

Progress in Redirecting Antiparasitic Drugs for Cancer Treatment

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Abstract: Drug repurposing is a feasible strategy in developing novel medications. Regarding the cancer field, scientists are continuously making efforts to redirect conventional drugs into cancer treatment. This approach aims at exploring new applications in the existing agents. Antiparasitic medications, including artemisinin derivatives (ARTs), quinine-related compounds, niclosamide, ivermectin, albendazole derivatives, nitazoxanide and pyrimethamine, have been deeply investigated and widely applied in treating various parasitic diseases for a long time. Generally, their pharmacokinetic and pharmacodynamic properties are well understood, while the side effects are roughly acceptable. Scientists noticed that some of these agents have anticancer potentials and explored the underlying mechanisms to achieve drug repurposing. Recent studies show that these agents inhibit cancer progression via multiple interesting ways, inducing ferroptosis induction, autophagy regulation, mitochondrial disturbance, immunoregulation, and metabolic disruption. In this review, we summarize the recent advancement in uncovering antiparasitic drugs' anticancer properties from the perspective of their pharmacological targets. Instead of paying attention to the previously discovered mechanisms, we focus more on newly emerging ones that are worth noticing. While most investigations are focusing on the mechanisms of their antiparasitic effect, more in vivo exploration in clinical trials in the future is necessary. Moreover, we also paid attention to what limits the clinical application of these agents. For some of these agents like ARTs and niclosamide, drug modification, novel delivery system invention, or drug combination are strongly recommended for future exploration.

Keywords: ferroptosis, autophagy, mitochondria, immunoregulation, glycolysis

Introduction

Cancer has become one of the biggest threats among all sorts of health concerns.¹ According to the Global Burden of Disease Study 2017, cancer-related deaths have increased by 25.4% over the past decade.¹ As one of the three main cancer treatments, chemotherapy is the major choice for most types of cancers. While scientists have made progress in reducing the death rates using these agents, existing traditional chemoagents generally have some side effects like nephrotoxicity or myelosuppression, which may limit their application in clinical practice.² Moreover, some cancers may develop resistance to these agents during the treatment, profoundly reducing the therapeutic effect.³ In this way, it is of great significance to include more effective chemo agents that exhibit antitumor properties in current cancer treatment. Novel medication invention is one of the main ways to develop new drugs. However, such an approach is relatively costly and time-consuming under the current drug designed and development model, based on

抗寄生虫药物用于癌症治疗的进展

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摘要：药物再利用是开发新型药物的可行策略。在癌症领域，科学家们不断努力将传统药物重新用于癌症治疗。这种方法旨在探索现有药物的新应用。抗寄生虫药物，包括青蒿素衍生物 (ART)、奎宁相关化合物、氯硝柳胺、伊维菌素、阿苯达唑衍生物、硝唑尼特和乙胺嘧啶，长期以来一直被深入研究并广泛应用于治疗各种寄生虫病。一般来说，它们的药代动力学和药效学特性是众所周知的，而副作用大致可以接受。科学家注意到其中一些药物具有抗癌潜力，并探索了实现药物再利用的潜在机制。最近的研究表明，这些药物通过多种有趣的方式抑制癌症进展，诱导铁死亡、自噬调节、线粒体紊乱、免疫调节和代谢紊乱。在这篇综述中，我们总结了从药理学靶点的角度揭示抗寄生虫药物抗癌特性的最新进展。我们关注的不是以前发现的机制，而是值得关注的新兴机制。虽然大多数研究都集中在其抗寄生虫作用的机制上，但未来需要在临床试验中进行更多的体内探索。此外，我们还关注了限制这些药物临床应用的因素。对于其中一些药物，如 ART 和氯硝柳胺，强烈建议在未来进行药物改造、新型给药系统发明或药物组合方面的探索。

关键词：铁死亡、自噬、线粒体、免疫调节、糖酵解

介绍

癌症已成为各种健康问题中最大的威胁之一。根据 2017 年全球疾病负担研究，癌症相关死亡人数在过去十年中增加了 25.4%。作为三种主要的癌症治疗方法之一，化疗是大多数类型癌症的主要选择。尽管科学家在降低使用这些药物的死亡率方面取得了进展，但现有的传统化疗药物通常具有一些副作用，例如肾毒性或骨髓抑制，这可能会限制其在临床实践中的应用。此外，一些癌症可能在治疗过程中对这些药物产生耐药性，从而大大降低治疗效果。因此，在当前的癌症治疗中加入更有效的抗肿瘤化疗药物具有重要意义。新药发明是开发新药的主要方式之一。然而，在目前的药物设计和开发模式下，这种方法相对昂贵且耗时，基于

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the fact that it would take more than ten years on average before an invented drug is applied clinically, regardless of the low overall success rate.⁴ Comparably, drug repurposing is more efficient and money-saving for the corporations, government and the patients, as such a strategy may help reduce the cost of drug invention, finally reduce the price of the medication. With more available preclinical experiments, clinical trials, and practice, it would take less time and lower cost to apply an approved drug in treating cancer.⁵

Antiparasitic drugs are a group of chemo agents that act against infections caused by parasites, including artemisinin derivatives (ARTs), quinine-related compounds, niclosamide, ivermectin, albendazole derivatives, nitazoxanide and pyrimethamine (Figure 1). These agents exhibit various modes of effect on parasites. Most of the FDA-approved antiparasitic agents have been applied clinically for a long time, and their pharmacokinetic and pharmacodynamic properties have been explored thoroughly. Moreover, their toxicity on normal human cells and possible adverse effects are well understood and mostly acceptable. In this way, scientists thought of the possibility of redirecting antiparasitic agents for treating cancers.

Inspiringly, some of these medications do exhibit anti-tumor properties. For some of these medications, the mechanism of how they kill cancer cells is similar to how they kill parasites. Moreover, researchers kept exploring and successfully uncovered several novel antitumor mechanisms that target other molecules and biological procedures that have not been discovered before. Multiple phenotypes and metabolisms are involved. Ferroptosis has been regarded as a new approach to induce cancer cell death, and interestingly, ARTs target the process to exert antitumor properties.⁶ Autophagy acts as a “Double-Edged Sword” in cancer cell metabolism, and its regulation is closely related to cancer cell death.⁷ Mitochondria is the cancer cells’ energy factory, and its dysfunction contributes a lot to cancer cell death.⁸ Aerobic glycolysis, known as the “Warburg Effect”, is an essential metabolic pathway and a therapeutic target for cancer cells.⁹ The tumor microenvironment is attracting scientists’ attention recently, and some of these antiparasitic medications exert immunoregulatory effects, which contribute to their antitumor properties.¹⁰ Several signal pathways are also involved in the anticancer potential of the antiparasitic agents. Altogether, these newly discovered

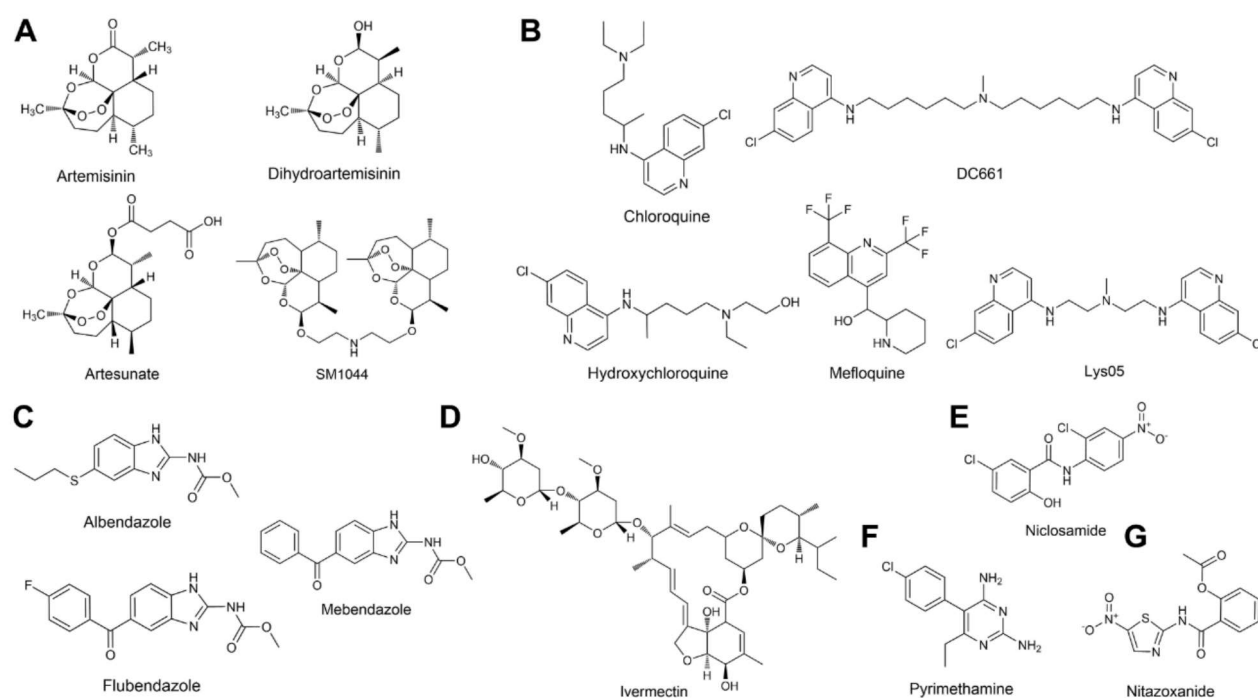


Figure 1 Chemical structure of the antiparasitic agents with anticancer properties: Artemisinin derivatives (**A**); Quinine related compounds (**B**); Albendazole derivatives (**C**); Ivermectin (**D**); Niclosamide (**E**); Pyrimethamine (**F**) and Nitazoxanide (**G**).

