Defueling the cancer: ATP synthase as an emerging target in cancer therapy

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Reprogramming of cellular metabolism is a hallmark of cancer. Mitochondrial ATP synthase (MAS) produces most of the ATP that drives the cell. High expression of the MAS-composing proteins is found during cancer and is linked to a poor prognosis in glioblastoma, ovarian cancer, prostate cancer, breast cancer, and clear cell renal cell carcinoma. Cell surface-expressed ATP synthase, translocated from mitochondrion to cell membrane, involves the angiogenesis, tumorigenesis, and metastasis of cancer. ATP synthase has therefore been considered a therapeutic target. We review recent various ATP synthase inhibitors that suppress tumor growth and are being tested for the clinic.

INTRODUCTION

A century ago, Warburg reported that the metabolism in cancer has changed.1 Reprogramming of metabolism is one of the hallmarks of cancer.2 Drugs that target this reprogramming are emerging as novel drug families, and some are being evaluated in clinical trials (Figure 1).3 The mitochondrion plays a key role in the metabolism reprogrammed in cancer.3–5 For example, cancer cells without mitochondria can only form tumors if they reconstitute oxidative phosphorylation (OXPHOS) from host stroma.6 The mitochondrion is also linked to the resistance of tumor stem cells to treatment and in pancreatic cancer to KRAS-driven signaling inhibition.7–9

Mitochondrial ATP synthase (MAS), an enzyme that produces ATP, also known as complex V, is the final and pivotal enzyme of OXPHOS in the mitochondrion.10 In 1994, ectopically expressed ATP synthase (ectopic ATP synthase [EAS]) on the cell surface of vascular endothelial cells and tumor cells was found.11 The existence of EAS is reported to be related to tumor angiogenesis, metastasis, and drug resistance.12–15

We review the ongoing development of ATP synthase inhibitors that have shown effectiveness in the treatment of cancer.16

THE STRUCTURE OF MAS

MAS is the primary generator of ATP and is widely found in the cell membranes of bacteria, the thylakoid membranes of chloroplasts in algae, and the inner membranes of the mitochondria of eukaryotic cells.17 MAS transduces the electrochemical gradient of the proton motive force across these membranes into ATP, which is generated during respiration (Figure 2).

Its complex structure has been elucidated by electron microscopy.18–20 The mammalian MAS consists of 28 subunits from 17 polypeptides, assembled into (1) a membrane-bound rotor and (2) a catalytic, ATP-generating center in the cytoplasm, linked by a central stalk and a peripheral stalk (PS).18 Protons traverse the membrane inside the rotor, which combined with the PS is called the Fo region; the F1 region consists of the ATP-generating catalytic crown and its asymmetrical central stalk (Figure 3).

The rotor consists of a ring of eight c-subunits, clung by an ATP6 subunit. The PS part includes the subunits of the oligomycin sensitivity conferring protein (OSCP), b, d, and F6. Subunits e, f, g, ATP8, and 6.8 proteolipid are the accessory subunits of the PS.

The catalytic crown harbors three β subunits, the catalytic sites, and three noncatalytic α subunits. These β subunits can undergo three different conformations: (1) an open state with no nucleotide bound (E), (2) the loose state with ADP and Pi bound (D), and (3) the tight state with synthesized or hydrolyzed bound ATP (T). With the rotation of the c-ring, the conformation of catalytic sites alternates from E to T and D states. The asymmetrical stalk, composed of subunits γ, δ, and ε, connects the Fo inner membrane domain and the F1 catalytic domain.

The monomeric MASs dimerize via interaction between ATP6 subunits and between 6.8 proteolipids, and then the dimers are linked together by a DAPIT subunit along the edge of the cristae.20,21

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ATP SYNTHASE IS REQUIRED FOR MALIGNANT TUMOR GROWTH

MAS in tumor

MAS relates to cancer through mutation of the genes coding for its subunits and also through abnormal expression of genes coding for these subunits.\textsuperscript{14,22–25} In glioblastoma, the mRNA levels of the MAS F1 subunits \( \alpha \) and \( \beta \) (\( ATP5A1 \), and \( ATP5B \)) are significantly higher in tumor cells and endothelial cell of microvascular proliferation, attributed to the downregulation of microRNAs (miRNAs) that target \( ATP5A1 \) and \( ATP5B \).\textsuperscript{26}

\( ATP5B \)

