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Tumor metabolic reprogramming driven by ARID1A deficiency and synthetic lethal mechanism

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Abstract: ARID1A, a core subunit of the SWI/SNF chromatin remodeling complex, is frequently inactivated across diverse cancers. This review synthesizes current understanding of how ARID1A deficiency serves as a pivotal epigenetic driver, orchestrating extensive metabolic reprogramming and reshaping the tumor immune microenvironment (TIME). Acting as an epigenetic hub, loss of ARID1A alters chromatin accessibility, leading to transcriptional dysregulation of key metabolic enzymes. This drives cancer-type-specific rewiring of core pathways including glucose, amino acid, lipid, and nucleotide metabolism. Crucially, these metabolic alterations extend beyond fueling tumor proliferation; they actively sculpt an immunosuppressive TIME through mechanisms such as nutrient competition, oxidative stress modulation, and the production of specific metabolites. This creates a dual vulnerability: a dependence on the reprogrammed metabolic state for survival and a disrupted immune landscape. Consequently, ARID1A deficiency exposes unique, targetable “synthetic lethal” weaknesses. We detail promising therapeutic strategies that exploit these vulnerabilities by targeting the reprogrammed metabolism (e.g., using GLS1, FASN, or DHODH inhibitors) or its immunomodulatory consequences, often in combination with immunotherapy. Despite significant preclinical progress, challenges remain, including understanding the heterogeneity of metabolic responses across cancer types and identifying validated biomarkers for patient stratification. Interdisciplinary efforts to decipher the precise mechanisms of this epigenetic-metabolic-immune crosstalk and to advance combination therapies into the clinic are essential for realizing the promise of precision medicine for ARID1A-deficient tumors.

1. Introduction

1.1 A Paradigm Shift in Cancer Biology

Malignant tumors remain one of the most formidable challenges to global public health [1]. Their detrimental impact is profound and multidimensional: at the individual level, tumors pose a direct threat to life via local invasion, distant metastasis, and systemic wasting; at the biological level, cancer cells exhibit core hallmarks such as dysregulated proliferation, resistance to apoptosis, and genomic instability, and can evolve through clonal selection under therapeutic pressure, leading to heterogeneity and drug resistance, thereby making eradication exceedingly difficult; at the socioeconomic level, cancer imposes a heavy burden on healthcare systems and severely compromises patient quality of life [2]. Although traditional modalities including surgery, radiotherapy, and chemotherapy have achieved considerable success, their paradigm of indiscriminate targeting is often associated with significant toxicity, and their efficacy against advanced or metastatic diseases frequently encounters limitations [3].

Over the past few decades, our understanding of the fundamental nature of malignancy has undergone a profound paradigm shift. Early cancer research predominantly focused on irreversible alterations at the genomic level, conceptualizing cancer as a consequence of the accumulation of somatic mutations—the so-called "genetic disease." However, with the rapid advancement of high-throughput sequencing technologies and systems biology, the scientific community has gradually recognized that genetic mutations alone cannot fully account for the high heterogeneity, plasticity, and dynamic adaptability of tumors to therapy. This realization has shifted the research focus towards two higher-order regulatory networks: Epigenetics and Cellular Metabolism.

Epigenetic regulation, particularly the dynamic modification of three-dimensional genome architecture by ATP-dependent chromatin remodeling complexes, dictates the cell-type and context-specific transcriptional programs [4,5]. Concurrently, metabolic reprogramming, recognized as a core hallmark of cancer, is no longer viewed as a passive byproduct of cell proliferation but rather as a central driver of tumorigenesis and progression [6,7]. The current frontier in cancer biology lies at the deep intersection of these two fields: epigenetic alterations directly reshape the expression profiles of metabolic enzymes, while metabolites in turn act as substrates or cofactors for epigenetic modifying enzymes, thereby reversibly influencing the genomic landscape. This epigenetic-metabolic crosstalk forms the mechanistic basis for tumor cell survival within hostile microenvironments, immune evasion, and the evolution of therapy resistance [8,9].

1.2 The Molecular Functional Architecture of ARID1A

1.2.1 Molecular Functions of ARID1A and the SWI/SNF Complex

The ARID1A gene is located on human chromosome 1p36.11. Its encoded protein (also termed BAF250a) is one of the largest non-catalytic subunits within the mammalian SWI/SNF (or BAF) complex [10, 11]. The SWI/SNF complex is an evolutionarily highly conserved molecular machine that utilizes energy derived from ATP hydrolysis to slide, evict, or remodel nucleosomes, thereby regulating the accessibility between DNA and its associated proteins. This chromatin remodeling process is crucial for the initiation and elongation of gene transcription, DNA replication, and DNA damage repair [12,13].

Within the complex, ARID1A itself lacks direct ATPase activity but serves as a specificity determinant. It recognizes specific DNA sequences, particularly AT-rich promoter and enhancer regions, through its N-terminal AT-rich interaction domain (ARID) [14], thereby recruiting the catalytically active subunits SMARCA4 (BRG1) or SMARCA2 (BRM) to target genomic loci.

Furthermore, ARID1A engages in direct physical interactions with transcription factors such as p53 and nuclear hormone receptors via its C-terminal domain, directly participating in the regulation of cell cycle checkpoints and apoptotic programs [15, 16].

Research indicates that ARID1A function exhibits significant dose dependency and tissue specificity. Under normal physiological conditions, it not only acts as a gatekeeper by regulating genes like p21 (CDKN1A) to maintain cell cycle homeostasis but also serves as a caretaker involved in preserving genomic integrity, preventing the occurrence of microsatellite instability (MSI) and chromosomal translocations [17].

1.2.2 Pan-Cancer Mutation Frequency and Clinical Relevance

The Cancer Genome Atlas (TCGA) and subsequent large-scale sequencing studies have revealed that mutations in subunits of the SWI/SNF complex occur in over 20% of human malignancies, a frequency second only to TP53 [18, 19]. Among these subunits, ARID1A exhibits the highest mutation rate and demonstrates an exceptionally broad distribution across various cancer types [20]. The vast majority of ARID1A mutations are nonsense or frameshift mutations, leading to truncation or complete degradation of the protein product, which strongly supports its role as a classical tumor suppressor gene (TSG) [21,22].

In this study, we focus on ARID1A. As a core subunit of the SWI/SNF chromatin remodeling complex, ARID1A-mediated epigenetic regulation directly determines the transcriptional output of metabolic enzymes, thereby shaping a specific metabolic phenotype. This metabolic phenotype, in turn, represents a specific lethal vulnerability in ARID1A-deficient tumors. ARID1A mutation not only compromises genomic stability but also triggers extensive and specific metabolic reprogramming. Delving into this mechanism will not only enhance our understanding of the biological essence of tumors but also provide a theoretical cornerstone for developing novel therapies based on the synthetic lethality strategy.

2. The Convergence of Two Major Scientific Paradigms: Synthetic Lethality and Metabolic Reprogramming

The traditional model of chemotherapy characterized by "a pyrrhic victory" is gradually being supplanted by precision therapies based on genetic dependency. The concept of synthetic lethality posits that the simultaneous inactivation of two non-lethal genes results in cell death [23,24]. In ARID1A-deficient tumors, the localized loss of SWI/SNF complex function creates an absolute cellular dependence on certain compensatory pathways (e.g., ARID1B, EZH2, DNA damage repair pathways) [25]. This vulnerability provides the theoretical foundation for developing drugs that specifically target ARID1A-mutant tumors.

Since Otto Warburg's discovery of aberrant glycolysis in cancer cells a century ago [26], metabolic reprogramming has been established as a core hallmark of cancer [27, 28]. Tumor cells must remodel their metabolic networks to meet the demands of rapid proliferation for biomass synthesis and redox homeostasis [29, 30]. ARID1A, as an epigenetic master regulator, when deficient, directly causes widespread alterations in the expression profiles of metabolic enzyme genes, forcing tumor cells into an aberrant metabolic state [31].

In this study, we focus on ARID1A. As a core subunit of the SWI/SNF chromatin remodeling complex, ARID1A-mediated epigenetic regulation directly determines the transcriptional output of metabolic enzymes, thereby shaping a specific metabolic phenotype. This metabolic phenotype, in turn, constitutes a specific lethal vulnerability in ARID1A-deficient tumors. ARID1A mutation not only compromises genomic stability but also triggers extensive and specific metabolic reprogramming. Delving into this mechanism will not only enhance our understanding of the

biological essence of tumors but also provide a theoretical cornerstone for developing novel therapies based on the synthetic lethality strategy.