事实是，一种发明的药物从研发到临床应用平均需要十年以上时间，尽管总体成功率很低。相比之下，药物再利用对企业、政府和患者来说更高效、更省钱，因为这种策略有助于降低药物研发成本，最终降低药物价格。随着更多可用的临床前实验、临床试验和实践，将一种获批的药物应用于治疗癌症所需的时间和成本将更低。

抗寄生虫药物是一类对抗寄生虫感染的化学药剂，包括青蒿素衍生物 (ART)、奎宁相关化合物、氯硝柳胺、伊维菌素、阿苯达唑衍生物、硝唑尼特和乙胺嘧啶 (图 1)。这些药物对寄生虫的作用方式多种多样。大多数 FDA 批准的抗寄生虫药物已在临床上应用了很长时间，其药代动力学和药效学特性也已得到深入研究。此外，它们对正常人体细胞的毒性和可能的不良反应已被充分了解，并且大多是可以接受的。这样，科学家们想到了将抗寄生虫药物重新定向用于治疗癌症的可能性。

令人振奋的是，其中一些药物确实表现出抗肿瘤特性。对于其中一些药物，它们杀死癌细胞的机制与杀死寄生虫的机制相似。此外，研究人员不断探索，成功发现了几种新的抗肿瘤机制，这些机制针对以前从未发现过的其他分子和生物程序。涉及多种表型和代谢。铁死亡被认为是一种诱导癌细胞死亡的新方法，有趣的是，ART 靶向该过程以发挥抗肿瘤特性。自噬是癌细胞代谢中的一把“双刃剑”，其调节与癌细胞死亡密切相关。线粒体是癌细胞的能量工厂，其功能障碍是癌细胞死亡的重要原因。有氧糖酵解，被称为“瓦博格效应”，是癌细胞的重要代谢途径和治疗靶点。肿瘤微环境最近引起了科学家的关注，其中一些抗寄生虫药物发挥免疫调节作用，这有助于它们的抗肿瘤特性。抗寄生虫药物的抗癌潜力还涉及多种信号通路。总而言之，这些新发现的

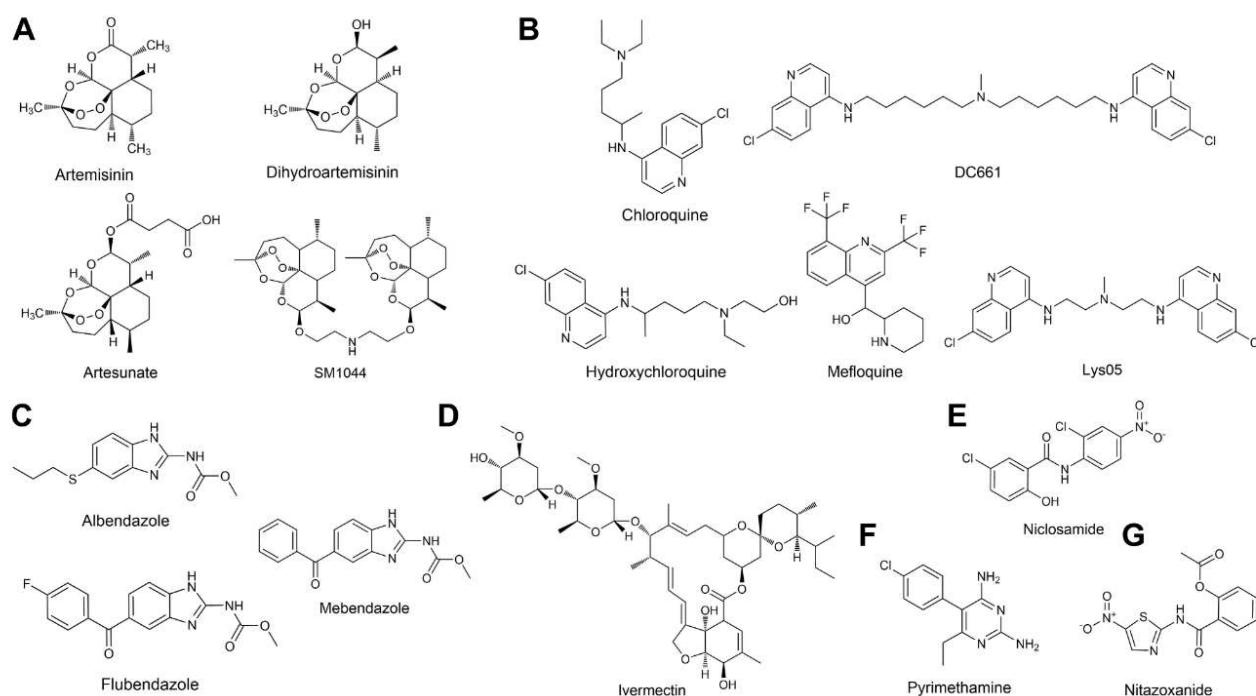


图 1 具有抗癌特性的抗寄生虫药物的化学结构：青蒿素衍生物 (A)；奎宁相关化合物 (B)；阿苯达唑衍生物 (C)；伊维菌素 (D)；氯硝柳胺 (E)；乙胺嘧啶 (F) 和硝唑尼特 (G)。

anticancer mechanisms profoundly bettered our understanding of these drugs.

In this review, we summarized and discussed the recent progress in redirecting antiparasitic drugs for cancer treatment, specifically from a view of the underlying mechanisms.

Ferroptosis Inducing Effect of Antiparasitic Agents

Scientists have explored the mechanism of how ART and its derivatives kill *Plasmodium* before. Heme and iron activate ARTs in vivo, and the cleavage of the endoperoxide bridge produces intracellular ROS, which is critical for its antimalarial effect.^{11,12} Although uncertainty and controversy still exist in its exact antimalarial mechanism, scientists believe that both iron and ROS play an essential role in its antiparasitic effect.

Interestingly, the antitumor effect of ARTs shares at least to some degree a similar mechanism with its antiparasitic effect (Table 1). In the early 21st century, scientists observed that ARTs' anticancer effect correlates with the existence of iron and ROS production.^{13,14} However, the big picture of how these two factors exert their tumor inhibitory function remains fuzzy for a long time. In 2012, Dixon et al firstly define the concept of

"Ferroptosis" as "Iron-dependent nonapoptotic cell death", which dramatically deepens understanding of iron-related cell death.¹⁵ Generally, ferroptosis refers to an iron-dependent and reactive oxygen species (ROS)-producing cell death procedure. Later, researchers recognized that ferroptosis induction is exactly how ARTs kill cancer cells.^{16–19}

ARTs function as multi-target ferroptosis inducers in cancer cells (Figure 2). One of the mechanisms is by stepping on the "accelerator" of the ferroptosis procedure. The transferrin receptor is the source of intracellular iron and thus is the upstream component in the ferroptosis pathway. Artesunate (ARS) and many other ARTs upregulate the expression level of the transferrin receptor, thus connecting the ferroptosis with ARS-induced cancer cell inhibition.^{19,20} The IRP/IRE (Iron Regulatory Proteins/Iron Responsive Element) system is probably the most critical regulator maintaining the intracellular iron hemostasis.²¹ It regulates the expression of a series of iron concentration-regulating proteins at the post-transcription level.²⁰ ARTs target this system and its downstream proteins to disturb the iron hemostasis in cancer cells. In normal situations, the IRP recognizes the free iron and reduces its binding capacity with IRE.²⁰ This results in upregulation of the ferritin expression. As the iron storage protein, ferritin helps maintain the normal intracellular

Table 1 Ferroptosis Inducing Effect of Antiparasitic Agents

Drug	Mechanism	Reference
Artemisinin	Targets the Iron Regulatory Proteins (IRP)/Iron Responsive Element (IRE) system and its downstream proteins to affect the iron hemostasis in cancer cells	[21]
	Directly associates with iron via redox reaction rather than interacting with the IRP/IRE system, thus results in no increase of ferritin	[23,24]
	Reduces the intracellular GSH level, and significantly promotes the Fenton reaction and peroxidation accumulation	[27]
	Induces ROS and causes mitochondrial damage, resulting in loss of mitochondrial membrane potential and decreased Bcl-2 level, finally results in intrinsic apoptotic pathway	[32]
	Induces ROS and causes DNA damage, resulting in DNA double-strand break(DSB), followed by upregulation of the DNA damage associated proteins, including γ H2AX. As a result, such DSB injury leads to G2/M phase cell cycle blockage.	33, [35–37]
Artesunate	Induces ferroptosis in cancer cells by interfering with the expression level of transferrin receptor	[19]
Dihydroartemisinin	Induces the autophagy-dependent degradation of ferritin by regulating the AMPK/mTOR/p70S6k pathway	[24,25]
	Induces the endoplasmic reticulum stress in glioma cells and further upregulates the expression level of GPX4 via the PERK-ATF4-HSPA5-GPX4 axis	[29]
	Induces ferroptosis via GPX4 expression inhibition in glioblastoma	[30]

抗癌机制极大地提高了我们对这些药物的理解。在这篇综述中，我们总结并讨论了抗寄生虫药物用于癌症治疗的最新进展，特别是从潜在机制的角度。

抗寄生虫药物的铁死亡诱导作用

此前，科学家对 ART 及其衍生物杀灭疟原虫的机制进行了探索，血红素和铁元素在体内激活 ART，内过氧化物键的断裂产生细胞内的 ROS，而 ROS 是其发挥抗疟作用的关键。虽然其确切的抗疟机制仍存在不确定性和争议，但科学家认为铁元素和 ROS 在其抗寄生虫作用中都发挥着至关重要的作用。有趣的是，ART 的抗肿瘤作用至少在某种程度上与其抗寄生虫作用具有相似的机制（表 1）。21 世纪初，科学家观察到 ART 的抗癌作用与铁的存在和 ROS 的产生有关。然而，这两个因素如何发挥其肿瘤抑制功能的大局长期以来仍不清楚。2012 年

Dixon 等首次将“铁死亡”这一概念定义为“铁依赖性非凋亡性细胞死亡”，大大加深了人们对铁相关细胞死亡的认识。一般认为，铁死亡是指一种依赖铁并产生活性氧（ROS）的细胞死亡过程。后来，研究人员认识到，诱导铁死亡正是 ART 杀死癌细胞的机制。ARTs 在癌细胞中作为多靶点铁死亡诱导剂发挥作用（图 2），其机制之一是踩下铁死亡过程的“加速器”。转铁蛋白受体是细胞内铁的来源，是铁死亡途径的上游成分。青蒿琥酯（ARS）等多种 ARTs 上调转铁蛋白受体的表达水平，从而将铁死亡与 ARS 诱导的癌细胞抑制联系起来。IRP/IRE（铁调节蛋白/铁反应元件）系统可能是维持细胞内铁止血的最关键调节器，它在转录后水平调节一系列铁浓度调节蛋白的表达。ARTs 靶向该系统及其下游蛋白，扰乱癌细胞的铁止血。在正常情况下，IRP 识别游离铁并降低其与 IRE 的结合能力，导致铁蛋白表达上调。作为铁储存蛋白，铁蛋白有助于维持细胞内正常