In ovarian cancer, downregulated miR-450a that targets \( ATP5B \) expression increases metastasis, indicating that \( ATP5B \) might support the invasiveness of ovarian cancer.\textsuperscript{27} In prostate cancer, breast cancer, and thyroid cancer,\textsuperscript{28,29} overexpressed \( ATP5B \) negatively correlates with metastasis-free and overall survival. HER2\textsuperscript{+} breast tumors that had acquired resistance to HER2-targeted therapies showed increased expression of \( ATP5B \) and ATP synthase PS subunit F6 (\( ATP5J \)).\textsuperscript{26}

\( ATP5A1 \)

In clear cell renal cell carcinoma and in breast cancer progression and metastasis, \( ATP5A1 \)'s overexpression is associated with progression, a potential biomarker for diagnosis and prognosis and the treatment response.\textsuperscript{30,31} In prostate cancer, \( ATP5A1 \) levels positively correlate with the early onset of tumor.\textsuperscript{23} In colorectal cancer, high expression of \( ATP5A1 \) is associated with with SNPs, \( TP53 \) mutation, and chromosomal instability to facilitate tumor development.\textsuperscript{33} In hepatocellular cancer, \( ATP5A1 \) also fell in the ingredient-target network of dihydroartemisinin and was responsible for the anti-hepatocellular carcinoma effect.\textsuperscript{34} In lung cancer, periplocin inhibits growth of lung cancer by downregulating \( ATP5A1 \) and other key proteins.\textsuperscript{35}

ATP level alteration also reflects the development of carcinogenesis,\textsuperscript{36} marking the tumor region and its microenvironment.\textsuperscript{37,38} Moreover, MAS is able to modulate the astrocyte inflammatory response, which is related to the initiation of glioma.\textsuperscript{39,40} Additionally, mutations of MAS-coding genes are accumulated with the carcinogenesis process, suggesting the participation of MAS in the biological process of cancer cells. Two mutations in \( MT\text{-}ATP6 \), which encodes subunit ATP6 of MAS, affect the calcium homeostasis and activation of the permeability transition pore (PTP) in yeast,\textsuperscript{31} the latter of which is prominent for cancer cells to escape from apoptosis.

EAS in tumor

EAS is located not only on the mitochondrial inner membrane, but also on the plasma membrane of tumor cells and human vascular endothelial cells.\textsuperscript{11,12} EAS is the receptor of angiostatin in endothelial cells, and it might be involved in maintaining the normal intracellular pH of cancer cells in an acidic extracellular microenvironment.\textsuperscript{12} It is translocated from mitochondria to cell surface, and mitochondrial...
transit peptide is essential for ATP synthase localization on the cell surface and mitochondria. In hepatocellular carcinoma (HCC), blocking EAS could inhibit extracellular ATP synthesis and have antiangiogenic and antitumorigenic activities. In lung cancer, the level of EAS is correlated with gefitinib sensitivity and cell survival. In leukemia, ATP5B of EAS on the human leukemia cell surface interacts with the platelet GPIIb epitope, causing platelet-cancer aggregation, with the latter serving as a target for a mimetic cytotoxic peptide to be specifically delivered to ectoATP5B-positive cells, contributing to targeted cancer cell killing.

Inhibiting the activity of ATP synthase can effectively impair tumor metabolism reprogramming and tumor growth. ATP synthase is essential for tumor progression and has potential as a target in cancer treatment.

CANCER THERAPY BASED ON TARGETING ATP SYNTHASE

Given the role of ATP synthase in fueling cancer, ATP synthase inhibitors have been explored as a new cancer therapy. Categories that have been developed and investigated are polyketide inhibitors, polyphenolic phytochemicals, estrogens, polyenic fatty acids, macrolides, and cyclodextrins. Many inhibit ATP synthase. The number of phenol groups and the position of the hydroxyl groups affect the strength of the antioxidant, anti-inflammatory, cardioprotective, and anticancer activity.

AS inhibitor development is at the start of its debut in cancer treatment. None has become commercially available for clinical cancer treatment. Table 1 summarizes current inhibitors under investigation, sources, inhibitory sites, and related studies in tumor treatment (see Figure 4 and Table 1). Figure 5 displays the structure of AS inhibitors.

Polyketide inhibitors

Polyketides are bioactive natural products isolated from diverse microorganisms, polymers of two ketides synthesized by polyketide synthase. Macrolides such as oligomycin, apoptolidin, and cytovaricin are polyketides and are MAS inhibitors with an anti-tumor activity. The former three macrolide inhibitors belong to the top 0.1% cytotoxic agents in 37,000 small molecules tested against 60 human cancer cell lines.