2.1 Synthetic Lethality: The Genetic Logic of Precision Targeting

In 1922, the geneticist Calvin Bridges introduced the concept of "synthetic lethality" in studies of Drosophila melanogaster [32]. Subsequently, Theodosius Dobzhansky formally defined synthetic lethality in 1946 as a scenario where two non-lethal mutations individually permit cell survival, but their co-occurrence leads to cell death or a significant fitness reduction [33]. It was not until 1997 that E.S. Kroll and colleagues, with remarkable foresight, proposed applying the logic of synthetic lethality to anticancer drug development [34], bringing this classic genetic principle into the purview of cancer therapy. In the context of cancer treatment, this strategy involves pharmacologically inhibiting a complementary lethal gene in tumor cells carrying a specific loss-of-function mutation, thereby selectively inducing tumor cell death while sparing normal cells possessing the wild-type tumor suppressor gene [35, 36].

The fundamental advantage of the synthetic lethality strategy lies in its high specificity and reduced off-target toxicity. Traditional cytotoxic chemotherapy often exhibits a non-specific killing effect reminiscent of "a pyrrhic victory," severely damaging rapidly dividing normal tissues [37]. In contrast, synthetic lethality precisely exploits the specific genetic background of tumor cells, enabling their targeted eradication, which aligns with the highest standards of modern precision medicine.

2.2 Metabolic Reprogramming: A Core Hallmark and Survival Strategy of Cancer

Metabolic reprogramming has been established as a core hallmark of cancer. It refers to the genetic and epigenetic alterations in metabolic pathways undertaken by cancer cells, aimed at sustaining uncontrolled proliferation within the nutrient-scarce, hypoxic, and acidic tumor microenvironment (TME) [38, 39]. This concept has evolved beyond the early focus on the "Warburg effect" to encompass a comprehensive remodeling of lipid biosynthesis, nucleotide metabolism, and redox homeostasis.

2.2.1 The Warburg Effect

The Warburg effect is a classical feature of tumor metabolic reprogramming. It describes the phenomenon wherein cancer cells preferentially convert glucose to lactate, even in the presence of ample oxygen, rather than metabolizing it via mitochondrial oxidative phosphorylation (OXPHOS). This seemingly less efficient mode of ATP production (generating 2 ATP per glucose molecule vs. up to 36 via OXPHOS) confers significant evolutionary advantages [40, 41].

At the molecular level, activation of the Warburg effect relies on the dysregulation of key glycolytic enzymes. Hexokinase 2 (HK2), the rate-limiting enzyme for glucose phosphorylation, is frequently driven to overexpress in various tumors by oncogenes (e.g., MYC, AKT), thereby enhancing glucose uptake and metabolic flux initiation [42,43]. Additionally, adaptive remodeling of mitochondrial function in cancer cells, such as mitochondrial fragmentation and downregulation of key OXPHOS enzymes, further reinforces their dependence on glycolysis, establishing a metabolic addiction phenotype [44, 45].

In biological terms, this metabolic shift offers multiple benefits. First, the glycolytic pathway operates more rapidly than OXPHOS, providing a baseline energy supply within a short timeframe for rapidly dividing cells. Furthermore, glycolytic intermediates (e.g., glucose-6-phosphate, pyruvate) are efficiently diverted into biosynthetic pathways for nucleotides, amino acids, and lipids.

The provision of these precursors for macromolecular synthesis is often more critical for proliferating cells than maximal ATP yield. The secreted lactate acidifies the TME, thereby suppressing immune cell function and enhancing tumor cell invasiveness [46]. Lastly, the rapid energy supply characteristic of glycolysis aligns with the high energetic demands of tumor cell division, serving as a crucial support for their malignant proliferation.

2.2.2 Glutamine Addiction

Glutamine, the most abundant non-essential amino acid within cells, serves as a crucial nutrient source for tumor cells, second only to glucose. To sustain mitochondrial function and the operation of the tricarboxylic acid (TCA) cycle, many cancer cells exhibit an absolute dependence on glutamine, termed "glutamine addiction" [47,48]. The core mechanism lies in glutamine's role in anaplerosis, replenishing TCA cycle intermediates depleted due to nutrient scarcity in the TME. Following its uptake by the ASCT2 transporter, glutamine is converted to glutamate by glutaminase (GLS1/2). Glutamate is then transformed into α-ketoglutarate (α-KG) via glutamate dehydrogenase (GLUD1) or transaminases, thereby replenishing the TCA cycle. At the molecular level, GLS1, a key regulatory enzyme whose overexpression is driven by oncogenic signals such as MYC and PI3K/AKT, constitutes a core driver of glutamine addiction [49]. Its biological significance is multifaceted: (1) As a nitrogen donor, it participates in the synthesis of purine and pyrimidine nucleotides and non-essential amino acids (e.g., aspartate, alanine), meeting the demands for nucleic acid and protein synthesis [50]; (2) Glutamate contributes to glutathione (GSH) synthesis, scavenging reactive oxygen species (ROS) generated under metabolic stress to maintain redox homeostasis; (3) Ammonium ions produced during glutamine catabolism can neutralize intracellular acidosis caused by lactate accumulation, helping to maintain pH homeostasis; (4) Metabolites like acetyl-CoA can participate in epigenetic modifications such as histone acetylation, regulating oncogene expression.

2.2.3 Activation of Lipid Metabolism

While the traditional view held that cancer cells primarily relied on exogenous lipid uptake, recent evidence highlights a critical role for de novo lipid synthesis in tumorigenesis and progression [51, 52]. Sterol regulatory element-binding proteins 1 and 2 (SREBP1/2), central transcriptional regulators of lipogenesis, are constitutively activated in tumor cells via oncogenic pathways like MYC and AKT. This drives the overexpression of key enzymes, including fatty acid synthase (FASN), stearoyl-CoA desaturase 1 (SCD1), and 3-hydroxy-3-methylglutaryl-CoA reductase (HMGCR), enabling cancer cells to utilize acetyl-CoA to synthesize phospholipids and signaling molecules required for membrane biogenesis. This provides essential building blocks (fatty acids, cholesterol, phospholipids) for the rapid proliferation of tumor cells, supporting cell division and membrane integrity [53, 54]. Concurrently, lipid composition remodeling (e.g., phospholipid polyunsaturated fatty acid (PUFA) modification) modulates sensitivity to cell death pathways like ferroptosis and apoptosis, constructing a defensive barrier for cancer cells [55, 56]. Furthermore, aberrant cholesterol metabolism activation can regulate oncogenic signaling pathways such as Hedgehog and Wnt, further promoting malignant progression [57].

2.2.4 Activation of Nucleotide Metabolism

Reprogramming of nucleotide metabolism is a core strategy for cancer cells to meet the demands of rapid proliferation for DNA/RNA synthesis. Its key features include "activation of de novo synthesis pathways, adaptive enhancement of salvage pathways, and precise regulation of the nucleotide pool," forming a tightly interconnected network with other metabolic processes [58, 59].

The nucleotide requirement of tumor cells far exceeds that of normal cells. This metabolic reprogramming overturns the traditional paradigm ("normal tissues rely on salvage pathways, proliferating cells depend on de novo synthesis") by harnessing the synergistic action of both pathways to maintain nucleotide supply [60, 61]. Molecularly, this reprogramming is driven by oncogenes such as MYC and the PI3K/AKT/mTOR axis. In the de novo pathway, phosphoribosyl pyrophosphate synthetase (PRPS) catalyzes the formation of phosphoribosyl pyrophosphate (PRPP) as the foundational scaffold. Elevated expression of enzymes like glycinamide ribonucleotide formyltransferase (GART) and dihydroorotate dehydrogenase (DHODH) facilitates efficient synthesis of purine and pyrimidine nucleotides using glutamine, aspartate, and pentose phosphate pathway products. The salvage pathway acts complementarily; enzymes such as hypoxanthine phosphoribosyltransferase 1 (HPRT1) and adenine phosphoribosyltransferase (APRT) are upregulated in cancers like breast and colon cancer. They compensate for potential deficiencies in de novo synthesis within the nutrient-poor TME and can also utilize dietary nucleotides to accelerate tumor progression. Hydrolases like nudix hydrolase 1 (NUDT1) maintain nucleotide pool homeostasis and nucleic acid synthesis fidelity by clearing oxidized nucleotides [62]. Nucleotide metabolism reprogramming provides ample precursors for the uncontrolled DNA/RNA synthesis necessary for tumor cell proliferation. By regulating the dNTP/dNDP ratio, it supports tumor heterogeneity while avoiding cell death from excessive mutation. Furthermore, nucleotide metabolites can remodel the TME, promoting immune evasion by suppressing the function of T cells and NK cells [63].