表 1 抗寄生虫药物的铁死亡诱导作用

Drug	机制	参考
青蒿素	靶向铁调节蛋白（IRP）/铁反应元件（IRE）系统及其下游蛋白，影响癌细胞的铁止血	[21]
	通过氧化还原反应直接与铁结合，而不是与 IRP/IRE 系统相互作用，因此不会导致铁蛋白增加	[23,24]
	降低细胞内 GSH 水平，显著促进 Fenton 反应和过氧化物积累	[27]
	诱导 ROS，造成线粒体损伤，导致线粒体膜电位丧失，Bcl-2 水平下降，最终导致内在凋亡途径	[32]
	诱导 ROS 引起 DNA 损伤，导致 DNA 双链断裂（DSB），进而引发与 DNA 损伤相关的蛋白（包括γH2AX）上调，导致 DNA 损伤，进而导致 G2/M 期细胞周期阻滞。	[35]
青蒿琥酯	通过干扰转铁蛋白受体的表达水平诱导癌细胞铁死亡	[19]
双氢青蒿素	通过调节 AMPK/mTOR/p70S6k 通路诱导自噬依赖性铁蛋白降解	[24,25]
	通过 PERK-ATF4-HSPA5-GPX4 轴诱导胶质瘤细胞内质网应激，进一步上调 GPX4 的表达水平	[29]
	通过抑制胶质母细胞瘤中的 GPX4 表达来诱导铁死亡	[30]

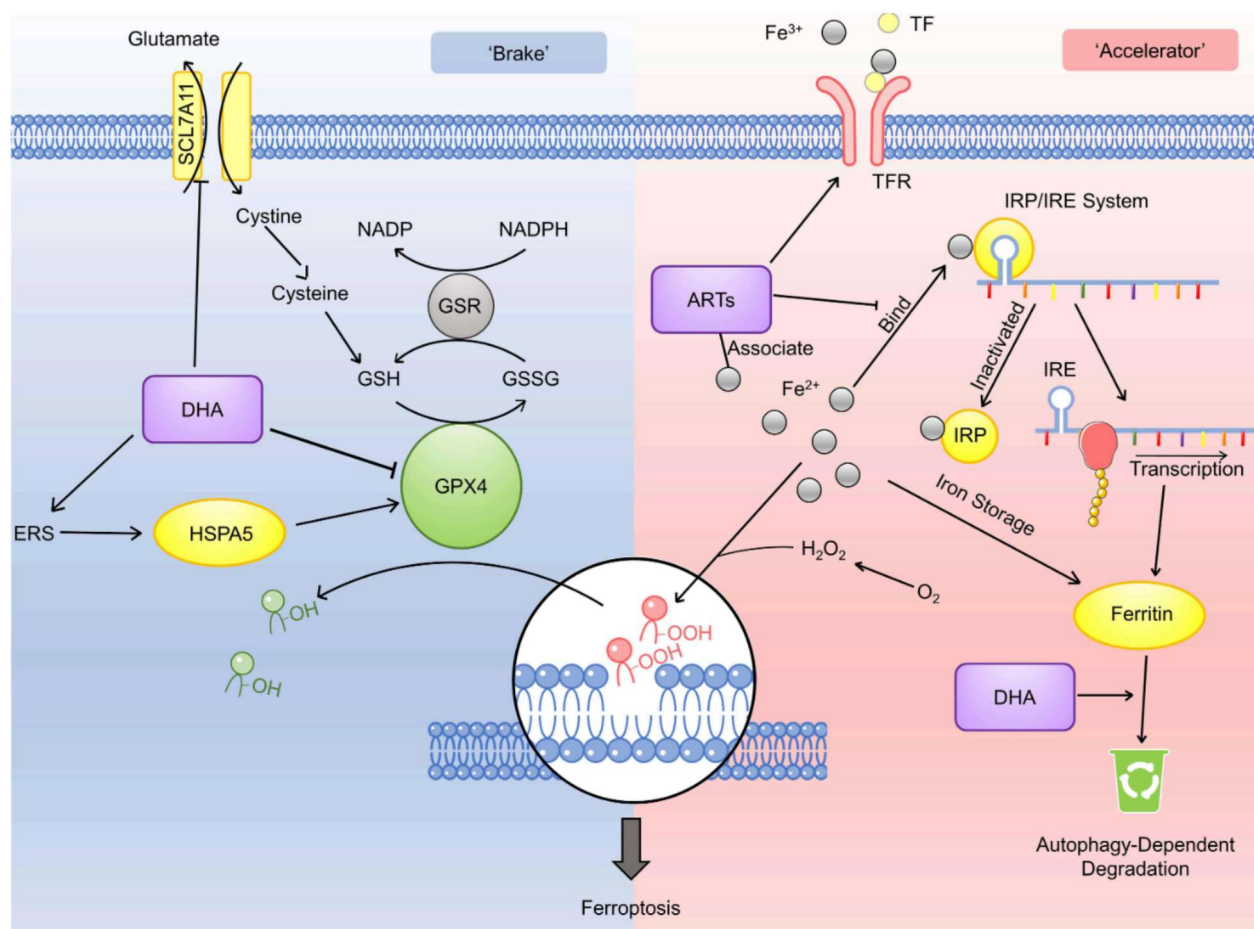


Figure 2 Mechanism of the ferroptosis regulating effect of the antiparasitic agents. The inhibitory regulation of ferroptosis (the “brake”) is shown on the left side and the promotive regulation (the “accelerator”) is shown on the right side. DHA downregulates the PRIM2/SLC7A11 axis and further suppresses the GSH production. DHA also downregulates the GPX4 expression and releases the brake of ferroptosis. However, there is also evidence suggesting that DHA may upregulate GPX4 via upregulating the endoplasmic reticulum stress (ERS) and the HSPA5 expression. ARTs upregulate the expression of TFR, which would subsequently increase the intracellular iron level. ARTs associate with Fe^{2+} and prevent its combination with the IRP/IRE system, thus inhibit the expression level of ferritin and increase the intracellular iron level. DHA can also promote the degradation of ferritin.

iron concentration.²² ARTs can directly associate with iron via Redox reaction.²³ However, Chen’s study revealed that these associated irons fail to interact with the IRP/IRE system, resulting in no increase of ferritin.²⁴ However, the ART-associated irons’ superoxidative reaction-catalyzing ability remains similar to free irons. In this way, free irons escape from ferritin’s regulation and accumulate in the cell while preserving its ability to promote ferroptosis.²⁴ Interestingly, scientists found another pathway that ARTs can influence ferritin level. Dihydroartisinin (DHA) induces autophagy-dependent ferritin degradation by regulating the AMPK/mTOR/p70S6k pathway. Again, this results in increased intracellular iron concentration.^{24,25}

ARTs may also regulate the negative-regulatory factors (the “brake”) of ferroptosis. As an anti-oxidative

substance, glutathione (GSH) reduces the oxidative injury caused by ROS, therefore reduces the injury caused by ferroptosis.²⁶ However, the administration of the artesunate or DHA reduces the intracellular GSH level.^{27,28} Further exploration suggests that DHA downregulates the PRIM2/SLC7A11 axis.²⁸ As a key cysteine concentration regulator, SLC7A11 regulates the GSH biosynthesis. In this way, DHA suppresses the intracellular GSH level. In a common ferroptosis pathway, glutathione peroxidase 4 (GPX4) functions as an inhibitory factor via facilitating the transition from GSH to oxidized glutathione (GS-SG).¹⁶ Scientists have demonstrated that DHA induces ferroptosis via downregulating GPX4 expression.²⁹ In Chen’s study, however, they showed the other aspect of DHA’s effect on GPX4 level. Their investigation demonstrated that DHA exerts endoplasmic reticulum stress in

