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Review

Targeting Folate Metabolism for Cancer Drug Development

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Abstract

Folate, also known as folic acid (FA), is an essential nutrient widely used as a dietary supplement. The association of FA with cancer risk has been extensively studied, yet the underlying mechanisms remain complex and context dependent. This review examines the role of folate metabolism in cancer pathogenesis, with a focus on the particular influence of FA on cancer initiation, proliferation, migration, and progression. We discuss how folate modulates key signaling pathways involved in cell proliferation and migration, and how folate metabolism-related genes directly affect cancer progression. Furthermore, we highlight recent advances in therapeutic strategies that leverage folate pathways, including folate receptor-targeted antibody–drug conjugates (ADCs), folate–nanoparticle conjugates, and folate–polymer-based antitumor agents. Collectively, these insights underscore folate metabolism and folate receptors as promising targets for the design and development of novel anticancer drugs. Further *in vivo* and *in vitro* studies are warranted to elucidate the precise relationship between folate status and cancer dynamics.

Keywords: folic acid; folate receptor; metabolism; antitumor therapy; cancer

1. Introduction

Folate ($C_{19}H_{19}N_7O_6$), also known as vitamin B9, is a water-soluble micronutrient that cannot be synthesized endogenously in the human body [1]. It is metabolized from pteridine, para-aminobenzoic acid, and glutamic acid, which exist in various forms in nature. The active metabolites of folate participate in multiple biological processes, including the synthesis of purines, pyrimidines, and amino acids, and are essential for cellular growth and proliferation [2]. Cellular uptake of folate is primarily mediated by the folate receptor (FR), a cell surface protein also referred to as folate-binding protein (FBP). FR exists in several isoforms (α, β, and γ) and facilitates the internalization of folate and its derivatives [3]. FRα has been widely utilized in the development of targeted drugs [4,5]. A sufficient intake of folate is necessary to prevent DNA damage and potential malignant transformation [6,7]. However, excessive intake or dysregulated folate metabolism can paradoxically promote the initiation and progression of certain cancer types by providing essential nucleic acid precursors to proliferating cells [8].

One-carbon metabolism is one of the core modules of the cellular metabolic network. It primarily mediates the generation and transfer of one-carbon units via the serine, glycine, and folate cycles, supporting key biological processes such as purine and pyrimidine synthesis, methylation reactions, and redox homeostasis. Among the key enzymes of one-carbon metabolism, serine hydroxymethyltransferase 2 (SHMT2) and methylenetetrahydrofolate dehydrogenase 2 (MTHFD2) have attracted considerable attention due to their specific high expression in tumor tissues and low expression in normal adult tissues [9]. SHMT2 is mainly localized in mitochondria, catalyzing the reversible conversion between serine and glycine and participating in the generation of one-carbon units. MTHFD2 possesses dual dehydrogenase and cyclohydrolase activities. It is the key enzyme in mitochondria that converts methylenetetrahydrofolate to formyltetrahydrofolate, directly affecting purine synthesis and redox balance [9,10]. Multiple studies have confirmed that SHMT2 and MTHFD2 are highly expressed in various solid tumors such as breast, lung, liver, and kidney cancers, and are also closely associated with tumor stage, metastasis, and poor prognosis [11]. More importantly, the inhibition of SHMT2 and MTHFD2 can significantly suppress cancer cell proliferation, induce cell death, and enhance sensitivity to chemotherapy, thus demonstrating good antitumor potential [11,12]. In addition to its classical metabolic functions, MTHFD2 has also been