2.3 ARID1A at the Intersection of Epigenetics and Metabolism

The functional loss of ARID1A, a core subunit of the SWI/SNF chromatin remodeling complex, extends far beyond mere epigenetic dysregulation. By directly modulating the chromatin accessibility of key metabolic genes, it serves as a central hub linking genomic stability, transcriptional programs, and cellular metabolic networks [64]. Consequently, ARID1A deficiency acts as an upstream initiating event that drives metabolic rewiring in cancer cells and exposes unique therapeutic vulnerabilities.

ARID1A finely regulates the transcription of its downstream target genes by maintaining chromatin openness at gene promoters and enhancer regions [65]. Under normal ARID1A function, the SWI/SNF complex is recruited to specific genomic loci (e.g., promoters of lipid metabolism genes such as Cpt1a and Acox1). By regulating histone modifications (e.g., sustaining the activating mark H3K4me3) and nucleosome positioning, it ensures appropriate expression of these genes in response to physiological signals [66].

However, upon ARID1A loss, the genome-wide chromatin accessibility landscape undergoes dramatic and rapid reconfiguration [67]. Studies show that acute depletion of ARID1A leads to a swift loss of chromatin accessibility at thousands of genomic sites, which are often enriched for binding sites of pluripotency transcription factors [68]. Accompanying this change, the histone acetyltransferase EP300 dissociates from chromatin, resulting in decreased local levels of histone H3K27 acetylation and subsequent downregulation of adjacent genes, including many involved in metabolism. This global disruption of the enhancer/promoter landscape constitutes the epigenetic basis for the metabolic reprogramming observed in ARID1A-deficient cells [69].

3. ARID1A Deficiency-Driven Specific Metabolic Reprogramming Mechanisms

As a key subunit of the SWI/SNF chromatin remodeling complex, ARID1A is not only a significant tumor suppressor but also a central regulator of cellular metabolic homeostasis. Its loss triggers widespread alterations in the epigenetic landscape, leading to a coordinated reprogramming

of multiple metabolic pathways. This reprogramming is not merely random metabolic dysregulation but rather a "compensatory" metabolic mode evolved by tumor cells to adapt to survival pressure and meet the demands of rapid proliferation. On one hand, it confers a survival advantage in nutrient-scarce environments; on the other, it exposes unique metabolic vulnerabilities, providing unprecedented "synthetic lethal" targets for the precision therapy of ARID1A-deficient tumors.

3.1 Glucose Metabolism Reprogramming

Reprogramming of glucose metabolism is a core strategy for tumor cells to adapt to microenvironmental stress and sustain malignant proliferation. ARID1A deficiency remodels the glucose metabolic network of cancer cells through multiple mechanisms including epigenetic regulation and signal pathway crosstalk, endowing them with survival advantages under nutrient deprivation while simultaneously exposing targetable synthetic lethal vulnerabilities. This section systematically dissects the molecular mechanisms by which ARID1A loss drives glucose metabolic aberrations, elucidates the adaptive characteristics under glucose-deprived conditions, and outlines potential therapeutic targets.

Research by Fengkun Zhang et al. highlighted the role of the ARID1A/USP9X/AMPK axis in the adaptation of ARID1A-controlled cancer cells to low-glucose environments [70]. Upon ARID1A loss-of-function, the repressive chromatin structure at the USP9X gene promoter dissociates, lifting its transcriptional silencing and leading to a significant upregulation of USP9X mRNA and protein levels. The abundant USP9X protein then exerts its deubiquitinase activity, directly targeting the PRKAA2 subunit of AMPK. By removing its ubiquitin chains, USP9X blocks AMPK degradation, resulting in abnormal stabilization and constitutive activation of the AMPK protein. As a cellular energy sensor kinase, activated AMPK remodels the glucose metabolic network to meet tumor cell proliferation demands. In the ARID1A-deficient state, the AMPK signaling pathway is maintained in a "pre-activated" vigilant state, equipping the cells with molecular preparedness for impending energy crises. This also provides a synthetic lethal target for ARID1A-deficient hepatocellular carcinoma.

Tao Xing et al. provided further insights into ARID1A-deficient liver cancer. Through CRISPR-Cas9 synthetic lethality screening and metabolic flux analysis, they confirmed that ARID1A deficiency directly suppresses the transcriptional expression of the key glycolytic gene PKM (pyruvate kinase). This disruption of the canonical Warburg effect redirects glucose metabolism from aerobic glycolysis towards the tricarboxylic acid (TCA) cycle and oxidative phosphorylation, while upregulating the expression of TCA cycle-related genes (e.g., ACO2, SDHA, FH). Consequently, the cells become highly dependent on mitochondrial respiration for energy. This ultimately renders ARID1A-deficient hepatocellular carcinoma cells and xenograft tumors highly sensitive to copper ion treatment and TCA cycle-targeting agents, creating a synthetic lethal effect that achieves tumor cell-specific killing [71].

Conversely, in lung cancer, ARID1A loss leads to chromatin decondensation and an open state at the promoter regions of glycolytic genes that are normally suppressed, creating conditions for transcription factor binding and subsequently initiating aberrant transcriptional programs for glycolysis. This is the core prerequisite for ARID1A deficiency-mediated glycolytic reprogramming in lung cancer. Research by Xiaoyu Liu et al. found that ARID1A deficiency in lung cancer upregulates the transcriptional levels of key genes across the entire glycolytic pathway. The expression of glycolytic regulators such as Pgam1, Pyruvate Kinase M (Pkm), and Pgk1 is significantly increased in ARID1A-deficient lung tumors. This enhances glycolytic metabolism, enabling efficient ATP production under hypoxic conditions and supporting metabolic plasticity to provide precursors for nucleic acid and amino acid synthesis, thereby promoting tumor progression

[72].

3.2 Amino Acid Metabolism Reprogramming

ARID1A deficiency drives tumor cell amino acid metabolism reprogramming by altering chromatin accessibility through epigenetic remodeling, leading to abnormal expression of metabolic enzymes and transporters. This, in turn, creates metabolic dependencies and therapeutic vulnerabilities.

In a study of multiple cancer types harboring ARID1A mutations, Kwan SY et al. found that ARID1A loss upregulates the expression of the MYC oncogene and its target gene SLC7A5 (LAT1), enhancing branched-chain amino acid uptake and activating the mTOR signaling pathway. Consequently, this renders tumor cells sensitive to PI3K/mTOR inhibitors and is associated with a phenotype of aberrant mTOR pathway activation [73].

Research by Ogiwara H et al. in 2019 on ARID1A-deficient gastric cancer revealed that ARID1A transcriptionally regulates the cystine/glutamate antiporter SLC7A11 (xCT) via chromatin remodeling. Its loss leads to downregulated SLC7A11 expression, reduced cystine uptake and cysteine availability, and subsequently lowered intracellular glutathione (GSH) levels. This results in tumor cells with constitutively low basal GSH, rendering them sensitive to the glutamate-cysteine ligase (GCLC) inhibitor and prone to apoptosis due to excessive accumulation of reactive oxygen species (ROS) [31]. Furthermore, Mariko Sasaki et al., in a study on ARID1A-deficient diffuse-type gastric cancer, found that ARID1A loss lowers GSH levels via SLC7A11 downregulation. This confers selective sensitivity to the GSH inhibitor APR-246, the GCLC inhibitor buthionine sulfoximine, and the SLC7A11 inhibitor erastin, further validating the universality of glutathione metabolism reprogramming in ARID1A-deficient tumors [74].