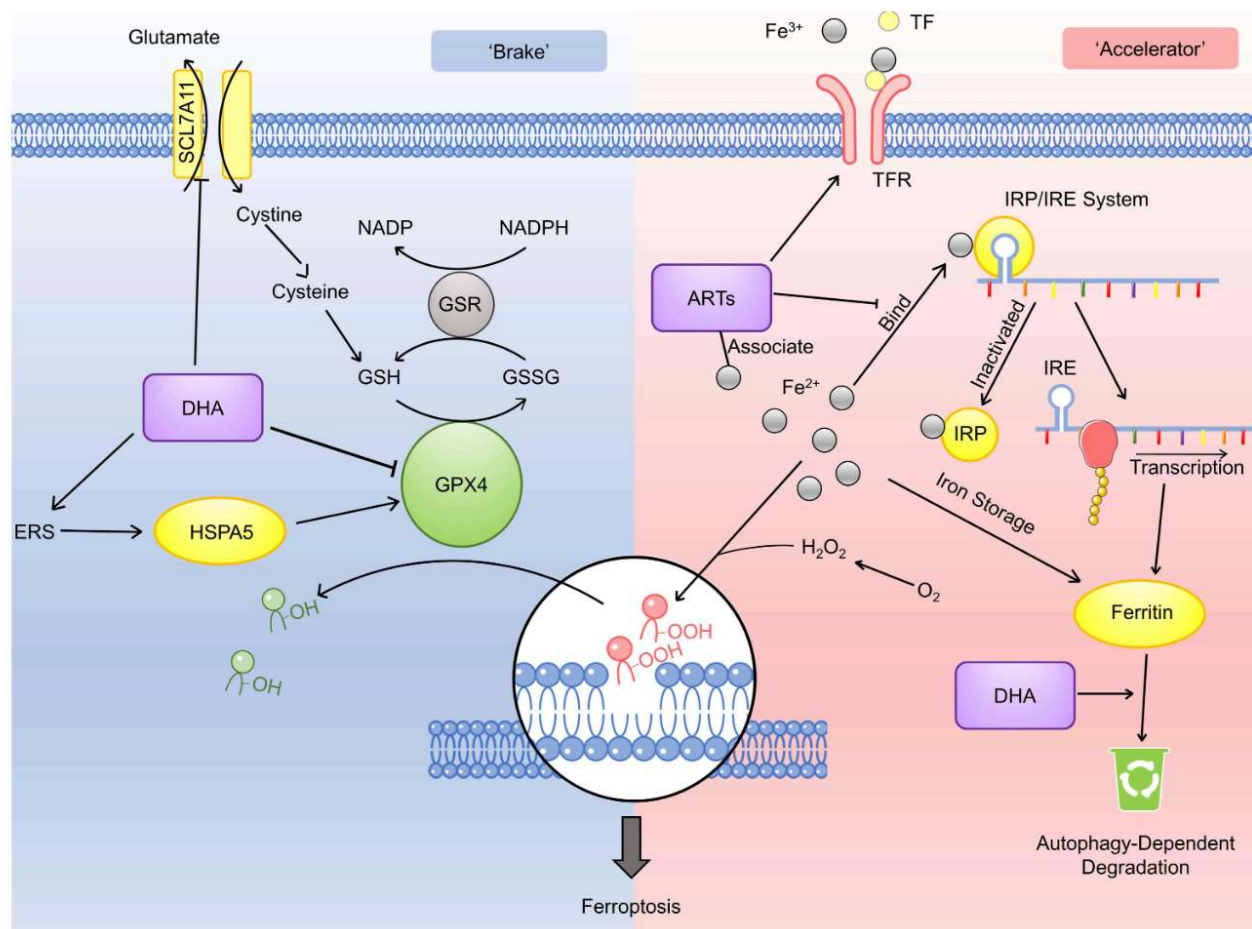


图 2 抗寄生虫药物调控铁死亡的机制。左侧为铁死亡的抑制调控（“刹车”），右侧为促进调控（“加速”）。DHA 下调 PRIM2/SLC7A11 轴，进而抑制 GSH 生成，同时下调 GPX4 表达，解除铁死亡的刹车。但也有证据表明 DHA 可能通过上调内质网应激（ERS）和 HSPA5 表达，上调 GPX4。ARTs 上调 TFR 表达，进而升高细胞内铁水平。ARTs 与 Fe 结合，阻止其与 IRP/IRE 系统结合，从而抑制铁蛋白表达，升高细胞内铁水平。DHA 还能促进铁蛋白的降解。

铁浓度。ARTs 可以通过氧化还原反应直接与铁结合。然而，陈的研究发现，这些结合的铁无法与 IRP/IRE 系统相互作用，导致铁蛋白不增加。然而，ART 相关铁的超氧化反应催化能力仍然与游离铁相似。这样，游离铁就逃脱了铁蛋白的调控，在细胞中积累，同时保留了其促进铁死亡的能力。24 有趣的是，科学家发现了 ARTs 影响铁蛋白水平的另一条途径。二氢青蒿素（DHA）通过调节 AMPK/mTOR/p70S6k 通路诱导自噬依赖性铁蛋白降解。这同样会导致细胞内铁浓度升高。

谷胱甘肽（GSH）能减轻 ROS 引起的氧化损伤，从而减轻铁死亡引起的损伤。然而，青蒿琥酯或 DHA 的给药会降低细胞内的 GSH 水平。进一步的研究表明，DHA 下调了 PRIM2/SLC7A11 轴。作为关键的半胱氨酸浓度调节剂，SLC7A11 调节 GSH 的生物合成。通过这种方式，DHA 抑制了细胞内的 GSH 水平。在常见的铁死亡途径中，谷胱甘肽过氧化物酶 4（GPX4）通过促进从 GSH 到氧化谷胱甘肽（GSSG）的转变起抑制因子的作用。科学家已经证明 DHA 通过下调 GPX4 的表达来诱导铁死亡。然而，在陈的研究中，他们展示了 DHA 对 GPX4 水平影响的另一个方面。他们的研究表明，DHA 在细胞中发挥内质网应激

ART 还可以调节铁死亡的负调节因子（“制动器”）。作为抗氧化剂

glioma cells. Subsequently, HSPA5 (heat shock protein family A (Hsp70) member 5) is upregulated, further increasing GPX4 expression.³⁰ In this way, the cells neutralized the DHA-induced ROS stress and escaped from ferroptosis. Not surprisingly, inhibition on the PERK/ATF4/HSPA5 pathway further strengthens the ferroptosis-inducing effect of DHA.²⁹ To further release the brake of the ferroptosis pathway, Chen et al combined DHA with a potent GPX4 inhibitor RSL3.²⁴ Such a combination synergistically promotes the ferroptosis procedure and strengthens the inhibitory effect on various cancer cell lines. In the future, animal experiments would be needed to evaluate the anticancer property of such combination in vivo. At the same time, it would be meaningful to try combining DHA with other GPX4 inhibitors, such as

ML-120 or ML-162, in treating cancer cells. Taken together, we can summarize that ARTs are multi-target ferroptosis promoters, both targeting the “accelerator” and the “brake” in this procedure.

The correlation between ferroptosis and cancer immunity regulation is attracting scientists’ attention.³⁸ On one hand, cancer cells that undergo ferroptosis may release signals like may AA (Arachidonic acid) metabolites that affect immune cells and regulate local immune reaction. Notably, such ferroptosis acts like a double-edged sword, meaning that it can be immunosuppressive or immunopromotive depending on the signal that a ferroptotic cell secretes.³⁸ On the other hand, ferroptosis also happens in immune cells (eg macrophage-1/2) under pharmaceutical induction, and will interfere with their function and

Table 2 Autophagy Regulating Effect of Antiparasitic Agents

Drug	Mechanism	Reference
Autophagy Inducer		
Dihydroartemisinin	Induces autophagy characterized by LC-II upregulation in leukemia cells	[43]
	Induces autophagy via phosphorylation of Bcl-2 at Ser 70, and also functions as an mTOR inhibitor in Hela cells	[32]
	Induces autophagy via promoting the DAPK1-induced phosphorylation of Beclin-1	[48]
ART dimer SM1044	Promotes the de novo synthesis of ceramide, thus promoting the CaMKK2-AMPK-ULK1 pathway	[50]
Flubendazole	Upregulates the LC-II level; disrupts normal microtubule, and thus interferes with the lysosomal function and results in mTOR's dislocation from the lysosome membrane induced acetylation of microtubule activates JNK and results in phosphorylation of Bcl-2	[56]
	Blocks the JNK/STAT3 pathway	[57]
	Binds with EVA1A at Thr113, thus induces EVA1A-mediated autophagy	[58]
Ivermectin	Induces ATP-release	[61]
	Induces autophagy via inhibiting P21-activated kinase 1 and the blockage of the whole PAK1/Akt/mTOR pathway ⁶²	[62]
Autophagy inhibitor		
Chloroquine	Impairs the autophagosome bulk's degradation and blocks autophagosome and lysosome fusion	[67]
Hydroxychloroquine, HCQ dimer DC611 and Lys05	Inhibits autophagy via PPT1-mediated lysosome inhibition	[68]
Mefloquine	Downregulates LAMP1/2 and inhibits RAB5/7	[72]
Nitazoxanide	Induces cell cycle arrest and upregulate ING by blocking the lysosome acidification and autolysosome maturation	[73]

胶质瘤细胞。随后，HSPA5（热休克蛋白家族 A（Hsp70）成员 5）上调，进一步增加 GPX4 表达。这样，细胞就中和了 DHA 诱导的 ROS 应激并逃脱了铁死亡。不出所料，抑制 PERK/ATF4/HSPA5 通路进一步增强了 DHA 诱导铁死亡的作用。为了进一步释放铁死亡通路的制动，陈等人将 DHA 与强效 GPX4 抑制剂 RSL3 相结合。这种组合协同促进了铁死亡过程并增强了对各种癌细胞系的抑制作用。未来需要进行动物实验来评估这种组合在体内的抗癌特性。同时，尝试将 DHA 与其他 GPX4 抑制剂组合也将很有意义

比如 ML-120 或 ML-162，在治疗癌细胞方面具有潜力。综上所述，我们可以总结出 ART 是多靶点铁死亡促进剂，既针对这一过程中的“加速器”，又针对“制动器”。铁死亡与癌症免疫调节之间的关联性正引起科学家的关注。一方面，发生铁死亡的癌细胞可能释放信号，如 AA（花生四烯酸）代谢物，影响免疫细胞，调节局部免疫反应。值得注意的是，这种铁死亡就像一把双刃剑，根据铁死亡细胞分泌的信号，它可以抑制免疫，也可以促进免疫。另一方面，铁死亡也会发生在药物诱导下的免疫细胞（如巨噬细胞-1/2），会干扰其功能并

表 2 抗寄生虫药物的自噬调节作用

Drug	机制	参考
自噬诱导剂		
双氢青蒿素	诱导白血病细胞中以 LC-II 上调为特征的自噬	[43]
	通过 Bcl-2 Ser 70 位点的磷酸化来诱导自噬，还可作为 Hela 细胞中的 mTOR 抑制剂	[32]
	通过促进 DAPK1 诱导的 Beclin-1 磷酸化来诱导自噬	[48]
ART 二聚体 SM1044	促进神经酰胺的从头合成，从而促进 CaMKK2-AMPK-ULK1 通路	[50]
氟苯哒唑	上调 LC-II 水平，破坏正常微管，从而干扰溶酶体功能，导致 mTOR 从溶酶体膜上移位，诱导微管乙酰化，激活 JNK，导致 Bcl-2 磷酸化	
	阻断 JNK/STAT3 通路	[57]
	与 EVA1A 在 Thr113 位点结合，从而诱导 EVA1A 介导的自噬	[58]
伊维菌素	诱导 ATP 释放	[61]
	通过抑制 P21 激活的激酶 1 和阻断整个 PAK1/Akt/mTOR 通路来诱导自噬	[62]
自噬抑制剂		
氯喹	损害自噬体本体的降解并阻止自噬体与溶酶体的融合 [67]	
羟氯喹、HCQ 二聚体 DC611 和 Lys05	通过 PPT1 介导的溶酶体抑制来抑制自噬	[68]
甲氟喹	下调 LAMP1/2 并抑制 RAB5/7	[72]
硝唑尼特	通过阻断溶酶体酸化和自溶酶体成熟来诱导细胞周期停滞并上调 ING	[73]