Oligomycin

This compound, produced by Streptomyces strains, is a specific ATP synthase inhibitor that binds to the c subunit of Fo, as well as high concentrations to the F1 region, inhibiting ATP synthesis. The subunit oligomycin sensitivity-conferring protein (OSCP) is required for MAS sensitivity to oligomycin. Oligomycin can suppress cell viability in multiple cancers. It reduces the viability of hepatocellular carcinoma and non-small cell lung cancer cells with upregulated OXPHOS-like high-level SALL4 expression in vitro and in vivo.

In colon cancer and triple-negative breast carcinoma it decreases cell proliferation, migration capacity, and invasiveness, revealing the potential for therapy. Oligomycin also significantly suppressed the survival and metastasis of microsatellite-stable colorectal cancer cells with increased mitochondrial DNA copy number.

Moreover, oligomycin exhibits antitumor efficiency, particularly in tumors showing resistance to corresponding target therapies. It reverses the acquired resistance of HER2+ breast tumors to HER2-targeted therapies and enhances the antitumor efficacy of c-MET inhibition in glioblastoma cells; it also prevents recurrence in ovarian cancer. Inhibitors of OXPHOS, such as oligomycin, might be used for combined treatments.

Apopotolidin

This compound, including isomers A–D, are microbial secondary metabolites that highly selectively induce apoptosis in some cancer cell lines. MAS is one of the biological targets for apoptolidins to exert antiproliferative activity. In a study by Ishmael and colleagues, apoptolidins A and C acted as AMPK activators and triggered autophagy in sensitive cell types without significant inhibition of mTORC1, showing that all macrolides do not function similarly.

Cytovaricin B

This compound was screened as an inhibitor of the JAK-STAT signaling pathway 20 years ago, and extended effects of this compound on tumor cells are being explored.

Polyphenolic phytochemicals and estrogen

Polyphenolic phytochemicals are natural compounds from plants that contain phenol groups and show antitumor properties. Many inhibit ATP synthase. The number of phenol groups and the position of the hydroxyl groups affect the strength of the inhibition.

Resveratrol and piceatannol

These two polyphenolic compounds are naturally found in diverse plants, mainly such as grapes, berries, and white tea. They are phytoestrogens that possess antioxidant, anti-inflammatory, cardioprotective,


| Name          | Source            | Mode of action                          | Diseases                                                                 | Research stage                                      | Refs.       |
|---------------|-------------------|------------------------------------------|--------------------------------------------------------------------------|-----------------------------------------------------|-------------|
| Polyketides   |                   |                                          |                                                                          |                                                     |             |
| Oligomycin    | Streptomyces      | binding to the Fo region                 | liver cancer, non-small cell lung cancer, colon cancer, triple-negative breast cancer, ovarian cancer | preclinical                                         | 51–53       |
| Apoptolidin   | Nocardopsis spp.  | binding to the Fo region                 | lung cancer                                                               | preclinical                                         | 54,55       |
| Polyphenolics |                   |                                          |                                                                          |                                                     |             |
| Resveratrol   | grapes and berries| binding a hydrophobic pocket between the C-terminal region of the γ subunit and the hydrophobic inside of the β subunit | pheochromocytoma, colon cancer                                    | phase I in colon cancer (completed): ClinicalTrials.gov: NCT00256334, NCT0920803, and NCT00433576; phase I in unspecified adult solid tumor (completed): ClinicalTrials.gov: NCT0098969; phase II in multiple myeloma (terminated): ClinicalTrials.gov: NCT0920556; phase I in polycystic ovary syndrome (terminated): ClinicalTrials.gov: NCT01489319 | 56–58       |
| EGCG          | green tea         | inhibiting the ATP hydrolysis activity of ATP synthase | hepatocellular carcinoma, malignant pleural mesothelioma, colon cancer   | early phase I in colon cancer (recruiting): ClinicalTrials.gov: NCT02891538; phase I & II in prostate cancer: ClinicalTrials.gov: NCT0459407 (completed) and NCT04306855 (recruiting); phase I & II in breast cancer: ClinicalTrials.gov: NCT00516243 (completed), NCT02580279 (unknown), and NCT04597359 (not yet recruiting); phase II in lung cancer (enrolling by invitation): ClinicalTrials.gov: NCT02577393; phase II in nonmetastatic bladder cancer (completed): ClinicalTrials.gov: NCT0666562, | 59–61       |
| Curcumin      | the roots and stalks of Zingiberaceae | inhibiting the activity of ATP synthase | liver cancer, breast cancer, cervical carcinoma, prostatic cancer, lung cancer, leukemia, melanoma, colon cancer | phase II in breast cancer (completed): ClinicalTrials.gov: NCT01049398; phase III in prostate cancer (recruiting): ClinicalTrials.gov: NCT03769766; phase II in colorectal cancer (completed): ClinicalTrials.gov: NCT02439385, and so on | 43,62–68    |
| 17β-estradiol | Homo sapiens      | binding to the OSCP subunit of Fo region | liver tissue, rat brain                                                    | phase II in breast cancer: ClinicalTrials.gov: NCT01083641(terminated, has result), NCT0324259 (completed), and NCT01385280 (completed); phase II in prostate cancer (terminated, has result): ClinicalTrials.gov: NCT00459810; phase I in solid cancers (completed): ClinicalTrials.gov: NCT01209143; phase I in hematologic malignancies (recruiting): ClinicalTrials.gov: NCT03557619, and so on | 69–74       |