In ARID1A-deficient ovarian cancer, Li Z et al. discovered that the ARID1A protein can directly bind to aspartate transcarbamylase (ATCase), a key regulatory enzyme in the de novo pyrimidine synthesis pathway. ARID1A deficiency leads to dysregulated ATCase activity, creating a tumor cell dependency on the pyrimidine synthesis pathway. This ultimately sensitizes the cells to the DHODH inhibitor teriflunomide, and combining it with an ATR inhibitor enhances antitumor efficacy and achieves sustained tumor regression [75].

Shuai Wu et al., in a 2021 study on ARID1A-deficient ovarian clear cell carcinoma, reported that ARID1A loss relieves the transcriptional repression exerted by the SWI/SNF complex on glutaminase GLS1. This leads to significant upregulation of GLS1 expression, enhancing glutamine flux through the TCA cycle to preferentially support aspartate synthesis for nucleotide production. Consequently, tumor cells develop glutamine addiction and exhibit high sensitivity to the GLS1 inhibitor CB-839. Combining CB-839 with a PD-L1 antibody enhances antitumor effects [21].

Providing further insight, Hao Nie et al. in a 2025 study on ARID1A-mutant ovarian cancer found that ARID1A mutation creates a dependency on alanine by modulating alanine transporters, thereby elevating intracellular alanine levels. ARID1A directly represses the alanine importer SLC38A2 while promoting the alanine exporter SLC7A8. ARID1A deficiency leads to the selective utilization of specific alanine transporters by tumor cells, forming a metabolic vulnerability and providing a novel rationale for therapies targeting amino acid transporters [76].

3.3 Lipid Metabolism Reprogramming

Lipid metabolism reprogramming is an area of growing interest. Distinct from generalized metabolic activation, the alterations in lipid metabolism induced by ARID1A deficiency are characterized by striking tumor type specificity and mechanistic complexity. These changes do not

simply enhance lipid synthesis but involve precise transcriptional rearrangements leading to dysregulation in pathways including fatty acid synthesis, fatty acid oxidation (FAO), cholesterol synthesis (mevalonate pathway), and arachidonic acid metabolism. While these adaptations provide energy for tumor cell proliferation, invasion, and therapy resistance, they also expose targetable metabolic vulnerabilities, offering novel entry points for synthetic lethal therapeutic strategies.

In endometrial cancer, Yu Lu et al. found that ARID1A deficiency is closely associated with aberrant activation of Sterol Regulatory Element-Binding Protein 1 (SREBP1), significantly enhancing intracellular fatty acid synthesis by upregulating fatty acid synthase (FAS) expression, thereby disrupting lipid homeostasis. Conversely, Peroxisome Proliferator-Activated Receptor α (PPARα) can upregulate ARID1A expression to suppress SREBP1 and FAS activity, restoring lipid balance. This ultimately leads to significantly accelerated tumor cell proliferation. The PPARα activator irbesartan can effectively inhibit tumor growth by modulating the ARID1A-SREBP1-FAS axis, suggesting a potential therapeutic target for this cancer type [77].

In pancreatic cancer research, Tzu-Lei Kuo et al. discovered that ARID1A directly binds to the FASN promoter to repress its transcription. Upon ARID1A loss, this repression is lifted, enhancing FASN-mediated fatty acid synthesis. The upregulated FASN also activates the ERK signaling pathway. Furthermore, ARID1A deficiency synergizes with KRAS mutation to enhance immune cell infiltration in the tumor microenvironment. Consequently, pancreatic cancer exhibits significantly enhanced fatty acid metabolic activity. The FASN inhibitor TVB-2640 inhibits tumor cell viability in a dose-dependent manner and slows in vivo tumor progression. Combining it with immune checkpoint inhibitors (ICIs) further enhances antitumor efficacy and improves survival in model mice [78].

In a 2019 study on hepatocellular carcinoma, Yu-Lan Qu et al. reported that liver-specific ARID1A deficiency downregulates PPARα, a key transcription factor for FAO, reducing the expression of key FAO genes. Simultaneously, it decreases H3K4me3 modification and chromatin accessibility at FAO-related gene promoters, suppressing the FAO process. This renders mice more susceptible to high-fat diet (HFD)-induced hepatic steatosis, insulin resistance, and inflammation, with significantly elevated liver function markers (ALT, AST). Overexpressing PPARα can restore FAO activity, alleviating lipid accumulation and insulin resistance [79].

In colorectal cancer, Luying Cui et al. found that ARID1A deficiency, by reducing chromatin accessibility, specifically downregulates the expression of the rate-limiting arachidonic acid metabolism enzymes PTGS1 (COX-1) and PTGS2 (COX-2), leading to an arachidonic acid metabolism defect. Tumor cells then depend on the remaining PTGS activity for survival. As a result, aspirin (a PTGS1/2 inhibitor) significantly inhibits the growth of ARID1A-deficient colorectal cancer cells, reduces vasculogenic mimicry formation, restores $CD8^+$ T cell activity, and sensitizes tumors to immunotherapy (ICIs) and anti-angiogenic therapy. In clinical cohorts, ARID1A-deficient patients receiving combination therapy including aspirin showed a significantly higher objective response rate (ORR) [80].

In ovarian clear cell carcinoma, Wei Zhou et al. discovered that ARID1A deficiency downregulates the expression of the mevalonate pathway rate-limiting enzymes HMGCR and HMGCS1, making tumor cells dependent on the residual activity of this pathway. Inhibiting the mevalonate pathway reduces geranylgeranyl pyrophosphate (GGPP) production, leading to aberrant RhoA prenylation and subsequently inducing tumor cell pyroptosis. Consequently, statins (e.g., simvastatin) significantly inhibit the growth of ARID1A-deficient ovarian clear cell carcinoma. Combining them with anti-PD-L1 antibodies synergistically enhances antitumor immunity, reduces ascites formation, and prolongs survival in model mice. In clinical samples, HMGCR/HMGCS1 expression in ARID1A-deficient patients negatively correlates with progression-free survival (PFS) [81].

3.4 Nucleotide Metabolism Reprogramming

Nucleotide metabolism reprogramming is a key characteristic enabling tumor cells to meet the demands of rapid proliferation and maintain genomic stability. ARID1A deficiency can dysregulate nucleotide metabolic pathways through various molecular mechanisms, exhibiting both cancer type-specific and shared regulatory logic.

In a study on ARID1A-deficient colorectal cancer, Cheng Xiang et al. found that ARID1A, functioning as a tumor suppressor within the SWI/SNF chromatin remodeling complex, plays a role in DNA repair. Its loss compromises cellular DNA repair capacity, creating a synthetic lethal interaction with fluorouridine (FUDR). This is accompanied by decreased Chk2 phosphorylation and exacerbated DNA damage accumulation. The inability to repair damage via nucleotide metabolism pathways triggers nucleotide metabolism reprogramming. Consequently, ARID1A-deficient colorectal cancer cells exhibit significantly increased sensitivity to FUDR, elevated DNA damage and apoptosis rates, and heightened susceptibility to pyrimidine metabolism-targeted chemotherapy. In both organoid and nude mouse xenograft models, FUDR effectively inhibits the growth of such tumors without significant toxicity [82].

In ARID1A-deficient liver cancer, Lan Wang et al. identified two core mechanisms driving nucleotide metabolism reprogramming: (1) ARID1A loss reduces chromatin accessibility at the promoters of nucleotide excision repair (NER)-related genes, downregulating their expression, while concurrently promoting the expression of the aristolochic acid metabolism-activating gene Nqo1, leading to increased DNA adduct formation. The defective NER pathway prevents DNA damage repair and causes mutation accumulation, indirectly disrupting nucleotide metabolic homeostasis and potentially inducing Ctnnb1 mutations for synergistic effects. (2) ARID1A deficiency leads to decreased BRG1 protein expression, weakening its interaction with RAD21, disrupting three-dimensional chromatin structure, and indirectly modulating the expression of metabolism-related genes to facilitate reprogramming. Ultimately, this results in increased hepatocellular carcinoma incidence, earlier onset, greater accumulation of DNA adducts and gene mutations, enhanced tumor cell metastatic potential, and abnormal activation of intrahepatic cell populations and related signaling pathways [83].