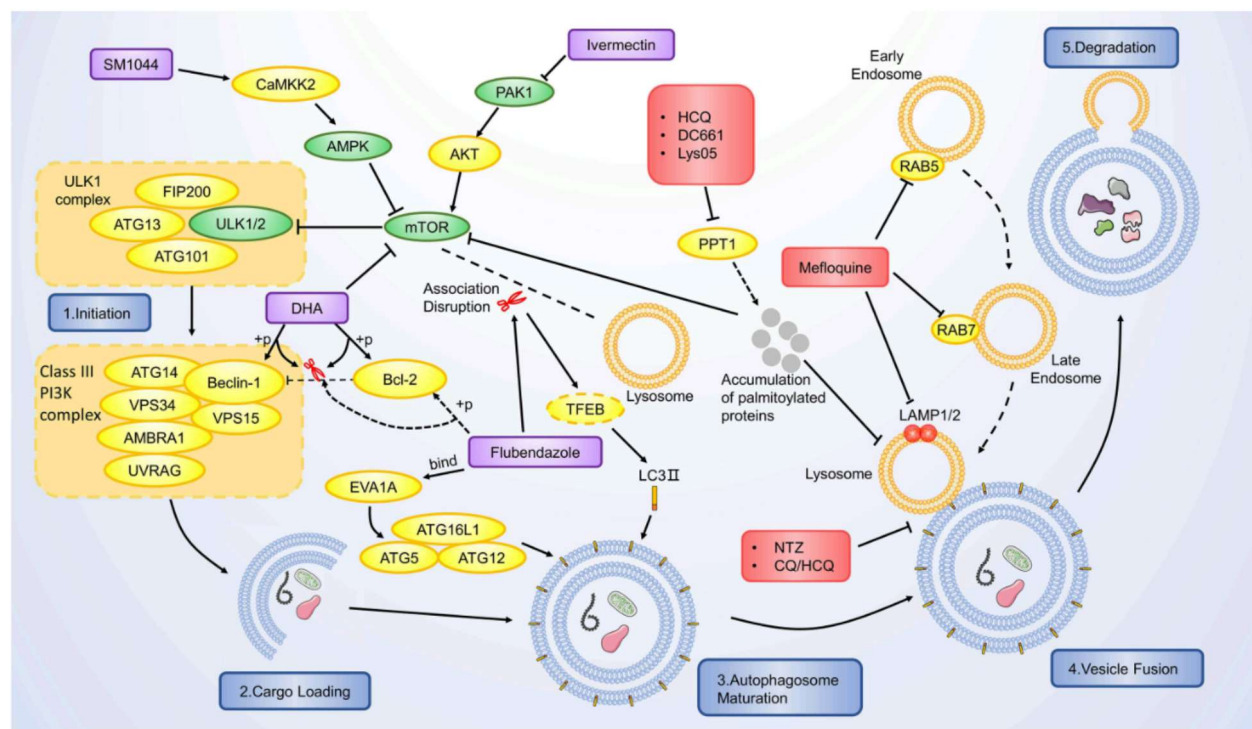


Figure 3 Mechanism of the autophagy regulating effect of the antiparasitic agents. The autophagy-promotive agents are shown in purple boxes and autophagy-inhibitory agents are shown in red boxes. mTOR is one of the major inhibitory elements that targets the initiation of the autophagic procedure. SM1044, DHA and ivermectin inhibit mTOR and subsequently activate the autophagic process. Flubendazole dissociates mTOR from the lysosome, leading to nuclear translocation of TFEB and finally upregulates LC3. It can also phosphorylate Bcl-2 via JNK-I activation and release its inhibition on Beclin-1, which is part of the Class III PI3K complex. Flubendazole also binds with EVA1A and further induces EVA1A mediated autophagy. HCQ, DC661 and Lys05 inhibit the PPT1 and result in accumulation of palmitoylated proteins, which would concurrently inhibit lysosome and mTOR. Nitazoxanide and CQ/HCQ inhibit the fusion between autophagosome and lysosome. Mefloquine targets RAB5/7 and LAMP1/2 to inhibit the lysosome maturation.

anticancer properties.^{38,39} Regarding the ARTs' research field, there are investigations focusing on how ARTs affect cancer immunity. However, there are currently no available papers focusing on whether their immunoregulating effect correlates with ferroptosis. In the future, it would be interesting to study how ART-induced ferroptosis influences the tumor microenvironment, will it cause immunosuppression or immunopromotion? Likewise, will immune cells undergo ferroptosis under the treatment of ARTs and what would be the downstream effects?

Autophagy Regulating Effect of Antiparasitic Agents

Autophagy functions as a double-edged sword in cancer cells and increasingly attracts scientists' attention since its discovery.^{40,41} It refers to a highly conservative process that degrades cytoplasmic components to survive critical stress.⁴² Collectively, there are mainly five steps in the autophagic process: (i) initiation; (ii) Cargo initiation; (iii) Autophagosome maturation; (iv) Fusion between

autophagosome and lysosome, (v) Formation of autolysosome and nutrient recycling.⁴² We observed an interesting phenomenon that most antiparasitic agents target autophagy procedure, either as inducer or inhibitor, and contribute to their anticancer property (Table 2). In this way, we will discuss the autophagy-regulating effect of the antiparasitic agents in detail (Figure 3).

Antiparasitic Agents as Autophagy Inducer

Wang et al were the first to link the ARTs' antitumor effect with autophagy. In 2012, they found that DHA induces autophagy characterized by microtubule-associated protein light chain 3-II (LC3-II) upregulation in leukemia cells.⁴³ From then on, research focusing on this field started to show up, and the past several years witnessed a significant advancement in understanding ARTs-related autophagy. The autophagy induction effect was validated in various cancers, including breast cancer, colorectal cancer, ovarian cancer, leukemia, and glioma.⁴⁴ Scientists revealed

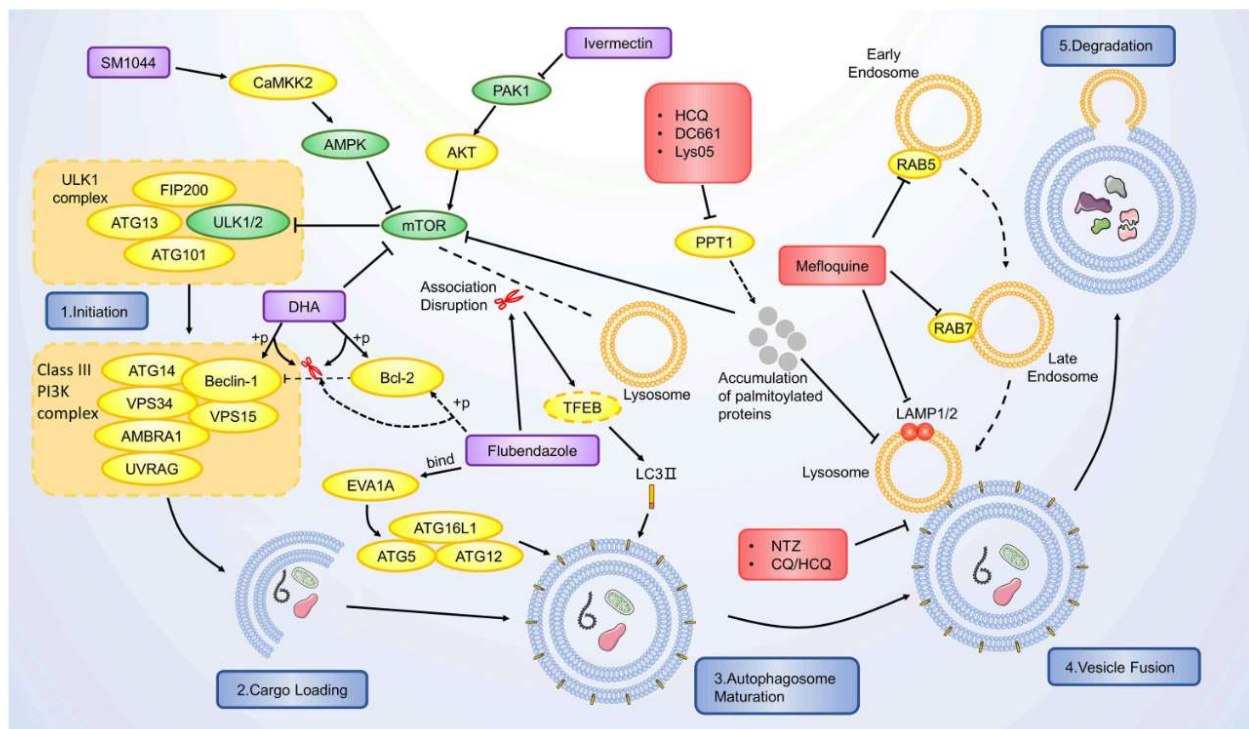


图3 抗寄生虫药物对自噬的调控机制。紫色框表示自噬促进剂，红色框表示自噬抑制剂。mTOR是启动自噬过程的主要抑制因子之一。SM1044、DHA和伊维菌素抑制mTOR，从而激活自噬过程。氟苯达唑使mTOR从溶酶体中分离，导致TFEB核转位，最终上调LC3。它还可以通过JNK-1激活磷酸化Bcl-2，从而释放对III类PI3K复合物的一部分Beclin-1的抑制。氟苯达唑还与EVA1A结合，进一步诱导EVA1A介导的自噬。HCQ、DC661和Lys05抑制PPT1，导致棕榈酰化蛋白的积累，从而同时抑制溶酶体和mTOR。硝唑尼特和CQ/HCQ抑制自噬体与溶酶体的融合，甲氧喹靶向RAB5/7和LAMP1/2，抑制溶酶体的成熟。

抗癌特性。关于ARTs的研究领域，有研究关注ART如何影响癌症免疫力。但目前还没有论文关注其免疫调节作用是否与铁死亡相关。未来，研究ART诱导的铁死亡如何影响肿瘤微环境，会引起免疫抑制还是免疫促进？同样，在ARTs治疗下，免疫细胞是否会发生铁死亡，下游效应是什么？这将是一个有趣的问题。

自噬过程主要有五个步骤：(i) 启动；(ii) 货物启动；(iii) 自噬体成熟；(iv) 自噬体与溶酶体融合；(v) 自噬体形成和营养循环。我们观察到一个有趣的现象，即大多数抗寄生虫药物以自噬过程为目标，无论是作为诱导剂还是抑制剂，并有助于其抗癌特性（表2）。通过这种方式，我们将详细讨论抗寄生虫药物的自噬调节作用（图3）。