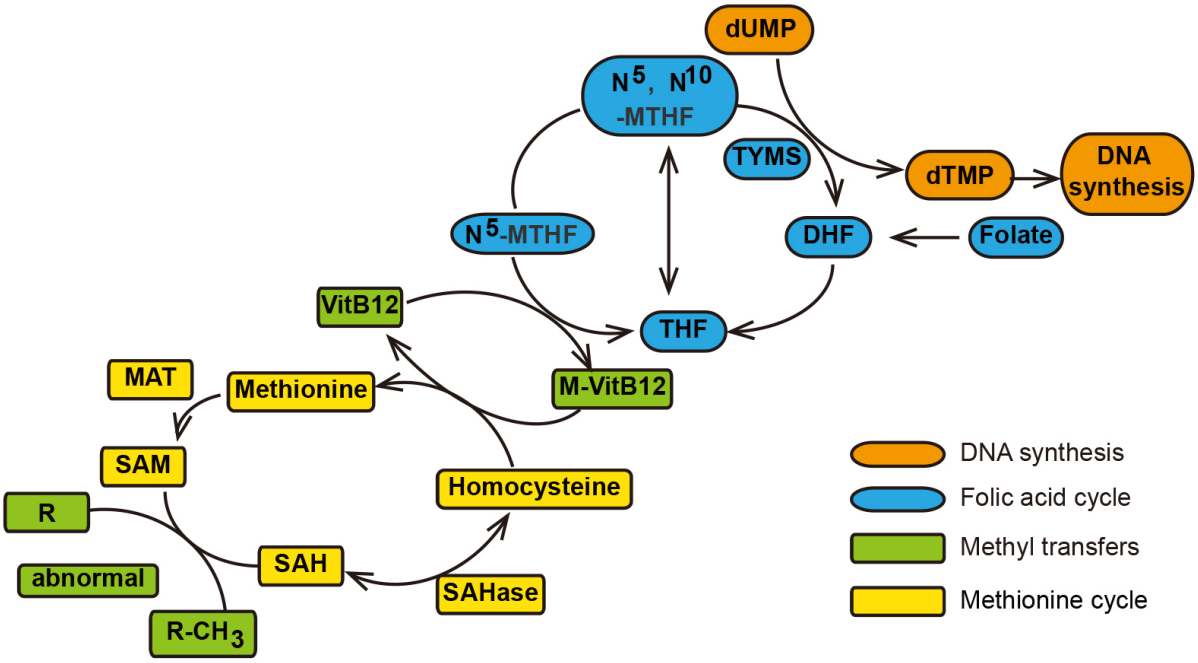

Fig. 1. The folate and methionine cycles in folate metabolism. TYMS, thymidylate synthase; THF, tetrahydrofolate; DHF, dihydrofolate; N5,N10-MTHF, 5,10-methylene tetrahydrofolate; N5-MTHF, 5-methyltetrahydrofolate; MET, methionine; SAM, S-adenosylmethionine; SAH, S-adenosylhomocysteine; MAT, methionine adenosyltransferase; Hcy, homocysteine; M-VitB12, methylene vitamin B12. Created with Adobe Illustrator.

found to have non-enzymatic functions, such as participating in DNA replication, RNA processing, and epigenetic regulation. This suggests it may have more complex regulatory roles in tumor initiation and progression [11]. Although various small-molecule inhibitors of SHMT2 and MTHFD2 have entered preclinical research stages, their mechanisms of action, regulatory networks, and combination therapeutic strategies in different tumor types still need to be further elucidated. Serine hydroxymethyltransferase (SHMT) exists as two isoforms: cytosolic serine hydroxymethyltransferase 1 (SHMT1) and mitochondrial SHMT2, mediating one-carbon metabolic pathways in different subcellular regions [13,14]. Recent studies have shown that SHMT is abnormally expressed in various malignant tumors and is closely related to tumor initiation, progression, prognosis, and the immune microenvironment, presenting a potential new target for metabolic therapy. In solid tumors such as renal cell carcinoma and gastric cancer, SHMT1/2 not only promotes tumor cell proliferation by regulating nucleotide synthesis, it also participates in tumor progression by remodeling the immune microenvironment and enhancing immune evasion [14]. Meanwhile, SHMT inhibitors (such as SHIN1) have shown good antitumor activity in various tumor models, exhibiting synergistic effects when combined with traditional chemotherapeutic agents such as 5-Fluorouracil (5FU), suggesting the potential to reverse drug resistance and enhance efficacy [15]. This review summarizes recent advances in the role and mechanism of folate metabolism in cancer, and the implications for drug development. The findings may contribute to a better understanding of folate metabolism and the development of cancer-specific therapeutics.

2. Folic Acid Metabolism

Folic acid (FA) plays crucial roles in cellular metabolism, DNA synthesis, and DNA repair [16]. After absorption by the body, FA is converted into physiologically active 5-methyltetrahydrofolate [17]. This conversion involves a series of enzymatic reactions that are indirectly regulated by the methionine cycle and vitamin B12 [17]. Deoxythymidine monophosphate (dTMP) is essential for DNA synthesis and is synthesized from deoxyuridine monophosphate (dUMP) by 5,10-methylenetetrahydrofolate (a folate metabolite) and thymidylate synthase (TYMS, the rate-limiting enzyme of pyrimidine nucleotide synthesis) [17]. The synthesis of thymidine is directly related to folate metabolism and is significantly reduced when folate metabolism is abnormal. This leads to misincorporation of dUMP into DNA, DNA methylation abnormalities, impaired DNA repair mechanisms, and chromosome mutations (Fig. 1) [6], all of which increase the possibility of malignant cell transformation [6,7]. Dysfunction of the folate cycle may contribute to the inactivation of tumor suppressor genes and elevated ex-

pression of oncogenes, thus increasing the risk of tumor development [18]. Dysfunction of the folate cycle disrupts the balance of one-carbon metabolism, leading to insufficient production of the methyl donor S-adenosylmethionine (SAM) and abnormal DNA synthesis/repair [19]. This results in hypermethylation of CpG islands in the promoter region of tumor suppressor genes such as *p16*, *RASSF1A*, and *BRCA1*, or the induction of gene mutations and functional defects. The overall result is transcriptional silencing and loss of tumor-suppressing functions [20]. On the other hand, dysfunction of the folate cycle can also activate proto-oncogenes (e.g., *c-myc*, *HER2*) through genome-wide hypomethylation [21]. Ultimately, this disrupts the regulatory balance between cell proliferation and apoptosis, promoting malignant transformation and significantly increasing the risk of tumor development and progression.

3. Folic Acid Metabolism in Tumor Progression

3.1 Folate and Folate Receptors Affect Different Cancer Types

Folate is internalized into the cell via FR-mediated endocytosis [22], with FRα having a high affinity for FA. Nonmalignant tissues have limited expression of FRα, whereas several solid tumor types express high levels of FR [23]. FRβ is frequently overexpressed in activated macrophages or degraded cells, but is expressed at low levels in normal tissues and nonactivated macrophages [4]. These characteristics of FRα have been reported to confer growth advantages to cancer cells, thus promoting tumor progression [5]. In addition, FRα is a signal transduction molecule that can directly affect intracellular signaling pathways [4]. Recently, some antitumor drugs have been delivered specifically to cancer cells by virtue of their high level of expression of FR. FRα is therefore becoming a promising target for anticancer drug development [4]. As a donor of carbon units, folate participates in amino acid metabolism and nucleic acid metabolism and has important roles in cell proliferation [24], with varying impacts on different cancer types. By reducing the intracellular SAM concentration, low folate status may increase the risk of colon cancer [16].

