expression programs that include enhanced oxidative stress responses and inflammatory signaling. This creates a self-perpetuating cycle where oxidative stress promotes ARID1A silencing, which in

turn facilitates further oxidative damage and genomic instability [9, 19].

Temporal progression of the oxidative stress-methylation-ARID1A axis shows distinct phases that may correspond to different stages of adenomyosis development. Early exposure to oxidative stress triggers reversible changes in ARID1A expression and promoter accessibility. With sustained exposure, DNA methylation accumulates and chromatin modifications become more stable, leading to persistent ARID1A silencing that may be difficult to reverse therapeutically [9, 19].

2.4.2. Cellular consequences

Proliferative advantage conferred by ARID1A loss in the context of oxidative stress may explain the clonal expansion observed in adenomyotic lesions. ARID1A normally functions as a tumor suppressor through regulation of cell cycle checkpoints and DNA repair processes. Its loss removes these growth constraints, allowing cells to proliferate despite ongoing DNA damage from oxidative stress. Genomic instability resulting from combined oxidative stress and ARID1A dysfunction creates a permissive environment for additional mutations. Cells with compromised DNA repair capacity are more susceptible to ROS-induced mutagenesis, potentially explaining the accumulation of driver mutations (KRAS, PIK3CA, FBXW7) observed in adenomyotic tissues with ARID1A alterations. Epithelial-mesenchymal transition may be promoted by the combination of oxidative stress and ARID1A loss [18]. ARID1A normally suppresses EMT programs through regulation of E-cadherin and other cell adhesion molecules. Its loss, combined with oxidative stress-induced TGF-β signaling, may facilitate the invasive phenotype characteristic of adenomyotic tissue infiltration into the myometrium [15, 10].

2.4.3. Therapeutic Implications

Epigenetic reversibility of ARID1A silencing through DNA methylation offers potential therapeutic opportunities. Treatment with DNA methyltransferase inhibitors, such as 5-azacytidine, can restore ARID1A expression in cell culture models. However, the effectiveness of such approaches may depend on the extent of chromatin remodeling and the presence of additional silencing mechanisms. Antioxidant strategies targeting the upstream oxidative stress component may prevent or slow the progression of ARID1A silencing. Compounds that enhance cellular antioxidant capacity or directly scavenge ROS might interrupt the oxidative stress-methylation cycle before stable epigenetic changes become established [9].

Combination approaches targeting both oxidative stress and epigenetic mechanisms may be most effective for restoring ARID1A function. Sequential treatment with antioxidants followed by epigenetic modulators could potentially reverse both the initiating oxidative damage and the resulting chromatin modifications. Natural antioxidants such as N-acetylcysteine, vitamin E, or polyphenolic compounds might reduce ROS levels and interrupt the oxidative stress-driven pathogenic cycle. Clinical studies would be needed to evaluate optimal dosing, timing, and patient selection for such interventions [19].

4. Conclusions

From our understanding, there are complex relationships among oxidative stress, ARID1A expression, and DNA methylation in the pathogenesis of adenomyosis. Oxidative stress initiates molecular events leading to the epigenetic silencing of ARID1A through promoter hypermethylation, primarily via DNMT1 upregulation and chromatin remodeling. This silencing results in a loss of tumor suppressor function, which promotes the pathological features of adenomyosis. The interactions between oxidative damage, chromatin dysfunction, and genomic instability suggest that adenomyosis is an epigenetic disease driven by oxidative stress.

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Statement on the Use of Artificial Intelligence in Manuscripts

The authors declare that we use AI assistance for the figure generation.

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