抗寄生虫药物的自噬调节作用

自噬在癌细胞中起着双刃剑的作用，自发现以来，越来越受到科学家的关注。它是指一种高度保守的过程，可以降解细胞质成分以抵御关键压力。

抗寄生虫剂作为自噬诱导剂

王等人首次将ART的抗肿瘤作用与自噬联系起来。2012年，他们发现DHA诱导白血病细胞中的自噬，其特征是微管相关蛋白轻链3-II（LC3-II）上调。从那时起，专注于该领域的研究开始出现，过去几年在理解ART相关自噬方面取得了重大进展。自噬诱导作用在多种癌症中得到验证，包括乳腺癌、结直肠癌、卵巢癌、白血病和神经胶质瘤。科学家揭示

multiple mechanisms involved in ARTs-induced autophagy, in which the Beclin-1/Bcl-2 complex is one of their main targets. The importance of Bcl-2 and Beclin-1 in autophagy has been demonstrated clearly.^{45,46} Beclin-1 plays a central role in autophagy as it regulates the formation and maturation of autophagosomes. Moreover, the dissociation of Beclin-1 from Bcl-2 is critical for its biological activity. Wang et al revealed that DHA induces autophagy via phosphorylation of Bcl-2 at Ser 70.³² According to the previous report, phosphorylation of Bcl-2 at this site would dissociate Beclin-1, thus triggering the autophagic pathway.⁴⁷ Similarly, in cholangiocarcinoma, DHA was reported to induce autophagy via promoting the Death Associated Protein Kinase 1(DAPK1)-induced phosphorylation of Beclin-1, again detaches Beclin-1 from Beclin-1/Bcl-2 complex.⁴⁸ ARTs also regulate some autophagy-related pathways. The mammalian target of the rapamycin (mTOR) pathway plays an inhibitory role in autophagy, and targeting the mTOR pathway to induce autophagy has become a cancer treatment therapy.⁴⁹ Wang et al reported that DHA functions as an mTOR inhibitor in Hela cells, thus inducing autophagy.³² Interestingly, a novel ART derivative, SM1044, also shows the autophagy-inducing property in a different manner.⁵⁰ It promotes the de novo synthesis of ceramide, promoting the CaMKK2-AMPK-ULK1 pathway, and finally induces autophagy.

Autophagy induced by ARTs also correlates with the other pharmaceutical effects. The relationship between autophagy and ferroptosis is worth discussing. On the one hand, Du's study suggested that DHA-induced autophagy accelerates the degradation of ferritin, and autophagy related 7 (ATG7)-knockdown abolishes cancer cells from DHA-induced cell death.²⁵ Further study revealed that DHA induces the lysosomal degradation of ferritin, as we have discussed before. On the other hand, Chen et al demonstrated that at low concentrations, DHA-induced ferroptosis is independent of autophagy.²⁴ Moreover, although knockdown of autophagy related 5 (ATG5) delayed DHA-induced ferroptosis, DHA can still sensitize cancer cells to erastin-induced ferroptosis in such condition, suggesting the DHA can induce autophagy in an autophagy-independent manner.²⁴ Collectively, these data suggest that DHA-induced autophagy contributes to the process of ferroptosis. However, the autophagy process is probably unnecessary for DHA-induced ferroptosis, as several autophagy-independent pathways result in ferroptosis. Autophagy also correlates with ARTs-induced cell

cycle arrest. Previous studies revealed that DHA/ARS-induced cell cycle arrest is dependent on autophagy, and inhibition of autophagy attenuates such cell cycle blockage.^{51,52} Interestingly, DHA downregulates the telomere shelterin component TBP-related factor 2(TRF2) via autophagy-mediated degradation, thus impairing the normal cell cycle.⁵¹ Regarding apoptosis, the autophagy process seems to play a protective role in ART-induced apoptosis. Jiang et al reported that autophagy inhibition augments ARS-induced apoptosis.⁵³ Similarly, Ganguli's study suggests that autophagy inhibition showed a synergistic effect with ART by promoting apoptosis.⁵⁴ It is conceivable that ARTs emerge as stress for cancer cells, as it may induce apoptosis. Autophagy may help cancer cells survive those critical situations, thus exhibiting a cytoprotective effect. Taken together, as a "Double-edged Sword", ARTs-induced autophagy mainly functions as a cancer killer. It will significantly help scientists better understand the pharmaceutical effect of ARTs if more investigations focus on how autophagy cross-talk with the other mechanisms of ARTs.

Recent years witnessed a considerable breakthrough in understanding autophagy-related mechanisms of benzimidazole derivatives. In 2015, Zhang et al screened out flubendazole as an autophagy-related 4B (Atg4B) docking molecule via the in-silico analysis, suggesting this agent's potential target.⁵⁵ Almost simultaneously, Chauhan et al identified flubendazole as an autophagy inducer through experiments.⁵⁶ It significantly upregulates the LC3-II level, suggesting that it augments the autophagic process.⁵⁶ As flubendazole disrupts normal microtubule, it interferes with the lysosomal function and results in mTOR's dislocation from the lysosome membrane.⁵⁶ The down-regulation of the mTOR pathway leads to the dephosphorylation and nuclear translocation of the transcription factor EB (TFEB), which is a critical transcript factor in lysosomal biogenesis and autophagy. Moreover, flubendazole-induced acetylation of microtubule activates JNK and results in phosphorylation of Bcl-2.⁵⁶ As a result, Beclin-1 is disassociated from Bcl-2 and again induces autophagy. Lin et al further revealed that flubendazole also blocks the JNK/STAT3 pathway, which is the upstream negatively regulating pathway of the autophagic process, resulting in autophagy induction.⁵⁷ Zhen et al revealed that flubendazole exerts autophagy inducing effect in an EVA1A-related manner.⁵⁸ EVA1A has been reported to induce autophagosome formation via interacting with ATG16L1.⁵⁹ Their analysis revealed that flubendazole

ARTs 诱导的自噬涉及多种机制, 其中 Beclin-1/Bcl-2 复合物是其主要靶点之一。Bcl-2 和 Beclin-1 在自噬中的重要性已被清楚证实。Beclin-1 在自噬中起着核心作用, 因为它调节自噬体的形成和成熟。此外, Beclin-1 与 Bcl-2 的分离对其生物活性至关重要。Wang 等人发现 DHA 通过 Bcl-2 在 Ser 70 处的磷酸化来诱导自噬。根据之前的报道, Bcl2 在此位点的磷酸化会使 Beclin-1 分离, 从而触发自噬途径。同样, 在胆管癌中, 据报道 DHA 通过促进死亡相关蛋白激酶 1 (DAPK1) 诱导的 Beclin-1 磷酸化来诱导自噬, 再次将 Beclin-1 从 Beclin-1/Bcl-2 复合物中分离。ARTs 还调节一些自噬相关通路。哺乳动物雷帕霉素靶蛋白 (mTOR) 通路在自噬中起抑制作用, 靶向 mTOR 通路诱导自噬已成为一种癌症治疗疗法。Wang 等报道 DHA 在 Hela 细胞中作为 mTOR 抑制剂发挥作用, 从而诱导自噬。有趣的是, 一种新型 ART 衍生物 SM1044 也以不同的方式表现出自噬诱导特性。它促进神经酰胺的从头合成, 促进 CaMKK2-AMPK-ULK1 通路, 最终诱导自噬。

ART 诱导的自噬也与其他药物效应相关。自噬与铁死亡之间的关系值得讨论。一方面, 杜的研究表明 DHA 诱导的自噬加速了铁蛋白的降解, 而自噬相关 7 (ATG7) 的敲低消除了癌细胞因 DHA 诱导的细胞死亡。进一步的研究表明, DHA 诱导铁蛋白的溶酶体降解, 正如我们之前讨论过的。另一方面, Chen 等人证明, 在低浓度下, DHA 诱导的铁死亡与自噬无关。此外, 尽管自噬相关 5 (ATG5) 的敲低延迟了 DHA 诱导的铁死亡, 但在这种情况下, DHA 仍然可以使癌细胞对 erastin 诱导的铁死亡敏感, 这表明 DHA 可以以自噬非依赖的方式诱导自噬。总之, 这些数据表明 DHA 诱导的自噬有助于铁死亡过程。然而, 自噬过程对于 DHA 诱导的铁死亡来说可能是不必要的, 因为几种自噬非依赖的途径会导致铁死亡

自噬也与 ARTs 诱导的细胞周期阻滞有关。先前的研究表明, DHA/ARS 诱导的细胞周期阻滞依赖于自噬, 抑制自噬可减弱这种细胞周期阻滞。有趣的是, DHA 通过自噬介导的降解下调端粒保护蛋白成分 TBP 相关因子 2 (TRF2), 从而损害正常的细胞周期。关于细胞凋亡, 自噬过程似乎在 ART 诱导的细胞凋亡中起着保护作用。Jiang 等人报道, 自噬抑制增强了 ARS 诱导的细胞凋亡。同样, Ganguli 的研究表明, 自噬抑制通过促进细胞凋亡与 ART 表现出协同作用。可以想象, ARTs 成为癌细胞的压力, 因为它可能诱导细胞凋亡。自噬可能帮助癌细胞在这些危急情况下生存, 从而表现出细胞保护作用。总而言之, ARTs 诱导的自噬是一把“双刃剑”, 主要发挥癌症杀手的作用。如果能更多地研究自噬如何与 ARTs 的其他机制相互影响, 将极大地帮助科学家更好地理解 ARTs 的药物效应。

近年来, 苯并咪唑类化合物在自噬相关机制方面的研究取得了重大突破。2015 年, Zhang 等通过计算机模拟筛选出氟苯达唑作为自噬相关的 4B (Atg4B) 对接分子, 提示该药物的潜在靶点。几乎与此同时, Chauhan 等通过实验发现氟苯达唑是一种自噬诱导剂, 它显著上调 LC3-II 水平, 提示它能增强自噬过程。56 氟苯达唑破坏了正常的微管, 干扰了溶酶体功能, 导致 mTOR 从溶酶体膜上移位。mTOR 通路的下调导致转录因子 EB (TFEB) 去磷酸化和核转位, 而 TFEB 是溶酶体生物合成和自噬中的关键转录因子。此外, 氟苯达唑诱导的微管乙酰化激活 JNK, 导致 Bcl-2 磷酸化, Beclin1 与 Bcl-2 分离, 再次诱导自噬。Lin 等进一步发现, 氟苯达唑还能阻断自噬过程上游负调控通路 JNK/STAT3, 从而诱导自噬。Zhen 等发现, 氟苯达唑通过 EVA1A 相关方式发挥自噬诱导作用。据报道, EVA1A 通过与 ATG16L1 相互作用诱导自噬体形成。他们的分析发现, 氟苯达唑

probably binds with EVA1A at Thr113, thus induces EVA1A-mediated autophagy. While most studies suggest that flubendazole/mebendazole generated autophagy function as an anticancer mechanism in cancer cells, controversy still exists. Sung et al demonstrated that while mebendazole functions as an antiangiogenic agent via inhibiting the proliferation of endothelial cells, mebendazole-induced autophagy is observed, and inhibiting such autophagy enhances its anti-proliferative effect.⁶⁰ In this way, mefloquine-induced autophagy seems to be cytoprotective. It would be interesting to validate the overall effect of mebendazole/flubendazole-induced autophagy on both carcinogenesis and angiogenesis in a mouse model, thus concluding whether it is a beneficial mechanism or potential therapeutic target.