3.2 FRα Expression in Various Cancer Types

In view of the important role of FRα in cancer, we used the UALCAN database to analyze the expression of FRα, FRβ, and FRγ in tumor and normal tissues (**Supplementary Tables 1–3**). FRα showed relatively lower expression in invasive breast carcinoma (BRCA), clear cell renal cell carcinoma (ccRCC), lung adenocarcinoma (LUAD), pancreatic adenocarcinoma (PAAD), and head and neck squamous cell carcinoma (HNSCC). In contrast, FRα showed high expression in ovarian cancer (OV), uterine corpus endometrial carcinoma (UCEC), and glioblastoma multiforme (GBM). However, the expression levels of FRβ and FRγ were slightly reduced in several cancer types compared to normal tissues. Thus, FRα-mediated antitumor drugs may have good efficacy in the treatment of OV, UCEC, and GBM.

Cancer cells rely on folate-mediated one-carbon metabolism for nucleotide synthesis and methylation. FRα, MTHFD2, and SHMT2 are specifically overexpressed in solid tumors (e.g., ovarian, renal, and breast cancers) compared to corresponding normal tissues [23,25]. Abnormal folate metabolism induces DNA instability and malignant transformation, making it a tumor-selective target [6]. FRα is highly expressed in many solid tumors, but is barely expressed in normal tissues. It efficiently internalizes payloads, enabling precise delivery of cytotoxins, CAR-T cells, or vaccines for tumor-specific killing with minimal side effects. This makes FRα an attractive target in modern cancer therapy [26].

3.3 The Dual Role of Folic Acid in Cancer

FA has dual effects in various cancer types. For example, it may not be appropriate to administer high doses of FA to people who are at high risk of cancer [27]. Excessive FA supplies precancerous cells with additional DNA synthesis material, thereby promoting aberrant cell proliferation and tumorigenesis [16]. In addition, individuals who are at risk of colorectal cancer were found to have consumed high doses of folic acid supplements, significantly increasing their risk of tumor development [27]. Folate deficiency restricts the synthesis of SAM, leading to reduced DNA methylation across the genome and derepression of proto-oncogenes. Simultaneously, hypermethylation of CpG islands in the promoter region of tumor suppressor genes can silence their expression, thereby promoting malignant cellular transformation [28]. Insufficient 5,10-methylene tetrahydrofolate leads to the accumulation of dUMP, which increases the erroneous incorporation of uracil during DNA synthesis. This leads to double-strand DNA breaks during repair, resulting in chromosomal instability and elevated mutation rates, further increasing the risk of tumor development, including colorectal, prostate, and lung cancers [29]. Genetic polymorphisms in folate metabolism enzymes, such as 5,10-methylenetetrahydrofolate reductase (MTHFR) and SHMT1, can also reduce enzyme activity, amplifying the aforementioned epigenetic and genetic damage effects. This renders some individuals more susceptible to the tumorigenic effects associated with folate dysregulation [30]. FA supplements have been used to prevent the development of cervical cancer [31]. Serum folate deficiency was associated with an increased risk of cervical cancer in two meta-analyses [31]. Given that the intake of FA varies greatly between individuals, FA supplementation should not be used casually [27]. It should be adjusted according to individual circumstances to avoid promoting tumor development, especially for those experiencing precancer symptoms or those at high risk of developing cancer [27].