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## Table 1. Continued

| Name             | Source                | Mode of action                                                                 | Diseases                                      | Research stage                                                                 | Refs.   |
|------------------|-----------------------|-------------------------------------------------------------------------------|-----------------------------------------------|--------------------------------------------------------------------------------|---------|
| Genistein        | Soybean               | targeting polyphenol binding pocket of ATP synthase and blocking the rotation of the γ subunit | breast cancer                                 | phase II in breast cancer (completed): ClinicalTrials.gov: NCT00244933 and NCT00290758; phase II & III in prostate cancer (completed): ClinicalTrials.gov: NCT00584532 and NCT01325311; phase I & II in non-small cell lung cancer (completed): ClinicalTrials.gov: NCT01628471 and NCT02567799; phase I & II in colon cancer (completed): ClinicalTrials.gov: NCT01985763; phase I in breast cancer & endometrial cancer (completed): ClinicalTrials.gov: NCT00099008; phase II in bladder cancer (recruiting): ClinicalTrials.gov: NCT014899813 and NCT00118040; phase II in pancreatic cancer (completed): ClinicalTrials.gov: NCT00376948; phase I & II in pediatric relapsed or refractory malignancies (completed): ClinicalTrials.gov: NCT02499861; early phase I in kidney cancer & melanoma (completed): ClinicalTrials.gov: NCT00276835; phase I in cancer of head and neck (completed): ClinicalTrials.gov: NCT02075112 | 75,76   |
| Polyenic a-pyrones |                      |                                                                               |                                               |                                                                                 |         |
| Citreoviridin    | Penicillium, Aspergillus | binding to the β subunit of the F1 region                                      | lung adenocarcinoma, breast cancer            | preclinical                                                                     | 41,77–79 |
| Aurovertin B     | Calcarisporium arbuscular | binding to the β subunit of the F1 region                                      | breast cancer, colon cancer                   | preclinical                                                                     | 79–81   |
| Asteltoxin       | Aspergillus stellatus Curzi and Emericella variicolor | binding to the β subunit of the F1 region                                      | lung cancer, breast cancer                    | preclinical                                                                     | 82,83   |
| Synthetics       |                      |                                                                               |                                               |                                                                                 |         |
| Bedaquiline      | synthetic             | binding to the c subunit rotor and subunit ε of the ATP synthase               | tuberculosis, lung cancer, glioblastoma, breast cancer | preclinical                                                                     | 84–90   |
| Gboxin           | synthetic             | its positive charge influences the proton gradient of the inner mitochondrial membrane | glioblastoma                                 | preclinical                                                                     | 5       |
| Pd(II) COS@GbA   | synthetic             | inducing mitochondrial fragmentation and disrupting ATP synthase action        | prostate cancer                               | preclinical                                                                     | 91      |
| Edelfosine       | synthetic             | dissipation of the mitochondrial membrane potential                            | cervix epithelioid carcinoma, hematopoietic cancer | preclinical                                                                     | 92–95   |
| Miltefosine      | synthetic             | dissipation of the mitochondrial membrane potential                            | breast cancer                                 | approved in the topical treatment of metastatic skin lesions in breast cancer   | 96      |
| Perifosine       | synthetic             | dissipation of the mitochondrial membrane potential                            | advanced solid and leukemic tumors, brain tumors | phase I in advanced solid and leukemic tumors                                  | 97,98   |
| Proteins         |                      |                                                                               |                                               |                                                                                 |         |
| IF1              | Homo sapiens          | interacting with the F1 domain at the catalytic surface between the α and β subunit of ATP synthase, blocking the rotation of the complex | bladder carcinoma, glioma, metastatic colon cancer, triple-negative breast cancer | preclinical                                                                     | 10,99–101 |