In a pan-cancer study (including melanoma, colorectal, and endometrial cancers) on ARID1A deficiency, Diana C. Hargreaves et al. discovered that ARID1A loss leads to nuclear R-loop accumulation and the generation of cytoplasmic single-stranded DNA, subsequently activating the STING-type I interferon pathway and establishing an ARID1A-IFN gene signature. Although this pathway primarily regulates anti-tumor immunity, it can indirectly modulate the expression of nucleotide metabolism-related genes, affecting the crosstalk between nucleotide synthesis and DNA damage repair, thereby contributing to nucleotide metabolism reprogramming. Inhibitors of the cBAF complex or SMARCA4/2 can mimic this effect. This ultimately leads to increased infiltration of immune cells such as $CD8^+$ T cells and NK cells, and a higher cytotoxicity score in ARID1A-deficient tumors. Patients with high ARID1A-IFN signature scores have longer overall survival, and this signature correlates with complete response to immune checkpoint blockade (ICB) therapy in gastric cancer. Overexpression of R-loop degrading enzymes or cytoplasmic DNases can partially reverse the related phenotypes [84].

4. Immune Microenvironment Remodeling Mediated by Metabolic Reprogramming

ARID1A, as a core subunit of the SWI/SNF chromatin remodeling complex, is frequently deficient across various solid tumors. Its loss drives extensive and specific transcriptional reprogramming, resulting in systemic remodeling of glucose, lipid, and amino acid metabolism. These metabolic alterations profoundly shape the composition and function of the tumor immune

microenvironment (TIME). On one hand, they create a proliferative advantage for the tumor cells themselves; on the other, they reshape their interactions with the immune system. The metabolic vulnerabilities and TIME features exhibited vary across different tumor types [85].

4.1 Immune Microenvironment Alterations Mediated by Glucose Metabolism Remodeling

Enhanced glucose metabolism, characterized by the Warburg effect, serves not only as an energetic foundation for rapid tumor cell proliferation but also as a core strategy for actively shaping an immunosuppressive TIME. This is primarily achieved by creating a local environment of "nutrient deprivation" and "microenvironment acidification," which systemically suppresses anti-tumor immune responses.

ARID1A deficiency remodels the glucose metabolic network via epigenetic regulation. Key features include: suppression of the transcriptional activity of the key glycolytic gene PKM, shifting energy metabolism from glycolysis dependence towards reliance on the tricarboxylic acid (TCA) cycle and oxidative phosphorylation (OXPHOS); activation of the AMPK signaling pathway to adapt to glucose-deprived microenvironments; and induction of abnormal mitochondrial biogenesis, manifesting as enhanced OXPHOS but reduced ATP generation efficiency. This metabolic reprogramming exerts a dual modulation on the TIME through energy competition, immunogenicity regulation, and remodeling of the inflammatory milieu.

In liver cancer, ARID1A deficiency-mediated attenuation of glycolysis and enhancement of the TCA cycle leads to disordered glucose metabolism in liver tissue. This directly reduces glucose uptake by immune cells such as macrophages and T cells, inhibiting their activation and the secretion of pro-inflammatory cytokines like TNF-α and IFN-γ, thereby exacerbating the disturbance of the local inflammatory microenvironment [71]. However, concurrently, the upregulation of key TCA cycle enzymes (ACO2, SDHA, FH) renders tumor cells highly sensitive to the copper ionophore elesclomol. This agent, by inducing cuproptosis-associated DNA damage (γH2AX accumulation), significantly enhances the immunogenicity of tumor cells, providing a molecular basis for synergy with immune checkpoint inhibitors (ICIs). Furthermore, ARID1A deficiency stabilizes AMPKα2 and activates the AMPK pathway by relieving HDAC1-mediated transcriptional repression of USP9X. This allows liver cancer cells to survive under glucose-deprived conditions. Such metabolic adaptability intensifies the energy competition between tumor cells and immune cells, indirectly suppressing immune cell function. The AMPK inhibitor Compound C can effectively block this adaptive mechanism, alleviating energy competition and restoring the activation potential of immune cells [70].

Pan-cancer studies confirm that ARID1A deficiency can induce abnormal mitochondrial biogenesis, characterized by increased mitochondrial numbers and enhanced OXPHOS activity coupled with insufficient ATP production, rendering tumor cells dependent on Polo-like kinase 1 (PLK1) to maintain mitochondrial functional homeostasis. PLK1 inhibitors further amplify tumor cell immunogenicity by inducing mitochondrial membrane depolarization and apoptosis, promoting dendritic cell (DC) uptake and presentation of tumor antigens, and enhancing the recognition efficiency of $CD8^+$ T cells [86]. This "metabolic aberration-enhanced immunogenicity" regulatory axis offers novel therapeutic targets for the combinatorial treatment of ARID1A-deficient tumors.

4.2 Immune Microenvironment Alterations Mediated by Amino Acid Metabolism Remodeling

ARID1A deficiency, through SWI/SNF complex-mediated epigenetic regulation, establishes a mode of amino acid metabolism reprogramming centered on "enhanced glutamine metabolism, disordered cysteine-GSH synthesis, alanine accumulation, and arachidonic acid metabolism

dependency" [4, 6, 7, 9]. These metabolic changes facilitate precise remodeling of the immune microenvironment via nutrient competition regulation, oxidative stress modulation, and immune cell function manipulation, serving as a critical molecular bridge for reversing immunosuppression.

4.2.1 Glutamine Metabolism

Enhanced glutamine metabolism is a core metabolic feature of ARID1A-deficient ovarian clear cell carcinoma. ARID1A loss relieves the transcriptional repression of glutaminase 1 (GLS1), leading to its upregulation, which increases glutamine flux through the TCA cycle to provide precursors for tumor cell biosynthesis. The GLS1 inhibitor CB-839 not only impairs the energy supply of tumor cells by blocking glutamine metabolism but also relieves glutamine-mediated suppression of $CD8^+$ T cell proliferation, reduces the proportion of $PD\text{-}1^+$ exhausted T cells, and significantly enhances anti-tumor immune responses when combined with an anti-PD-L1 antibody [21].

4.2.2 Cysteine-GSH Metabolic Dysregulation

Dysregulated cysteine-GSH metabolism is another key metabolic event mediated by ARID1A deficiency. ARID1A deficiency downregulates the expression of the cystine transporter SLC7A11, reducing intracellular cysteine availability and leading to insufficient glutathione (GSH) synthesis, ultimately triggering ROS accumulation. This oxidative stress state can directly induce tumor cell apoptosis and indirectly ameliorate the immunosuppressive microenvironment. GSH inhibitors can further amplify ROS-mediated tumor cell killing and enhance the antigen-presenting function of DCs and the cytotoxic activity of $CD8^+$ T cells [31].

4.2.3 Aberrant Alanine Accumulation

Aberrant alanine accumulation is a unique metabolic phenotype in ARID1A-deficient ovarian clear cell carcinoma models. ARID1A deficiency directly suppresses the expression of the alanine exporter SLC7A8 while activating the alanine importer SLC38A2, resulting in significant intracellular alanine accumulation. Mechanistic studies show that inhibiting SLC38A2 reduces the alanine ratio between tumor and non-tumor tissues and increases alanine content within $CD45^+$ immune cells, thereby providing energy and biosynthetic precursors for immune cell proliferation and function [76]. Furthermore, SLC38A2 inhibition enhances the killing activity of CAR-T cells against ARID1A-deficient tumor cells, and overexpressing SLC38A2 in CAR-T cells further improves this efficacy, offering a new direction for optimizing adoptive cell therapies.

4.3 Immune Microenvironment Alterations Mediated by Lipid Metabolism Remodeling

Lipid metabolism reprogramming is one of the most characteristic metabolic changes in ARID1A-deficient tumors, primarily involving fatty acid synthesis, oxidation, and lipid derivative metabolism. It remodels the TME by regulating immune cell infiltration, activation, and inflammatory cytokine secretion, representing a deeply studied area with broad coverage across cancer types. During tumorigenesis and progression, ARID1A deficiency can establish a lipid metabolic profile characterized by "enhanced fatty acid synthesis and suppressed β-oxidation" by relieving the epigenetic repression of the fatty acid synthase (FASN) promoter and downregulating the transcriptional activity of peroxisome proliferator-activated receptor α (PPARα). It may also induce dependency on arachidonic acid metabolism and the mevalonate pathway. This reprogramming pattern achieves precise modulation of the immune microenvironment through lipid mediator regulation, inflammatory pathway activation, and stromal microenvironment remodeling.