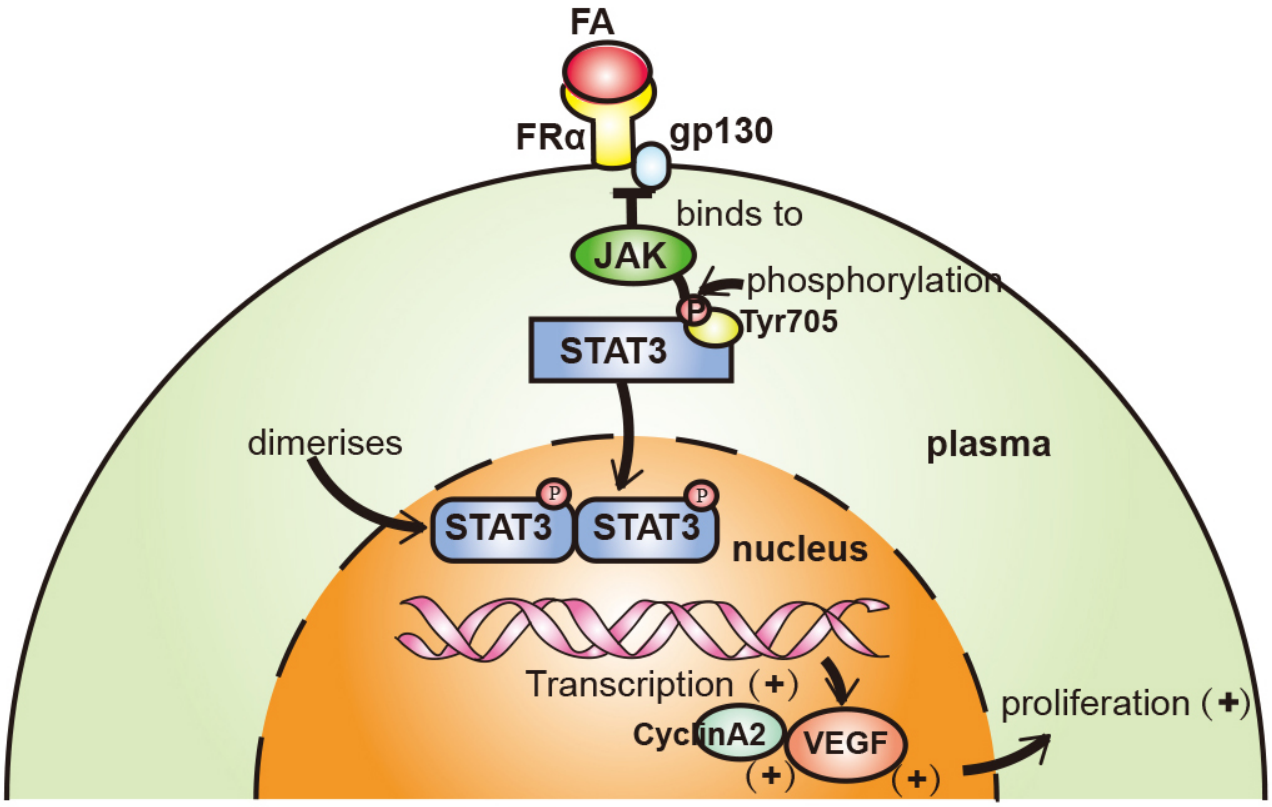

Fig. 2. Folic acid influences cell proliferation by regulating the janus kinase/signal transducer and activator of transcription (JAK/STAT) signaling pathway. (+) indicates increased expression/accelerated process. FA, folic acid; VEGF, vascular endothelial growth factor. Created with Adobe Illustrator.

4. Mechanisms by Which Folate Regulates Cancer Progression

4.1 Expression and Modification of JAK/STAT Signaling Pathway Components are Linked to Folic Acid-Mediated Cancer Progression

The janus kinase/signal transducer and activator of transcription (JAK/STAT) signaling pathway includes many cytokines and growth factors [32]. Activation of this pathway stimulates cell proliferation, differentiation, migration, and apoptosis through tyrosine phosphorylation of downstream receptors via JAK and the binding of STAT [32]. Folate can activate STAT3 in a PyMT-treated mouse model of breast cancer, thereby promoting the proliferation of tumor cells (Fig. 2) [33]. Gp130 is a common signal transduction receptor that binds to interleukin-6 (IL-6)-type cytokines. It is reportedly involved in folate-induced signaling pathways as a coreceptor of FRα [34]. The binding of gp130 to FRα activates JAK, which subsequently activates a series of tumor growth-associated genes, such as CyclinA2 and vascular endothelial growth factor (VEGF) [34]. Furthermore, JAK phosphorylates STAT3 at Tyr705, which dimerizes and subsequently translocates to the nucleus, where it initiates the transcription of target genes [34,35]. The JAK inhibitor AG490 can significantly reduce folate- and folate analog-mediated STAT3 activation [34]. Inhibition of FRα also reduces folate-induced STAT3 activation [34]. In brief, the promotive effect of FA on cancer progression may occur via its regulation of cell proliferation-related signaling pathways, such as the JAK/STAT signaling pathway.

4.2 Modification of Methionine Adenosyltransferase (MAT), MTHFD1L, and MTHFD2 is Linked to Folic Acid-Regulated Cancer Progression

FA-regulated cancer progression has been linked to the modification of methionine adenosyltransferase (MAT), such as methionine adenosyltransferase 2A (MAT2A), which has different isoforms in the folate cycle [17,35]. MAT2A encodes MAT IIa, a key enzyme in methionine metabolism [8] that is tightly regulated by the level of FA [8]. When the cellular folate level is sufficient, MAT IIa is stabilized by deacetylation and deubiquitination mediated by Histone Deacetylase 3 (HDAC3) and valosin-containing protein p97/p47 complex–interacting protein, p135 (VCIP135). The accumulation of MAT IIa promotes tumor growth. However, when folate is deficient, tumor growth is inhibited by the acetylation and ubiquitination of MAT IIa (Fig. 3a) [8,36].

Moreover, it has been suggested that a low FA concentration results in decreased expression of methylenetetrahydrofolate dehydrogenase 1-like (MTHFD1L) in col-