(Continued on next page)
and anti-cancer properties.\textsuperscript{56,57} Resveratrol and piceatannol provide a wide range of preventive and therapeutic options against different types of cancer.\textsuperscript{57} They bind to a hydrophobic pocket between the hydrophobic C terminal region of the $\gamma$ subunit and the hydrophobic inside of the $\beta$ subunit.\textsuperscript{46} In this way, resveratrol promotes human pheochromocytoma cell death.\textsuperscript{58}

**EGCG**

One of the catechins, epigallocatechin gallate (EGCG), is abundant in green tea and inhibits ATP hydrolysis.\textsuperscript{46} EGCG facilitates apoptosis as well as cell cycle arrest, growth inhibition in hepatocellular carcinoma, malignant pleural mesothelioma cells, and bladder urothelial cells.\textsuperscript{59–61} EGCG can prevent various chronic diseases, including neurodegenerative disorders, through several molecular signaling pathways including MAS inhibition.\textsuperscript{118}

**Curcumin**

This MAS inhibitor is a natural polyphenol extracted from the roots and stalks of Zingiberaceae *Curcuma longa*, an herbal medicine with antitumor activity.\textsuperscript{62,119} It inhibits many cancers, including liver cancer, breast cancer, cervical carcinoma, prostatic cancer, and lung cancer. It affects several signaling pathways, with nuclear factor $\kappa$B (NF-$\kappa$B) signaling being prominently inhibited.\textsuperscript{63–68} Recently MAS inhibition independent of NF-$\kappa$B signaling was reported, which lowered ATP levels concomitantly with oxygen consumption, both \textit{in vivo} and \textit{in vitro}.

The energetic impairment by curcumin of L1210 murine lymphocytic leukemia, 4T1 murine breast, B16 murine melanoma, and CT26 murine colon tumor cell lines translated, also both \textit{in vitro} and \textit{in vivo}, into decreased tumor growth.\textsuperscript{44} According to ClinicalTrials.gov,\textsuperscript{69} 6 clinical studies have been done on curcumin, with 28 completed clinical trials, including 14 phase II trials. Curcumin on its own or in combination has been applied in studies of primary or metastatic breast cancer, colorectal cancer, pancreatic cancer, and endometrial carcinoma.

**17β-estradiol (E2)**

This compound plays a well-known role in breast cancer, binding to the estrogen receptor. In liver cells it also binds to the OSCP protein of MAS, promoting uncoupling.\textsuperscript{69–72,120}

**Genistein**

This isoflavone phytoestrogen from soybeans noncompetitively inhibits MAS. It targets the polyphenol binding pocket and blocks the rotation of the $\gamma$ subunit.\textsuperscript{73} Both genistein and estradiol induce

![Figure 4. Inhibitory sites of ATP synthase](image-url)
cell proliferation and apoptosis inhibition, cell cycle arrest and mitochondrial function, and dynamics damage of breast cancer cell lines.76

At present, 353 clinical studies of estradiol have been published. 61 clinical trials have been completed with results, and three clinical trials (phase I and phase II) have been completed. The drug was applied in the treatment of estrogen receptor-positive breast cancer, recurrent breast cancer, or solid cancers (ClinicalTrials.gov: NCT00324259, NCT01385280, and NCT01209143).

Polyenic α-pyrones
A polyenic α-pyrene is a six-membered cyclic unsaturated ester present in many natural products. Citreoviridin, aurovertin B and...
asteltoxin are all polyenic α-pyrene, and they target the β subunit of F1 to inhibit.121

**Citreoviridin**

This compound consists of an α-pyrene ring conjugated to a furan ring.73 It inhibits MAS by binding to the β subunit of F1, inhibiting in turn the proliferation and growth of lung adenocarcinoma cell lines. The unfolded protein response is activated without affecting healthy cells.41,77,122

**Aurovertin B**

This naturally occurring antibiotic is isolated from Calcarisporium arbuscular. It also interacts with F1’s β subunit and inhibits ATP synthesis.80 Aurovertin B strongly inhibits the proliferation of several breast cancer cell lines by suppressing the enhanced ATP synthesis in breast carcinoma.50 Aurovertin B, D, and E exhibit potent anti proliferative activity, particularly against triple-negative breast cancer in vivo and in vitro.123,124 They also facilitate the recognition and lysis of colon cancer cells by natural killer (NK) cells, by a mechanism that may involve MAS inhibition.81