Scientists discovered the significance of autophagy in the ivermectin-induced anticancer effect in 2015. Draganov et al demonstrated that ivermectin induces ATP-release and further induces autophagy in breast cancer cells.⁶¹ Later, Dou et al revealed that ivermectin inhibits cancer cell proliferation in an autophagy-mediated manner.⁶² Such ivermectin-induced autophagy correlates with inhibition of P21-activated kinase 1 and the whole PAK1/Akt/mTOR pathway blockage.⁶² Similarly, Liu et al demonstrated a similar mechanism in glioma cells.⁶³ Mitophagy, an emerging concept, refers to selective autophagic degradation of mitochondria.⁶⁴ Zachari et al reported that ivermectin induces mitophagy in embryonic fibroblasts.⁶⁵ It would be interesting to validate whether ivermectin induces such mitophagy in cancer cells in future exploration.

Antiparasitic Agents as Autophagy Inhibitor

While autophagy induction promotes cancer cell death, inhibiting autophagy may also contribute to anticancer property. The autophagy inhibitory effect of chloroquine (CQ) and its derivatives has attracted scientists' interest for a long time. While more and more studies focused on its application in various cancer types, the detailed mechanism of how CQs induces autophagy remained insufficiently understood. The past several years witnessed several inspiring progress in understanding the underlying mechanisms. It has been known that CQ, HCQ and Lys05 mainly target autophagy by blocking autophagosome and lysosome fusion.⁶⁶ Mauthe et al revealed that CQ induces autophagy inhibition differently from BafA1, a commonly

used autophagy inhibitor.⁶⁷ It impairs the autophagosome bulk's degradation, while the lysosomal acidity is not interfered with.⁶⁷ Interestingly, Rebecca et al demonstrated a different autophagy-inducing mechanism of CQ derivatives.^{68,69} They identified palmitoyl-protein thioesterase 1 (PPT1) as a common target of CQ derivatives including hydroxychloroquine (HCQ), DC661, and Lys05.^{68,69} PPT1 functions as a thioester bond breaker of the palmitoylated proteins. It promotes tumor proliferation growth, and targeting PPT1 inhibits tumor progression. Their studies revealed that inhibition on PPT1 leads to accumulation of palmitoylated proteins, which would disrupt the lysosome catabolism. Inspiringly, their investigations revealed that PPT1 inhibition also results in direct inhibition of mTORC1, which is similar to the pharmaceutical mechanism of the autophagy inducers. While the upstream of autophagy is activated, the downstream events (lysosome function) is totally blocked. In this way, PPT1 inhibitors would harvest the anticancer effect of both autophagy inhibitors and autophagy inducers. To some degree, this is similar to co-administration of the autophagy inducer and autophagy inhibitor, which have shown synergistic anticancer effect, however with one single agent.⁷⁰ Comparing the final anticancer effect between PPT1 inhibition and coadministration of autophagy inducer and inhibitor would be interesting. Current publications are still insufficient to evaluate the other downstream effects of PPT1 inhibition, and how cancer cells would response to such concurrent inhibition of autophagy and mTORC1 remains fuzzy. It is worthy to pay more attention on PPT1 inhibitors and to see if it could be applied in clinical practice. Mefloquine (MQ), another CQ derivative, was also found to induce mitochondrial autophagy in esophageal squamous carcinoma cells.⁷¹ Takeda investigated deeper and revealed that MQ inhibits the expression of Lysosomal Associated Membrane Protein 1/2 (LAMP1/2), the lysosome markers that are essential for the normal function of the lysosome and the autophagy process.⁷² Further investigation revealed that it targets the lysosomal function via inhibiting RAB5/7 expression, which is critical in lysosome formation.⁷²

Nitazoxanide (NTZ) is another worth noticing autophagy inhibitor. Wang et al revealed that NTZ induces cell cycle arrest by upregulating ING (Inhibitor of Growth 1) in glioblastoma, which is mediated by inhibiting its autophagic degradation.⁷³ Further exploration demonstrated that NTZ blocks the lysosome acidification and autolysosome maturation, thus reducing the late-stage autophagic flux. In

可能与 EVA1A 在 Thr113 位点结合,从而诱导 EVA1A 介导的自噬。虽然大多数研究表明氟苯咪唑/甲苯咪唑产生的自噬在癌细胞中起着抗癌作用,但仍然存在争议。Sung 等人证明,虽然甲苯咪唑通过抑制内皮细胞增殖发挥抗血管生成剂的作用,但可以观察到甲苯咪唑诱导的自噬,抑制这种自噬会增强其抗增殖作用。因此,甲氟喹诱导的自噬似乎具有细胞保护作用。在小鼠模型中验证甲苯咪唑/氟苯咪唑诱导的自噬对致癌作用和血管生成的整体影响将会很有趣,从而得出结论它是否是一种有益的机制或潜在的治疗靶点。2015 年,科学家们发现了自噬在伊维菌素诱导的抗癌作用中的重要性。Draganov 等人证明伊维菌素诱导 ATP 释放,进而诱导乳腺癌细胞中的自噬。后来, Dou 等人发现伊维菌素以自噬介导的方式抑制癌细胞增殖。伊维菌素诱导的自噬与抑制 P21 活化激酶 1 和整个 PAK1/Akt/mTOR 通路阻断有关。同样,刘等人在胶质瘤细胞中也证明了类似的机制。线粒体自噬是一个新兴概念,是指线粒体的选择性自噬降解。Zachari 等人报道伊维菌素在胚胎成纤维细胞中诱导线粒体自噬。在未来的探索中验证伊维菌素是否在癌细胞中诱导这种线粒体自噬将是有趣的。

一种常用的自噬抑制剂。它阻碍自噬体本体的降解,而不影响溶酶体的酸性。有趣的是, Rebecca 等人证明了 CQ 衍生物诱导自噬的不同机制。他们发现棕榈酰蛋白硫酯酶 1 (PPT1) 是 CQ 衍生物的共同靶点,包括羟氯喹 (HCQ)、DC661 和 Lys05。PPT1 充当棕榈酰化蛋白的硫酯键断裂剂。它促进肿瘤增殖生长,而靶向 PPT1 可抑制肿瘤进展。他们的研究表明,抑制 PPT1 会导致棕榈酰化蛋白的积累,从而扰乱溶酶体的分解代谢。更鼓舞人心的是,他们的研究表明,抑制 PPT1 也会导致直接抑制 mTORC1,这与自噬诱导剂的药物机制类似。当自噬的上游被激活时,下游事件(溶酶体功能)被完全阻断。这样,PPT1 抑制剂将获得自噬抑制剂和自噬诱导剂的抗癌作用。在某种程度上,这类似于自噬诱导剂和自噬抑制剂的共同给药,它们已显示出协同抗癌作用,但仅使用一种药物。比较 PPT1 抑制和自噬诱导剂和抑制剂共同给药之间的最终抗癌效果将会很有趣。目前的出版物仍然不足以评估 PPT1 抑制的其他下游效应,癌细胞对这种同时抑制自噬和 mTORC1 的反应仍不清楚。值得更多地关注 PPT1 抑制剂,看看它是否可以应用于临床实践。另一种 CQ 衍生物甲氟喹 (MQ) 也被发现能诱导食管鳞状癌细胞的线粒体自噬。武田进行了更深入的研究,发现 MQ 可抑制溶酶体相关膜蛋白 1/2 (LAMP1/ 2) 的表达,而溶酶体相关膜蛋白 1/2 (LAMP1/ 2) 是溶酶体正常功能和自噬过程所必需的溶酶体标志物。进一步的研究表明,它通过抑制 RAB5/7 表达来靶向溶酶体功能,而 RAB5/7 表达对溶酶体的形成至关重要。

硝唑尼特 (NTZ) 是另一个值得关注的自噬抑制剂。Wang 等发现 NTZ 通过上调胶质母细胞瘤中的 ING (生长抑制剂 1) 来诱导细胞周期停滞,这是通过抑制其自噬降解来介导的。进一步的研究表明,NTZ 阻断了溶酶体的酸化和自噬溶酶体的成熟,从而减少了晚期自噬通量。在

抗寄生虫剂作为自噬抑制剂

虽然自噬诱导会促进癌细胞死亡,但抑制自噬也可能有助于抗癌。氯喹 (CQ) 及其衍生物的自噬抑制作用长期以来引起了科学家的兴趣。虽然越来越多的研究集中在其在各种癌症类型中的应用,但 CQ 诱导自噬的具体机制仍未得到充分了解。过去几年,人们在理解潜在机制方面取得了一些令人鼓舞的进展。已知 CQ、HCQ 和 Lys05 主要通过阻断自噬体和溶酶体融合来靶向自噬。Mauthe 等人发现 CQ 诱导自噬抑制的方式与 BafA1 不同

the future, validating such autophagy inhibitory effect of NTZ in other cancer cells and exploring the other downstream effect of such autophagic inhibition would be of great significance.

Generally, the autophagy inhibitory effect has two main significance. First, based on the fact that autophagy can help cancer cells suffer intolerant situations, autophagy inhibition decreases cancer cells.^{74,75} Once the cancer cells fail to perform the autophagy procedure fully, apoptosis is often triggered and causing cell death.^{74,75} Second, autophagy inhibition profoundly decreases cancer cells' surviving ability under other anticancer agents' treatment, thus enhancing their pharmacologic effect. In recent years, scientists moved on to investigate more downstream effects of autophagy inhibition. While most researches focused on the direct impact of CQ-induced autophagy on cancer cells, New et al paid more attention to its impact on cancer-associated fibroblasts (CAF).⁷⁶ They observed a relatively high level of basal autophagy in CAF cells and demonstrated that the autophagy-dependent secretion of CAF promotes the progression of HNSCC. Targeting CAF autophagy with CQ inhibits proliferation, migration, and invasion of cancer cells, suggesting its therapeutic effect. Interestingly, in another study, Zhao et al revealed that CAF might promote cancer cell stemness via inducing autophagy.⁷⁷ In this way, CQ may inhibit the CAF-induced stemness via inhibiting CAF-induced autophagy.