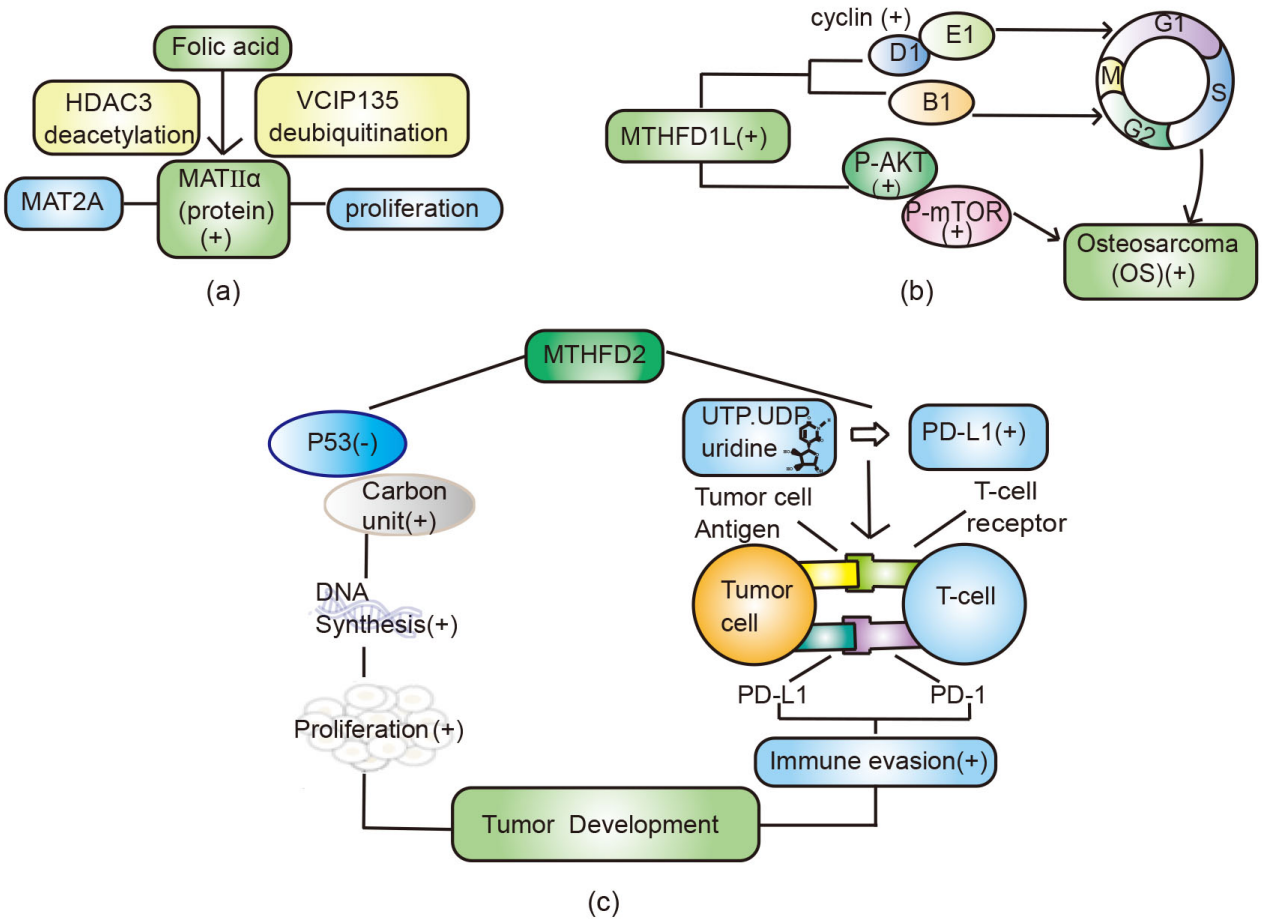

Fig. 3. Folate metabolism-related genes regulate cancer progression. MAT (a), MTHFD1L (b), and MTHFD2 (c) are involved in cancer progression. (+) indicates increased expression or accelerated process; (-) indicates decreased expression or delayed process. MTHFD1L, methylenetetrahydrofolate dehydrogenase 1-like; MTHFD2, methylenetetrahydrofolate dehydrogenase 2. Created with Adobe Illustrator.

orectal cancer and the suppression of tumor progression [37]. MTHFD1L is also involved in the progression of several cancer types [37,38,39]. For example, Wang et al. [38] reported that MTHFD1L expression is significantly upregulated in osteosarcoma (OS) tissues compared with normal tissues. Moreover, MTHFD1L was reported to facilitate the progression of OS by accelerating the cell cycle and activating the AKT/mechanistic target of rapamycin (AKT/mTOR) pathway [38,39]. Thus, MTHFD1L may be a promising therapeutic target for OS treatment (Fig. 3b).

Methylenetetrahydrofolate dehydrogenase 2 (MTHFD2) is a mitochondrial methylenetetrahydrofolate dehydrogenase and cyclohydrolase involved in one-carbon metabolism. It plays a pivotal role in cellular proliferation [25], serving as a driver of the folate cycle and supporting cell proliferation in embryonic tissues. MTHFD2 expression is substantially upregulated during malignant transformation [25], with high expression and increased folate intake providing more materials for the folate cycle and thus promoting tumor development [40]. Several studies have shown much higher expression of MTHFD2 in tumor tissues compared to normal tissues [25,41]. Patients with high tumor expression of MTHFD2 have significantly worse overall survival than those with low expression [42]. Moreover, a positive correlation was reported between upregulated MTHFD2 expression and PD-L1/PD-1 expression, while MTHFD2 was negatively correlated with *p53* expression (Fig. 3c) [40,43].

4.3 The Role of Folate in Immune Regulation and Surveillance in Cancer

Folate has also been reported to influence cancer progression by regulating the immune system. Excessive intake of FA leads to a reduction in natural killer (NK) cell activity and an increased risk of infection [44]. Deficient folate status is associated with an increased incidence of immune- or inflammation-related chronic diseases [44]. In addition, regulation of the FA cycle in myeloid-derived suppressor cells (MDSCs) blocks their immunosuppressive ability and enhances the efficacy of immune checkpoint inhibitors in tumor treatment [45].

Natural immunoglobulin M (IgM) in blood was reported to be a folate-binding protein that can negatively regulate the *in vivo* performance of folate-modified nanomedical drugs. Folate was subsequently reported to affect drug delivery and immunogenicity [46]. Moreover, a study by Shang et al. [40] revealed that MTHFD2 promotes immune escape in various cancer types by increasing PD-L1 expression, indicating the FA cycle plays a role in tumor immune escape.