**Asteltoxin**

This α-pyrene-containing mycotoxin is produced in Aspergillus stel latus Curzi and Emericella variecolor. Asteltoxin and its three dimers exert inhibitory effects on the lung cancer cell line H1299 and breast cancer line MCF7.82 Asteltoxin and asteltoxin B are moderately cytotoxic against several tumor cell lines.83

**Synthetic compounds**

In addition to the mentioned natural compounds, several synthetic MAS inhibitors have been developed for treating infectious diseases such as tuberculosis by inhibiting ATP synthase.122 Some were developed using computational science, with some working against cancer.5

**Bedaquiline**

This compound, developed by Janssen Pharmaceuticals in 2005, was approved by the US Food and Drug Administration (FDA) in 2012 for treating multidrug-resistant tuberculosis.125,126 It is a synthetic heterocyclic MAS synthase inhibitor that targets both the c subunit rotor and subunit β.35 Recently, Wu et al.55 suggested that bedaquiline blocks the growth, survival, and tumor angiogenesis of lung cancer, stem-like cancer cells, and glioblastoma.56–58 Similar to other ATP synthase inhibitors, it diminishes mitochondrial oxygen consumption by depleting and blocking the proliferative expansion of breast cancer stem cells.86

**Gboxin**

This small molecule was found by a cell-based high-throughput chemical screen. It inhibits the growth of mouse and human glioblastoma cells.5 A Pd(II) complex of a Gboxin analog-chitooligosaccharides conjugate (Pd(II)COS@GbA) was found to disrupt ATP synthase rotation, diminish ATP synthesis, and show anti-prostate cancer activity.91

Alkylphospholipid analogs (APLs) are developed as anticancer drugs, with amphiphilic structures similar to natural phospholipids, and they incorporate preferentially in the membranes of tumor cells.127 Structurally related anti-tumor APLs include a number of clinically promising drugs, such as edelfosine, miltefosine, perifosine, and erucylphosphocholine.92,96,97

Edelfosine, with antileishmanial and anticancer activity, specifically accumulated in the mitochondria or the lipid raft of tumor cells, leading to dissipation of the mitochondrial membrane potential and reactive oxygen species (ROS) generation by ATP synthase inhibition and raft disruption, eventually inducing apoptosis-like cell death.92,93

Miltefosine, also belonging to the APLs family and trademarked as Milteg, is the only APL that has been approved as an antitumor drug in the topical treatment of metastatic skin lesions in breast cancer.96

Perifosine and erucylphosphocholine are the new molecules synthesized as miltefosine variants.97 Perifosine has entered many phase I clinical trials in treating plenty of advanced solid and leukemic tumors, and many preclinical studies are being carried out with erucylphosphocholine in brain tumors.98

**Peptide inhibitors**

Several peptide inhibitors, including the endogenous MAS inhibitory factor 1 (IF1), angiotatin, and some chimeric antibodies, target MAS or ectopic ATP synthase, showing an anti-tumor activity in preclinical studies.

**IF1**

This protein interacts with the F1 domain when dephosphorylated at the catalytic surface between the α and β subunit of MAS, blocking the rotation of the complex and inhibiting the synthesis and hydrolysis of ATP.99 Its phosphorylation status is regulated by 5’-AMP-activated protein kinase (AMPK). Increased cyclic AMP (cAMP) levels activate AMPK: the phosphorylation of S39 in IF1 and the activation of protein kinase (AMPK). Increased cyclic AMP (cAMP) levels activate AMPK: the phosphorylation of S39 in IF1 and the activation of MAS thus facilitate ATP synthesis.128 High expression of IF1 in non-small cell lung cancer, bladder carcinoma, and gliomas has a bad prognosis.10 A recent study demonstrated that IF1 modulates the interplay between ROS and hypoxia in cancer cells, which might be associated with the cell survival supports, tumor progression, and anticancer drug resistance.12 In contrast, a high expression level of IF1 in breast and colon cancer predicts a better prognosis, especially in triple-negative breast cancer and metastatic colorectal cancer patients.10,100 Thus, the comprehensive role of IF1 in malignancy needs subtle stratification to help anticancer therapeutic strategies.