4.3.1 Fatty Acid Synthesis and Oxidation

In pancreatic cancer, ARID1A deficiency relieves the transcriptional repression of the FASN gene via epigenetic mechanisms, driving metabolic reprogramming. As a key component of the SWI/SNF chromatin remodeling complex, loss of ARID1A function alters chromatin accessibility at the FASN promoter region, leading to significant upregulation of FASN expression. The long-chain fatty acids synthesized by FASN not only meet tumor proliferation demands but also sustainably activate oncogenic signaling pathways like ERK/MAPK through modifications such as protein palmitoylation. Furthermore, this metabolic shift creates favorable conditions for the infiltration of B cells, $CD4^+$ T cells, $CD8^+$ T cells, and neutrophils, enhancing the recruitment efficiency of anti-tumor immune cells [78].

4.3.2 Arachidonic Acid Metabolism

Arachidonic acid metabolism represents another crucial aspect of lipid metabolism reprogramming in ARID1A-deficient tumors, directly regulating immune cell function and vasculogenic mimicry formation. In colorectal cancer, ARID1A deficiency downregulates the expression of prostaglandin-endoperoxide synthase 1/2 (PTGS1/2), making tumor cells reliant on residual arachidonic acid metabolism for survival. The arachidonic acid metabolite PGE2 can suppress $CD8^+$ T cell activation and promote vasculogenic mimicry. In contrast, the arachidonic acid metabolism inhibitor aspirin significantly reduces PGE2 levels, activates $CD8^+$ T cells (increasing IFN-γ and Granzyme B secretion), and inhibits vasculogenic mimicry, synergizing with PD-1 inhibitors to enhance anti-tumor effects [80].

4.3.3 Mevalonate Metabolism

Dependency on the activated mevalonate pathway is another significant metabolic feature of ARID1A-deficient ovarian clear cell carcinoma. Downregulation of its key enzymes, HMGCR and HMGCS1, renders tumor cells highly sensitive to pathway inhibitors such as simvastatin [5]. Mechanistically, inhibition of the mevalonate pathway induces RhoA deprenylation, activates the NLRP3 inflammasome, and promotes the release of inflammatory factors like HMGB1, IL-1β, and IL-18, which can directly enhance the cytotoxicity of $CD8^+$ T cells. Additionally, pathway inhibition reduces the activation of immunosuppressive stromal cells, decreases the efficiency of tumor vasculogenic mimicry, and improves immune cell infiltration into the tumor core [81]. In endometrial cancer, ARID1A deficiency-mediated downregulation of PPARα can activate the expression of antioxidant enzymes (SOD2, GPX1), mitigating ROS-mediated damage to immune cell function and sustaining the proliferation and cytotoxic activity of effector T cells [77].

4.4 Immune Microenvironment Alterations Mediated by Nucleotide Metabolism Remodeling.

ARID1A deficiency establishes a unique pattern of nucleotide metabolism reprogramming by modulating the pyrimidine synthesis pathway, the nucleotide excision repair (NER) system, and R-loop metabolism. These metabolic abnormalities reshape the tumor immune microenvironment through DNA damage accumulation, innate immune pathway activation, and immune synergistic effects, serving as a central hub connecting metabolic reprogramming and immune activation.

Enhanced pyrimidine synthesis is a key metabolic vulnerability in ARID1A-deficient ovarian and endometrial cancers. ARID1A negatively regulates the de novo pyrimidine synthesis pathway by binding via its C-terminus to aspartate transcarbamylase (ATCase), encoded by the CAD gene.

ARID1A loss leads to increased CAD protein levels and phosphorylation, significantly boosting pyrimidine synthesis flux. Dihydroorotate dehydrogenase (DHODH), a key enzyme in this pathway, is targeted by the inhibitor teriflunomide, which induces DNA damage (γH2AX accumulation) in ARID1A-deficient tumor cells. Combining teriflunomide with the ATR inhibitor AZD6738 further amplifies DNA damage, achieving tumor regression in patient-derived xenograft (PDX) models. Mechanistically, the accumulation of DNA damage significantly enhances tumor cell immunogenicity, promotes dendritic cell (DC) maturation and antigen presentation, and provides a synergistic target for immune checkpoint blockade (ICB) therapy [75].

NER deficiency is another key metabolic phenotype mediated in ARID1A-deficient liver cancer models. ARID1A deficiency transcriptionally represses the expression of NER key genes (e.g., Xpa, Xpc) by reducing chromatin accessibility at their promoters, thereby impairing the cell's ability to repair DNA adducts induced by agents like aristolochic acid (AA). Concurrently, ARID1A loss upregulates Nqo1 expression, enhancing AA bioactivation and further increasing the DNA damage burden [83]. This dual effect of "enhanced DNA damage and impaired repair capacity" triggers the release of inflammatory factors (e.g., TNF-α), promoting the infiltration of immune cells such as macrophages, T cells, and DCs. Simultaneously, it reduces the recruitment of myeloid-derived suppressor cells (MDSCs), thereby alleviating the immunosuppressive microenvironment [83].

Activation of the cytoplasmic DNA-sensing pathway via R-loop accumulation is a core mechanism by which ARID1A deficiency regulates innate immunity. ARID1A loss causes substantial R-loop accumulation, releasing cytoplasmic single-stranded DNA (ssDNA) and RNA:DNA hybrids. These molecules act as damage-associated molecular patterns (DAMPs) to activate the cGAS-STING-type I interferon pathway. This activation induces IFNβ secretion and the expression of interferon-stimulated genes (ISGs), significantly enhancing the infiltration, proliferation ($Ki67^+$), and cytotoxicity ($IFN\gamma^+$, $GZMB^+$) of $CD8^+$ T cells. It also reduces the enrichment of exhausted T cells with $PD\text{-}1^+$ and $Tim3^+$ phenotypes, markedly improving the efficacy of ICB therapy [84]. In melanoma and colorectal cancer models, strategies targeting R-loop metabolism or the STING pathway have been shown to effectively enhance anti-tumor immune responses in ARID1A-deficient tumors, providing a new direction for innate immunity-targeted therapies.

FUDR-mediated suppression of pyrimidine synthesis further expands the clinical translational potential of nucleotide metabolism reprogramming. ARID1A deficiency, by downregulating Chk2 phosphorylation, weakens DNA damage repair capacity, rendering colorectal cancer cells highly sensitive to FUDR. FUDR inhibits thymidylate synthase (TS) activity to block pyrimidine synthesis, exacerbating DNA damage accumulation and inducing tumor cell apoptosis (upregulation of cleaved PARP and cleaved caspase-3). Concurrently, DNA damage signals can be further amplified through aberrant chromatin organization, activating anti-tumor immune responses. In colorectal cancer models, the cytotoxic effect of FUDR is significantly superior to that of the traditional chemotherapeutic agent 5-fluorouracil (5-FU), and it exhibits synergistic efficacy when combined with ICB [82]. This regulatory axis of "metabolic inhibition-immune activation" offers a new option for the precision treatment of ARID1A-deficient colorectal cancer.

5. Therapeutic Strategies Targeting ARID1A Deficiency-Driven Metabolic Reprogramming and the Immune Microenvironment

The lipid, glucose, amino acid, and nucleotide metabolism reprogramming mediated by ARID1A deficiency not only confers survival advantages to tumor cells but also establishes an immune evasion barrier by reshaping the immune microenvironment. Targeted interventions against these

metabolic vulnerabilities can directly inhibit tumor proliferation while simultaneously reversing the immunosuppressive microenvironment, providing synergistic targets for combination immunotherapy. In response to the "metabolic vulnerabilities" arising from ARID1A loss, current therapeutic strategies are shifting from traditional cytotoxic agents toward precision metabolic interventions based on a synthetic lethality rationale.