5. Development and Application of Folate-Related Drugs

5.1 Folate Receptor-Mediated ADC Drugs

Folate and small molecules conjugated to folate are used as medicines or supplements in the clinic. Antibody-drug conjugates (ADCs) are a class of drugs produced by combining an antibody with a toxic cellular drug. ADCs can specifically target cell surface receptors through the antibody component. The expression level of target receptors directly affects the amount of ADC targeted to the tumor tissue and its degree of internalization. FRs are highly expressed on tumor cells but only at low levels on normal cells, making them highly useful for the development of ADC drugs. FR-mediated ADC drugs are in development (**Supplementary Table 4**), including mirvetuximab soravtansine (MIRV or IMGN853), MORAb-202, CT900, STRO-002 and so on [47,48].

MIRV is an antibody-drug conjugate that selectively targets FRα. It consists of a humanized antibody (M9346A) with a high affinity for FRα, linked via a cleavable disulfide-containing hydrophilic junction to the potent microtubular toxin maytansinoid DM4 [49]. IMGN853 binds selectively to FRα on tumor cells and is internalized through FR-mediated endocytosis [50]. DM4 can accumulate intracellularly and inhibit microtubule dynamics, acting as a potent antimitotic agent [50]. Oroudjev et al. [51] reported that MIRV can effectively inhibit the proliferation of MCF7 breast cancer cells at low concentrations. By inhibiting the dynamic instability of microtubules, MIRV arrested MCF7 cells at the middle stage of mitosis and exerted a potent antimitotic effect [51]. In addition to targeting and eliminating FRα-positive tumor cells, MIRV was also found to destroy FRα-negative cells adjacent to FRα-positive cells [50]. Moreover, MIRV was reported to have antitumor activity in platinum-resistant ovarian cancer patients with high FRα expression [49].

Several phase II and III clinical trials have shown significant efficacy for MIRV [52,53]. In the SORAYA trial, the objective response rate (ORR) of MIRV was 32.4% in treatment of patients with FRα-high, platinum-resistant, advanced high-grade serous ovarian cancer (PROC), and the median duration of response (DOR) was 6.9 months compared to historical single-agent chemotherapy data ($\approx$12% ORR and $\approx$5.4 months DOR) reported in prior trials of PROC [53]. The MIRASOL study also showed that MIRV has the potential to improve progression-free survival (PFS) and overall survival (OS) [54]. The reported adverse events for MIRV included blurred vision, keratopathy, fatigue, and peripheral neuropathy, most of which were mild or reversible. Ocular toxicity is a major concern in the clinic and can be mitigated with preventive measures, such as the use of steroid eye drops [54]. In clinical trials, adverse reactions can be controlled by adjusting the drug dose and administering adjuvant therapy. MIRV was shown to enhance the efficacy of combination therapy with bevacizumab in platinum-resistant ovarian cancer patients [54]. Combination therapy of MIRV with other drugs, such as carboplatin, pegylated-liposomal-doxorubicin (PLD), or pembrolizumab, has also been reported to improve outcomes in various clinical trials [54].

A phase III randomized clinical trial enrolled 366 platinum-resistant and FRα-positive ovarian cancer patients. Outcomes for the MIRV treatment group were not significantly different from the other chemotherapy groups in terms of PFS across the intent-to-treat population (ITT). The PFS in the MIRV treatment group was 4.1 months, compared to 4.4 months in the chemotherapy group. In the subgroup with high FRα expression, the MIRV treatment group had a better PFS (median 4.8 months) than the chemotherapy treatment group (median 3.3 months) [27].

MORAb-202 is another FR-mediated ADC drug, consisting of farletuzumab, histone B, and eribulin. It targets FRα, exhibiting potent cytotoxicity specifically toward FRα-positive cells, with limited effects on FRα-negative cells [55]. After targeting and binding to FRα on tumor cells, farletuzumab from MORAb-202 exerts antitumor effects through multiple mechanisms: (1) antibody-dependent cytotoxicity (ADCC) (Fig. 4a) and complement-dependent cytotoxicity (CDC) (Fig. 4b); (2) induction of tumor cell autophagy (Fig. 4a); and (3) suppression of the interaction between FRα and Lyn kinase (Fig. 4c) [17,56]. Eribulin is an inhibitor of microtubule polymerization and binds to high-affinity sites at the extended ends of microtubules [57]. It can suppress microtubule growth in interphase cells and promote spindle formation. Eribulin blocks the G2–M phase, leading to irreversible blockage of mitosis and the induction of cell apoptosis, even at low concentrations [57]. Transforming growth factor β (TGFβ) plays an important role in the regulation of cell proliferation and apoptosis [58]. Eribulin can also suppress epithelial-to-mesenchymal transition (EMT) and facilitate mesenchymal-to-epithelial transition by blocking the TGFβ signaling pathway [59]. Thus, the anticancer efficacy of MORAb-202 is synergistically enhanced by the actions of its components, farletuzumab and eribulin. MORAb-202 has shown durable antitumor efficacy *in vivo*, and this has been directly linked to the expression level of FRα on tumor cells [60,61].