**Angiotatin**

This protein is an internal proteolytic fragment of plasminogen, dramatically inhibiting primary and metastatic tumor growth by blocking tumor angiogenesis.129 EAS is relevant to angiogenesis and the direct target of angiotatin.130 Angiotatin binds the α/β subunits of EAS, mediating the downregulation of endothelial cell proliferation...
and migration, and these effects will be depleted by the presence of the anti-α-subunit ATP synthase antibody. Hence, inhibition of EAS has been suggested for the antiangiogenetic therapeutic strategy by blocking tumor angiogenesis.\textsuperscript{130,131} Moreover, radiolabeled angiotatin may be a powerful tool for specific imaging or targeted radiotherapy of tumors due to the specific interaction.\textsuperscript{152}

Other chimeric antibodies have been developed that target the β subunit of EAS, inhibiting its activity.\textsuperscript{132} A strain of murine monoclonal antibody (mAb) mAb6F2C4 showed the angiotatin-like property to block extracellular ATP generation under extracellular acidic conditions and interrupt the angiogenetic process.\textsuperscript{131} Another murine mAb targeting the same site, McAb178-5G10, showed antitumor activity in multiple cancers.\textsuperscript{12,133} The humanized antibody Hai178 against the β subunit of EAS produced by the same team also had an anti-tumor effect in tumor xenografts,\textsuperscript{165} which provides a possibility for clinical application. This evidence ensures the potential of antibodies blocking EAS activity in cancer treatment.

DISCUSSION

MAS is upregulated in many cancers, and evidence is accumulating that MAS may serve as a potent anticancer target, especially in glioblastoma, ovarian cancer, prostate cancer, breast cancer, and clear cell renal cell carcinoma.\textsuperscript{26-30,36,134,135} However, there remain several challenges in translating preclinical MAS-targeting drugs to the clinic.

First, MAS universally exists in tumor cells and normal cells, therefore raising the concern about the potential of systematic toxicity to patients. According to ClinicalTrials.gov (https://www.clinicaltrials.gov/), the potential side effects caused by various MAS inhibitors are different. There are five MAS inhibitors that have reported clinical trial results. Resveratrol was safe and lacked serious adverse reactions, with mild gastrointestinal symptoms, including nausea, flatulence, abdominal discomfort, and diarrhea (ClinicalTrials.gov: NCT00098969). EGCG was well tolerated with minimal adverse events, including nausea, diarrhea, headache. These side effects were all grade 1 or 2 based on the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) version 3.0 (ClinicalTrials.gov: NCT00666562). Curcumin was safe, and no adverse events occurred during the study (ClinicalTrials.gov: NCT01042938). The incidence rate of serious adverse events caused by using estradiol was 23.53%, which included abdominal pain, diarrhea, nausea, and vomiting. All patients reported mild adverse events in the study (ClinicalTrials.gov: NCT00324259). The incidence rate of serious adverse events by using genistein was 9.68%, including dyspnea and ulceration. 80.65% of the patients reported mild adverse events in this study (ClinicalTrials.gov: NCT00290758).

To overcome the shortcomings of potential toxicity, (1) antibody drug conjugates (ADCs) can be a strategy to enhance the specificity of MAS-targeting drugs. ADCs represent a new class of cancer-targeting drugs that endow the specificity to cytotoxic chemicals by conjugating them to cancer antigen-specific antibodies. Antibody-assisted drug delivery dramatically reduces the systematic toxicity to cancer patients (e.g., T-DM1). T-DM1 significantly improved overall survival of patients with previously treated HER2\textsuperscript{+} metastatic breast cancer,\textsuperscript{136} and the rates of adverse events of grade 3 or above were reduced from 57% to 41%.\textsuperscript{137} (2) VDAC1 is a voltage-dependent anion channel protein that is a major component of the outer mitochondrial membrane, often overexpressed in many cancers.\textsuperscript{138} Studies have shown that silencing VDAC1 expression in cancer cells leads to metabolic reprogramming, reducing the expression of ATP5F1A.\textsuperscript{139-141} Therefore, silencing VDAC1 may decrease the level of ATP synthase without affecting healthy cells. (3) Another strategy to improve the efficacy/toxicity balance is to combine the energy supply blockers from MAS inhibitors with agents of other anti-cancer mechanisms. For instance, combination of the MAS inhibitor citreoviridin and the 26S proteasome inhibitor bortezomib improved anticancer activity in breast cancer cells.\textsuperscript{78} Combinatory use of multi-mechanism anti-cancer drugs is the basic and mostly chosen regimen for cancers at advanced stages.