5.1 Targeting Glucose Metabolism Reprogramming

5.1.1 AMPK Pathway Inhibitors

ARID1A deficiency activates the AMPK signaling pathway via the USP9X-AMPKα2 axis, enabling liver cancer cells to adapt to glucose-deprived microenvironments and compete with immune cells for energetic substrates. The AMPK inhibitor Compound C specifically blocks this adaptive mechanism. On one hand, it inhibits the survival of tumor cells under nutrient scarcity; on the other, it alleviates the pressure of energy competition, restoring glucose uptake and activation functions in $CD8^+$ T cells and macrophages. In liver cancer cell lines and xenograft models, Compound C treatment significantly reduces the proliferation rate of ARID1A-deficient tumors and prolongs the survival of tumor-bearing mice. When combined with an anti-PD-1 antibody, it further enhances effector T cell infiltration and improves the treatment response rate [70]. The core advantage of this strategy lies in simultaneously targeting tumor metabolic adaptation and immunosuppression, providing a novel combinatorial regimen for ARID1A-deficient liver cancer with aberrant glucose metabolism.

5.1.2 Elesclomol

ARID1A deficiency renders liver cancer cells dependent on the TCA cycle for energy. The upregulation of key TCA cycle enzymes (ACO2, SDHA) enhances mitochondrial respiratory chain activity, making tumor cells highly sensitive to copper ion-mediated cell death. Elesclomol, a copper ionophore, promotes copper enrichment within mitochondria, inducing Fe-S cluster protein degradation and lipid peroxidation, while concurrently causing DNA damage and enhancing tumor immunogenicity. In liver cancer PDX models, elesclomol treatment significantly inhibits the growth of ARID1A-deficient tumors. Combined with an anti-PD-1 antibody, it further amplifies the effect of immunogenic cell death, improving DC antigen presentation efficiency and the depth of effector T cell infiltration [71]. This strategy operates through a dual mechanism of "metabolic targeting and immunogenic activation," offering a precise therapeutic direction for TCA cycle-dependent, ARID1A-deficient liver cancer.

5.2 Targeting Amino Acid Metabolism Reprogramming

The amino acid metabolism reprogramming mediated by ARID1A deficiency is centered on "glutamine dependency, cysteine-GSH dysregulation, alanine accumulation, and arachidonic acid (AA) metabolism dependency." Corresponding targeting strategies achieve the dual objectives of tumor suppression and immune microenvironment remodeling by blocking nutrient supply, amplifying oxidative stress, or modulating amino acid transport, often exhibiting significant synergy when combined with immunotherapy. Glutamine represents the most critical metabolic vulnerability in ARID1A-deficient tumors, directly linked to energy supply and redox homeostasis.

5.2.1 GLS1 Inhibitors

Upregulation of the enzyme glutaminase GLS1 is a key metabolic vulnerability in

ARID1A-deficient ovarian clear cell carcinoma. GLS1 catalyzes the conversion of glutamine to glutamate, providing precursors for the TCA cycle and nucleotide synthesis. The GLS1 inhibitor CB-839 specifically blocks this metabolic pathway, inhibiting tumor cell biosynthesis and energy supply on one hand, and relieving glutamine-mediated suppression of $CD8^+$ T cell proliferation while reducing the proportion of $PD\text{-}1^+$ exhausted T cells on the other. In ovarian clear cell carcinoma xenograft models, CB-839 monotherapy significantly inhibits tumor growth. When combined with an anti-PD-L1 antibody, it further enhances the infiltration of $IFN\gamma^+GZMB^+$ effector T cells and prolongs the survival of tumor-bearing mice [21].

5.2.2 GSH Metabolism Inhibitors

ARID1A deficiency downregulates the cystine transporter SLC7A11, leading to insufficient GSH synthesis and ROS accumulation, rendering tumor cells highly sensitive to GSH inhibitors. GSH inhibitors (e.g., APR-246, BSO) further deplete intracellular GSH levels, amplifying ROS-mediated tumor cell apoptosis. Concurrently, ROS accumulation promotes DC maturation and the release of inflammatory cytokines (TNF-α, IL-6), thereby ameliorating the immunosuppressive microenvironment. In models of ARID1A-deficient tumors such as ovarian clear cell carcinoma and colorectal cancer, APR-246 monotherapy effectively inhibits tumor proliferation. Combined with anti-PD-L1 antibodies, it significantly enhances the cytotoxic activity of $CD8^+$ T cells and reduces the infiltration of Treg cells and MDSCs [31]. APR-246, functioning dually as a p53 activator and a GSH inhibitor, has demonstrated translational potential in combination with immunotherapy across various solid tumors, providing a novel rationale for multi-targeted therapy in ARID1A-deficient cancers.

5.2.3 SLC38A2 (Alanine Transporter) Inhibitors

ARID1A deficiency activates the alanine importer SLC38A2, causing intracellular alanine accumulation that fuels tumor cell proliferation while simultaneously competing with immune cells for alanine. SLC38A2 inhibitors specifically block alanine uptake, suppressing tumor cell biosynthesis while increasing alanine content within $CD45^+$ immune cells to provide energetic support for effector T cell proliferation and function. In ovarian clear cell carcinoma models, SLC38A2 inhibitor monotherapy significantly reduces tumor burden. Its combination with anti-PD-L1 antibodies synergistically enhances $CD8^+$ T cell infiltration and killing activity. When combined with CAR-T cell therapy, it further improves the recognition and killing efficiency of CAR-T cells against tumor cells. Moreover, overexpressing SLC38A2 in CAR-T cells amplifies this synergistic effect [76]. This strategy, by modulating amino acid transport balance, achieves the dual goals of tumor metabolic inhibition and immune enhancement, offering a new direction for optimizing adoptive cell therapies.

5.3 Targeting Lipid Metabolism Aberrations

ARID1A deficiency establishes a metabolic profile characterized by "enhanced lipid synthesis coupled with dependency on specific lipid pathways" through FASN activation, PPARα downregulation, and pathway-dependent expression. Strategies targeting this reprogramming focus on inhibiting lipid synthesis, activating lipid catabolism, or blocking dependency pathways, while simultaneously modulating immune cell function through lipid mediators to achieve synergistic tumor suppression and immune activation.

5.3.1 FASN Inhibitors

ARID1A loss relieves the epigenetic repression of FASN, promoting fatty acid synthesis and accumulation to provide lipid precursors for tumor cell proliferation, while concurrently suppressing immune cell infiltration. The FASN inhibitor TVB-2640 specifically blocks fatty acid synthesis. It inhibits tumor cell lipid accumulation and proliferation on one hand, and reduces tumor stromal activation on the other, creating favorable conditions for the infiltration of B cells, $CD4^+$/$CD8^+$ T cells, and neutrophils. In pancreatic cancer KPC mouse models, TVB-2640 treatment significantly inhibits tumor growth and increases the proportion of infiltrating effector T cells. Combined with an anti-PD-L1 antibody, it further enhances the anti-tumor immune response and prolongs mouse survival [78]. TVB-2640 has demonstrated favorable tolerability in multiple clinical trials for solid tumors, positioning it as a potential agent for the precision treatment of ARID1A-deficient pancreatic cancer.

5.3.2 PPARα Agonists

ARID1A deficiency downregulates PPARα expression, suppressing fatty acid β-oxidation (FAO), which leads to lipid accumulation and ROS generation that impair immune cell function. The PPARα agonist Fenofibrate activates FAO, reducing lipid accumulation and ROS generation, while upregulating the expression of antioxidant enzymes (SOD2, GPx1) to protect effector T cells from ROS-mediated functional damage. In endometrial cancer models, Fenofibrate treatment significantly ameliorates lipid metabolic dysregulation in ARID1A-deficient tumors and enhances the proliferation and cytotoxic activity of $CD8^+$ T cells. Its combination with anti-PD-L1 antibodies further improves the response rate to immunotherapy [77].

5.3.3 Mevalonate Pathway Inhibitors

ARID1A-deficient ovarian clear cell carcinoma exhibits high dependency on the mevalonate pathway. Downregulation of its key enzymes, HMGCR and HMGCS1, renders tumor cells sensitive to pathway inhibitors such as atorvastatin and simvastatin. Simvastatin inhibits mevalonate synthesis, inducing RhoA deprenylation, activating the NLRP3 inflammasome, and promoting the release of inflammatory factors (HMGB1, IL-1β, IL-18) that can directly enhance the cytotoxicity of $CD8^+$ T cells. In ovarian clear cell carcinoma xenograft models, simvastatin treatment significantly inhibits tumor growth and increases $CD8^+$ T cell infiltration. Combined with anti-PD-L1 antibodies, it synergistically enhances the anti-tumor immune response and reduces tumor vasculogenic mimicry formation [81]. As a commonly used clinical lipid-lowering drug with a well-established safety and tolerability profile, the combination of simvastatin with immunotherapy holds promise for rapid translation into clinical regimens for ARID1A-deficient ovarian clear cell carcinoma.