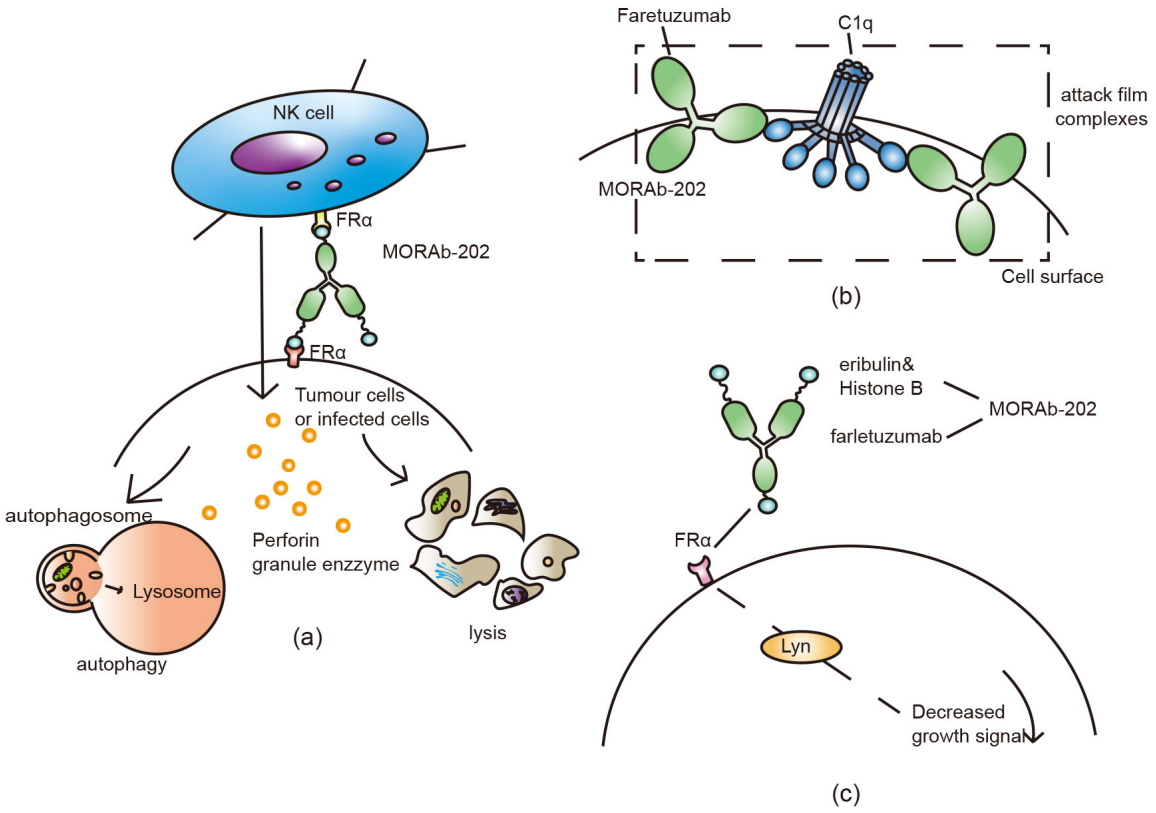

Fig. 4. Schematic diagram illustrating the pharmacological mechanism of MORAb-202. This FR-mediated ADC targets FR-positive cells and exerts antitumor effects through ADCC (a), CDC (b), and signal transduction suppression (c) mechanisms. FRα, folate receptor α; EMT, epithelial-mesenchyme transformation; ADC, antibody-drug conjugate; ADCC, antibody-dependent cytotoxicity; CDC, complement-dependent cytotoxicity. Created with Adobe Illustrator.

5.2 Folate-Nanoparticle Conjugates and Folate-Polymer-Conjugated Antitumor Drugs

FA-modified chitosan nanoparticles and FA-modified liposome nanoparticles have shown significant potential in drug delivery [62,63,64]. Several research highlighted the crucial role of folic acid and chitosan in constructing targeted nanodrug delivery systems. The targeting capabilities of folic acid and the biocompatibility of chitosan effectively enhance the specific cytotoxic effects of anticancer drugs on tumor cells and improve drug release characteristics [62,64]. Folate-modified chitosan nanoparticles can be used to target tumor cells with high FR expression, thereby avoiding damage to normal cells [64,65]. For example, Mehata et al. [65] developed single- and double-receptor targeted therapeutic chitosan nanoparticles functionalized with estrone (ES) and FA for the imaging and treatment of breast cancer. These ES- and FA-functionalized nanoparticles (NPs) are loaded with palbociclib (PB) and ultrasmall magnesium nanoclusters (UMNs). Cytotoxicity studies on MCF-7 breast cancer cells expressing estrogen receptor (ER) and FR have shown that single-targeted and dual-targeted NPs can more effectively inhibit cell cycle progression from the G1 phase to the S phase compared to unbound PB [65].

Liposomes and nanoparticles are passively targeted by cell endocytosis, and are regarded as good carriers for drug targeting to the liver and spleen. Folate-modified liposomes can be used to deliver many agents, including chemotherapy drugs (e.g., paclitaxel and doxorubicin), natural products (e.g., curcumin), and local anesthetics (e.g., lidocaine) [66,67]. de Oliveira Silva et al. [68] evaluated the cardiac toxicity of drug liposomes in mice. These authors found that compared to mice treated with the same dose of unencapsulated doxorubicin, mice treated with SpHL-DOX-Fol had significantly reduced myocardial tissue damage, reduced myocardial cell lesions, and decreased serum markers associated with myocardial injury (such as creatine kinase-MB) and cardiac toxicity [68]. FA-modified liposomes can increase the drug loadings, prolong the effective drug duration, and improve the therapeutic effect [63]. Folate-modified liposomes can also be combined with imaging technology to achieve “theranostic” applications, which may lead to future breakthroughs in the early diagnosis and monitoring of cancer [69].