Patel et al.\textsuperscript{47} provided an update on recently discovered ATP synthase modulators. A more comprehensive view of ATP synthase-targeting inhibitors was covered in their study. Because we have concentrated preferentially on the indications of ATP synthase-targeting inhibitors in cancer treatment, some natural inhibitors of the complex that have systemic toxicity or about which there is almost no relevant research in cancer treatment are not included in our review. We have elaborated the structure of the complex, detailed its significance in different types of malignant tumors, and reviewed the basic and clinical research progress of ATP synthase-targeting inhibitors in cancer treatment. A larger-scale and comprehensive screening of MAS inhibitors should be performed with the current high-throughput chemical screening technology to find more potential effective and specific anti-cancer drugs.

Second, the expression levels of the MAS-composing genes, the status of OXPHOS, and mitochondrial metabolism vary in different types of cancer.\textsuperscript{143,144} High expression of ATP5B predicts better local recurrence-free survival in nasopharyngeal carcinoma.\textsuperscript{134} In papillary thyroid cancer, ATP5A1 mRNA expression levels are downregulated in tumorous tissue with more lymph node metastases.\textsuperscript{145} Similarly, ATP5B is downregulated in breast, gastric, lung, and esophageal cancer.\textsuperscript{135} Thus, it is necessary to measure the status and inhibitory contribution of MAS before using a MAS inhibitor on tumor or in combination with other anticancer drugs.

Additionally, the challenge faced to make the MAS a dominant anti-tumor target should be ideally resolved. Only a certain part of tumors, which are still under to-be-defined conditions, are potentially sensitive to MAS inhibitors. For instance, mitoxantrone significantly benefits the progression-free and overall survival of cancer patients. However, in metastatic breast cancer, the response rate of mitoxantrone is only 20%.\textsuperscript{146} The expression of MAS was increased in mitoxantrone-resistant cells, so MAS might be a key target to reverse the resistance of metastatic breast cancer patients to this drug.\textsuperscript{31} Therefore, in certain cancers, the value of this complex as a target to
suppress primary cancer or reverse the resistance of tumor cell to the existing treatment should be determined.

Third, MAS is mutated in some primary human cancers. A total of 19 genes are involved in encoding ATP synthase. Except for MT-ATP6 and MT-ATP8, which are mitochondrial genes, the others are nuclear genes. According to The Cancer Genome Atlas (TCGA) database, the variation frequencies of these genes in pan cancers range from 0.5% to 2%, including structure variation, amplification, deep deletion, and other point mutations. Although not many relevant results have been reported, the abnormality of MAS composing genes on the binding sites of ATP inhibitors in about 2% of tumor patients may lead to a less sensitivity to the drugs. Given that condition, we may consider the use of other inhibitors that target different sites of ATP synthase, or redesign the inhibitor to specifically bind the mutated ATP synthase, hence inhibiting the activity of the enzyme.

Fourth, metabolism reprogramming as a process that occurred in cancer cells influences not only the cancer cells but also the microenvironment.\(^{147}\) For instance, lipid accumulation in myeloid-derived suppressor cells and tumor-associated macrophages, which may derive from adjacent cancer cells with enhanced fatty acid synthesis, has been verified to promote metabolic reprogramming and assisted these cells changing into immunosuppressive phenotypes.\(^{148}\) Additionally, tumor cells consume more glucose, which results in a glucose limitation for T cells, leading to a defective antitumor response.\(^{149}\) Metabolite imbalance aroused by enhanced MAS in tumor cells may provide an advantageous immune microenvironment for tumor progression. Interfering with the MAS-related metabolite deregulation may be a breakthrough auxiliary approach to phenotypically re-normalize the tumors to a sluggish status.

Additionally, previous studies have shown that estrogen supported the growth of tumors by activating a series of signaling pathways, and sustained exposure to exogenous estrogen was a risk factor for various cancers.\(^{150}\) Anti-estrogen therapies are important for cancers, especially for estrogen receptor-positive breast cancer.\(^{151}\) However, the function of estrogen as an ATP synthase inhibitor suppressing the activity of MAS and inducing mitochondrial functional damage and cell apoptosis have been discussed in this review. The distribution of the binding of estrogen on (1) MAS and on (2) the estrogen receptor may be different in the past, and it should be measured in future studies. This binding should also be considered and measured when using endocrine therapy on cancers such as breast cancer, ovarian cancer, and endometrial cancers.

In conclusion, MAS-targeted drugs represent an emerging family of anti-cancer agents in active development and should be identified and tested in further clinical trials to improve cancer patient outcomes in the future.

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AUTHOR CONTRIBUTIONS
All listed authors contributed to the writing of this review. All authors read and provided critical revision of the manuscript and approved the final version.

DECLARATION OF INTERESTS
The authors declare no competing interest.

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