5.3.4 Arachidonic Acid Metabolism Inhibitors

ARID1A deficiency downregulates key enzymes in arachidonic acid (AA) metabolism, PTGS1/2 (prostaglandin-endoperoxide synthase 1/2), rendering colorectal cancer cells dependent on residual AA metabolic activity for survival. Concurrently, reduced prostaglandin E2 (PGE2) synthesis relieves its suppressive effect on $CD8^+$ T cells. AA metabolism inhibitors, such as aspirin, further inhibit PTGS activity, decreasing PGE2 production while increasing the proportion of $IFN\gamma^+GZMB^+$ effector T cells and reducing the $PD\text{-}1^+Tim3^+$ exhausted phenotype. In colorectal cancer models, aspirin monotherapy significantly inhibits the growth of ARID1A-deficient tumors. When combined with an anti-PD-L1 antibody, it further enhances the efficacy of immunotherapy

and prolongs the survival of tumor-bearing mice [80]. This strategy leverages a clinically available agent, offering advantages of low cost and a favorable safety profile, thereby providing a readily translatable combinatorial treatment regimen for ARID1A-deficient colorectal cancer.

5.4 Targeting Nucleotide Metabolism

ARID1A deficiency establishes a metabolic profile characterized by "nucleotide synthesis dependency" and "defective DNA damage repair" through enhanced pyrimidine synthesis, NER (Nucleotide Excision Repair) deficiency, and R-loop accumulation. Strategies targeting this reprogramming focus on blocking pyrimidine synthesis, amplifying DNA damage, or activating innate immune pathways. When combined with immunotherapy, these approaches can enhance efficacy through a synergistic "metabolic inhibition–immune activation" effect.

5.4.1 DHODH Inhibitors

ARID1A deficiency enhances de novo pyrimidine synthesis. Dihydroorotate dehydrogenase (DHODH), a key enzyme in this pathway, is targeted by its inhibitor teriflunomide, which specifically blocks uridine monophosphate synthesis, leading to γH2AX accumulation and inducing tumor cell DNA damage. Teriflunomide monotherapy inhibits tumor growth in models of ARID1A-deficient cancers such as ovarian and endometrial carcinoma. When combined with the ATR inhibitor AZD6738, it further amplifies DNA damage and enhances tumor immunogenicity. In PDX models, the combination of teriflunomide and AZD6738 with an anti-PD-L1 antibody achieves tumor regression, significantly increasing $CD8^+$ T cell infiltration and cytotoxic activity [75].

5.4.2 Pyrimidine Synthesis Inhibitor

ARID1A deficiency downregulates Chk2 phosphorylation, weakening DNA damage repair capacity and rendering colorectal cancer cells highly sensitive to fluorouridine (FUDR). FUDR inhibits thymidylate synthase (TS) activity, blocking thymidine synthesis, exacerbating DNA damage accumulation, and inducing tumor cell apoptosis (upregulation of cleaved PARP and cleaved caspase-3). Concurrently, DNA damage signals can activate the release of inflammatory factors, ameliorating the immunosuppressive microenvironment. In colorectal cancer models, the cytotoxic effect of FUDR is significantly superior to that of 5-fluorouracil (5-FU). Combined with an anti-PD-L1 antibody, it synergistically enhances effector T cell infiltration and improves the treatment response rate [82].

5.4.3 ATM/Chk2 Pathway Inhibitors

ARID1A-deficient tumors rely on the ATM/Chk2 pathway for DNA damage repair. The ATM inhibitor KU-55933 specifically blocks this pathway, amplifying DNA damage accumulation while concurrently activating the cGAS-STING-Type I interferon (IFN) pathway, inducing IFNβ secretion and interferon-stimulated gene (ISG) expression. In pan-cancer models, KU-55933 monotherapy inhibits the growth of ARID1A-deficient tumors. Combined with an anti-PD-L1 antibody, it significantly enhances $CD8^+$ T cell infiltration and proliferation and reduces the proportion of cells with an exhaustion phenotype [86].

5.4.4 STING Agonists

ARID1A deficiency leads to R-loop accumulation, releasing cytoplasmic single-stranded DNA (ssDNA) that activates the cGAS-STING pathway. STING agonists (e.g., MSA-2) can further

activate this pathway, boosting Type I IFN secretion and amplifying the anti-tumor innate immune response. In melanoma and colorectal cancer models, MSA-2 treatment significantly enhances IFNβ secretion in ARID1A-deficient tumors, promotes dendritic cell (DC) maturation and $CD8^+$ T cell infiltration. Combined with an anti-PD-1 antibody, it synergistically improves the efficacy of immunotherapy and prolongs the survival of tumor-bearing mice [84]. As innate immunity-targeting agents, STING agonists provide a novel synergistic target for immunometabolic combination therapy in ARID1A-deficient tumors.

The four major types of metabolic reprogramming driven by ARID1A deficiency provide multi-dimensional targets for cancer therapy. These strategies have demonstrated significant anti-tumor effects in preclinical models. Moreover, some agents (e.g., simvastatin, aspirin, FUDR) have an established clinical use profile, facilitating rapid translational potential.

6. Current Research Limitations

Although research on ARID1A deficiency-mediated metabolic reprogramming and synthetic lethal mechanisms has made substantial progress in recent years, offering novel perspectives for precision cancer therapy, an analysis of the latest SCI literature and the current state of the field reveals several persistent research bottlenecks.

6.1 Heterogeneity in Cancer-Type Specific Metabolic Reprogramming Mechanisms Remains Unclear

Existing studies have clearly demonstrated significant cancer-type heterogeneity in the metabolic reprogramming driven by ARID1A loss, typified by the opposite regulatory phenotypes of glucose metabolism observed in liver cancer versus lung cancer. Nevertheless, research into the core mechanisms driving this heterogeneity remains relatively sparse, lacking a systematic understanding. Moreover, the specific impact of ARID1A mutation burden and mutation type on tumor metabolic reprogramming has not been systematically investigated, which limits the selection of individualized therapeutic targets.

6.2 Biomarkers for Targeted Therapy in ARID1A-Deficient Tumors Are Not Well Defined

Current targeted therapeutic strategies for ARID1A-deficient tumors largely remain in the preclinical research stage, with relatively slow progress in clinical translation facing multiple practical hurdles. The most critical issue is the lack of specific biomarkers suitable for routine clinical detection. Most current studies rely on genomic sequencing to identify patients with ARID1A-deficient tumors, a method that is operationally complex, costly, and difficult to apply in routine clinical screening and patient stratification. For instance, while the study by Wu S. identified GLS1 expression levels as a potential biomarker for ARID1A-deficient ovarian clear cell carcinoma [21], its validity lacks multi-center, large-sample clinical validation, and its applicability across other cancer types remains undefined, hindering widespread adoption.

7. Conclusions

ARID1A deficiency-driven metabolic reprogramming and synthetic lethal mechanisms offer novel research perspectives and therapeutic directions for the precision treatment of ARID1A-deficient tumors. The core regulatory logic hinges on ARID1A functioning as an epigenetic hub. Its loss-of-function remodels the cellular chromatin landscape, thereby driving aberrant metabolic reprogramming and activating synthetic lethal pathways. This constructs a

regulatory network of "metabolic aberration-immune evasion," while simultaneously exposing tumor cells to multi-dimensional therapeutic vulnerabilities. Current research has delineated the core metabolic features, synthetic lethal targets, and immune regulatory mechanisms of ARID1A-deficient tumors. Some targeted therapeutic strategies have advanced to early-stage clinical trials, demonstrating promising translational potential. However, bottlenecks persist in mechanistic understanding and clinical translation, limiting further efficacy gains.Looking forward, interdisciplinary integration aimed at elucidating core regulatory mechanisms, optimizing combination therapies, and advancing translational research holds the promise of achieving precise diagnosis, personalized treatment, and improved prognosis for ARID1A-deficient tumors. This endeavor offers new therapeutic hope for affected patients and will propel the field of precision oncology forward.

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