Folate modification improves drug-targeting ability, and drug uptake is increased in cancer cells with high FR expression. In addition, folate- and nanoparticle-modified drugs have shown greater stability, greater an-

ticancer activity, and lower cytotoxicity than unmodified drugs [70]. For example, poly(2-hydroxyethylacrylate)-b-poly(*N*-isopropylacrylamide) (PHEA-b-PNIPAAm) is made from chitosan, polyethylene glycol (PEG), and a thermoresponsive material. FA-modified PHEA-b-PNIPAAm shows high cytotoxicity in HeLa, DLD-1, Caco-2, and HT-29 cancer cells, but reduced toxicity in normal cells [71]. In colorectal cancer cell models, FA-modified PHEA-b-PNIPAAm nanoparticles have also shown strong cytotoxic effects in 5-FU-resistant cancer cell lines and multidrug-resistant cell lines [71]. These findings provide an effective way to overcome the limitations of traditional 5-FU therapy, with potential clinical translational value.

Finally, folate polymer-conjugated antitumor drugs are also being developed. For example, the FA-DABA-SMA polymer designed by DeCarlo et al. [72] is a conjugate of FA, 2,4-aminobutyric acid, and styrene-maleic anhydride. This folate–polymer conjugate can also act on cancer cells through FR-mediated endocytosis. The FA-DABA-SMA polymer was found to upregulate FR expression in breast cancer cells and induce cell apoptosis by interfering with FR signaling pathways [72].

6. Discussion

Folate metabolism and folate-related drug development in cancers were covered in this review. Folate influences cancer progression by regulating the expression and modification of JAK/STAT, methionine adenosyltransferase (MAT), MTHFD1L, MTHFD2, and other related signaling genes. It can slow the progress of cancer by inhibiting the proliferation and migration of endothelial and tumor cells.

Whether FA can regulate additional pathways or interfere with the surrounding tumor environment to reduce the invasion and metastasis of tumor cells remains to be further investigated. The immune system also plays an important role in recognizing and eliminating cancer cells, and the relationship between cancer and the immune system is critical and complex. Whether FA is involved in immune surveillance and immune regulation will be an interesting research direction in future studies.

Cyclin-dependent kinase (CDK)-targeted inhibitors, such as palbociclib and ribociclib, and tumor angiogenesis-targeted inhibitors, such as bevacizumab, have proven therapeutic effects on tumor growth by blocking the tumor cell cycle and reducing the nutrient supply [73,74]. The combination of FA with these antitumor drugs may lead to more effective cancer treatments, warranting further exploration of the synergistic mechanism between FA and antitumor drugs. Recently, from a clinical report, high dose FA supplementation prevents the pre-eclampsia in pregnancy with hypertension [75]. Thus, the dosage of FA seem been need more noted in clinic and real world.

FA has shown great potential in drug modification, broadening the prospects for antitumor drug development. It can be coupled with antitumor drugs to target FR-overexpressing tumors. The encapsulation of anticancer drugs in FA-modified nanoparticles may also be a viable method for drug development. The synergistic effect of FA and nanoparticles may enhance the targeting and physicochemical properties of drug molecules. This can improve the concentration of FA-encapsulated drugs in tumors via precise delivery, thereby reducing systemic toxicity. FA is a water-soluble vitamin, and its liposomes can be used in the preparation of water-soluble anticancer drugs to improve their pharmacokinetic properties and enhance their selectivity and antitumor effects. Further research on FA-modified drug design and delivery technology should benefit antitumor drug development.

Future research should also focus on developing robust FRα expression-based biomarkers to enable precise patient stratification, thereby optimizing the selection of candidates most likely to benefit from folate-targeted therapies. Additionally, the systematic investigation of combination therapeutic strategies designed to overcome intrinsic and acquired resistance mechanisms, such as FRα downregulation, activation of alternative metabolic pathways, and impaired drug internalization, is essential to improve treatment durability and efficacy. Further refinement of folate-conjugated nanocarriers is needed to improve drug delivery, with emphasis on enhancing targeting precision, biocompatibility, and *in vivo* stability, while reducing off-target accumulation. Advanced engineering of these nanoplatforms to improve tumor penetration and enable controlled drug release within the tumor microenvironment may significantly increase the therapeutic index of folate-based delivery systems.

Folate small molecule-conjugated drugs, FR-mediated ADC drugs, folate–nanoparticle conjugates, and folate–polymer–conjugated antitumor drugs were also introduced in this review. These folate- or FR-targeting drugs have shown promising pharmaceutical effects in clinical trials and real-world applications. The findings demonstrate that folate and FRs are effective mediators or carriers for the development of antitumor drugs and next-generation drug delivery systems.

7. Conclusion

In conclusion, the role, mechanism, and drug development of folate and FA metabolism in cancer are reviewed here. FA is beneficial for human health, but its dual role in cancer progression is also worth noting. FA is tightly linked to the occurrence, proliferation, migration, and progression of cancers. Based on the characteristics of folate and its metabolism, several folate-related drugs are in development and undergoing trials. Even more folate- and folate metabolism-related treatment options for cancer are

likely to be developed in the future. This may help clinicians and the general public to reassess their view on folate, particularly regarding FA supplementation and the development of folate-related drugs.

Author Contributions

SL, FL, and YL developed the concept of the project. YL and FL conducted the literature search and analysis with the help of ZL and JC. YL, FL, and ZL prepared the figures. YL, FL, and HT conducted data extraction and drafted the original manuscript. SL, YM, XD, and BL conceived the study and edited the manuscript. All authors contributed to editorial changes in the manuscript. All authors read and approved the final manuscript. All authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate

Not applicable.

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Conflict of Interest

The authors declare no conflict of interest.

Supplementary Material

Supplementary material associated with this article can be found, in the online version, at https://doi.org/10.31083/IJP48141.

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