Application of Autophagy Regulators: Future Directions

Autophagy functions as a double-edged sword in cancer cells.^{78,79} On one hand, mutation-induced autophagy reduction helps cancer cells accumulate ROS and abnormal organelles, contributing to malignant transformation during tumorigenesis.⁷⁴ On the other hand, strengthened autophagy help cancer cells survive under stress condition (eg hypoxia or medication) in the later stage of cancer progression.⁷⁴ Moreover, while autophagy enhances tumor immunity from some aspects (eg autophagy enhances MHCII process and presentation, which are critical in malignancy recognition), it attenuates the immune response from other aspects (eg autophagy degrades NK-derived granzyme B so that NK-mediated cell death is attenuated).⁸⁰ In this way, the proper application of autophagy regulators would be of great importance.

There have been many preclinical studies and clinical trials focusing on autophagy inhibitors (eg CQ and HCQ) in the cancer field (discussed later in section 3). In most of these trials, autophagy inhibitors are applied combined with other medications to reduce chemo-resistance. This is a good strategy but not all we can do. Although both autophagy enhancement and inhibition may bring benefits to cancer reduction, it should be highlighted that a basal level autophagy flux is essential for cancer cell survival.⁸¹

Table 3 Mitochondria Disrupting Effect of Antiparasitic Agents

Drug	Mechanism	Reference
Chloroquine	Induces mitochondrial damage, results in mitochondrial membrane depolarization and the release of cytochrome c; inhibits cytochrome c oxidase activity, thus increases the ROS level	[83]
Niclosamide	Disturbs mitochondrial respiration and induces mitochondrial depolarization, thus promotes glycolysis and decreases glycolytic capacity and reserve	[86]
	Upregulates pyruvate influx into mitochondria and lowers the pentose phosphate pathway and phosphoglycerate activity dehydrogenase pathway	[87]
	Triggers intracellular calcium flux via mitochondrial uncoupling, thus disturbs the arachidonic acid metabolism in a p53 deficit-dependent manner	[88]
	Induces apoptosis via the intrinsic mitochondrial pathway	[89]
Ivermectin	Induces mitochondrial dysfunction and oxidative stress via inhibiting the Akt/mTOR pathway	[90]
	Induces mitochondrial damage leads to increased Bax/Bcl-2 ratio, which leads to cytoplasm c release and caspase-mediated cancer cell apoptosis	[93]
Nitazoxanide/RM4819	Both NTZ and RM4819 exhibit mitochondria uncoupling effect, only RM4819 shows mitochondria complex III inhibitory effect	[94,95]

未来在其他癌细胞中验证 NTZ 这种自噬抑制作用以及探索这种自噬抑制的其他下游效应将具有重要意义。

总体而言，自噬抑制效应主要有两点意义。首先，由于自噬可以帮助癌细胞承受不耐受的环境，因此自噬抑制会减少癌细胞。一旦癌细胞无法充分进行自噬程序，通常会引发细胞凋亡并导致细胞死亡。其次，自噬抑制会大大降低癌细胞在其他抗癌药物治疗下的存活能力，从而增强其药理作用。近年来，科学家开始研究自噬抑制的更多下游效应。虽然大多数研究集中在 CQ 诱导的自噬对癌细胞的直接影响，但 New 等人更关注其对癌症相关成纤维细胞 (CAF) 的影响。他们观察到 CAF 细胞中基础自噬水平相对较高，并证明自噬依赖性 CAF 的分泌促进了 HNSCC 的进展。用 CQ 靶向 CAF 自噬可抑制癌细胞的增殖、迁移和侵袭，从而表明其具有治疗作用。有趣的是，在另一项研究中，Zhao 等人揭示了 CAF 可能通过诱导自噬来促进癌细胞干性。这样，CQ 可能通过抑制 CAF 诱导的自噬来抑制 CAF 诱导的干性。

自噬调节剂的应用：未来方向

自噬在癌细胞中是一把双刃剑，一方面，突变诱导的自噬降低有助于癌细胞在肿瘤发生过程中积累 ROS 和异常细胞器，从而促进恶性转化；另一方面，自噬增强有助于癌细胞在癌症进展后期应激条件下（如缺氧或药物）存活。此外，自噬虽然从某些方面增强了肿瘤免疫力（例如自噬增强了 MHC I/II 过程和呈递，这对恶性肿瘤识别至关重要），但它从其他方面减弱了免疫反应（例如自噬降解了 NK 衍生的颗粒酶 B，从而减弱了 NK 介导的细胞死亡）。因此，正确使用自噬调节剂将至关重要。

在癌症领域，已经有许多临床前研究和临床试验专注于自噬抑制剂（例如 CQ 和 HCQ）（第 3 节后面将讨论）。在大多数这些试验中，自噬抑制剂与其他药物联合使用以降低化学耐药性。这是一个很好的策略，但并不是我们能做的全部。虽然自噬增强和抑制都可能对癌症减少有益，但应该强调的是，基础水平的自噬通量对于癌细胞存活至关重要。

表 3 抗寄生虫药物的线粒体破坏作用

Drug	机制	参考
氯喹	诱导线粒体损伤，导致线粒体膜去极化，释放细胞色素 c；抑制细胞色素 c 氧化酶活性，从而增加 ROS 水平	[83]
氯硝柳胺	干扰线粒体呼吸，诱导线粒体去极化，从而促进糖酵解，降低糖酵解能力和储备	[86]
	上调丙酮酸流入线粒体，降低戊糖磷酸途径和磷酸甘油酸活性脱氢酶途径	[87]
	通过线粒体解偶联触发细胞内钙通量，从而以 p53 缺陷依赖的方式扰乱花生四烯酸代谢	[88]
	通过内在线粒体途径诱导细胞凋亡	[89]
伊维菌素	通过抑制 Akt/mTOR 通路诱发线粒体功能障碍和氧化应激	[90]
	诱导线粒体损伤导致 Bax/Bcl-2 比率增加，从而导致细胞质 c 释放和 caspase 介导的癌细胞凋亡	[93]
硝唑尼特/ RM4819	NTZ 和 RM4819 均表现出线粒体解偶联作用，只有 RM4819 表现出线粒体复合物 III 抑制作用	[94,95]

From this aspect, a complete inhibition on autophagy may be a practical approach to kill cancer cells, regardless of what role autophagy is functioning. Combining CQ, HCQ, or MQ with other autophagy inhibitors like GSK690693 or Autophinib may be a potent combination in cancer inhibition. Regarding autophagy inducers, we believe that future exploration should focus more on its cancer immunity regulatory effect. Although autophagy is considered to have a complicated effect on immune response, it improves the effectiveness of antigen-presenting cell (APC) and cytotoxic T lymphocytes (CTL), which are the major players in cancer immunity. Similarly, although autophagy upregulates many cytokines in the tumor micro-environment, the majority are immunoreactive ones.⁸⁰ In this way, it is worth trying the combination of autophagy inducers with immunotherapies, like CAR-T (chimeric antigen receptor T-cell) therapy or other adoptive cellular immunotherapies.

Mitochondria Disrupting Effect of Antiparasitic Agents

Mitochondrial damage is another worth noting mechanism involved in the antiparasitic agents' anticancer property (Table 3). Generally, targeting mitochondria may lead to two results. First, direct injury on mitochondria will trigger the intrinsic apoptosis pathway, leading to cell death. Second, as the energy factory, mitochondrial dysfunction will significantly disrupt normal cell metabolism, leading to energy insufficiency and reducing viability.

Recent studies continue to deepen our understanding of the mechanism in CQs.^{82,83} Liang et al revealed that CQ targets the invasiveness and migrating ability of cancer stem-like cells of triple-negative breast cancer (TNBC) by inducing mitochondrial damage, characteristic of abnormal mitochondrial structure.⁸³ Such mitochondrial damage leads to mitochondrial membrane depolarization and the release of cytochrome c.⁸³ CQ also inhibits cytochrome c oxidase activity, which transfers the electron from cytochrome c to oxygen, leading to an increased level of ROS.⁸³ In this way, the CQ-induced ROS results in DNA double-strand damage characteristic of γ -H2AX accumulation. Besides inducing DNA damage, CQ also impairs the DNA repair ability of TNBC cancer cells, thus further worsening its DNA-related injury.⁸³ Both autophagy inhibition, mitochondrial damage, and downstream ROS production may contribute to cancer cell death. Notably, Vessoni et al pointed out that, although

CQ induces all these pathologic processes, only the mitochondrial membrane potential loss is responsible for the cancer cell sensitivity to CQ.⁸⁴ Their experiments suggest that although CQ does induce purine oxidation, no DNA double-strand damage occurs when the loss of MMP is already detectable, suggesting that the DNA injury happens after the loss of MMP and cell death induced by CQ.⁸⁴ Combining these two studies, we can conclude that both ROS generation and DNA double-strand damage are the downstream events of CQ-induced mitochondrial damage, while the CQ-related cancer cell death relies more on the loss of MMP. Mefloquine exhibits a similar mechanism in inducing mitochondrial damage followed by ROS generation.⁸² Altogether, these studies strongly suggest that the mitochondria-targeted strategy plays a critical role in CQs' anticancer property.

As an anti-helminth agent, niclosamide functions mainly as a mitochondrial uncoupler that inhibits oxidative phosphorylation and reduces ATP production at the therapeutic dose.⁸⁵ However, it can also inhibit human mitochondrial function at a higher dose in vitro. Based on such a pharmacologic mechanism, scientists thought of redirecting it as an anticancer agent. In recent years, many studies focus on its inhibitory effect on oxidative phosphorylation in cancer cells mitochondria. Such inhibition on mitochondria interferes with cellular metabolism. Shangguan et al validated that niclosamide inhibits ovarian cancer cells both in vitro and in vivo.⁸⁶ They showed that niclosamide disturbs mitochondrial respiration and induces mitochondrial depolarization in ovarian carcinoma cells.⁸⁶ In this way, niclosamide promotes glycolysis and decreases glycolytic capacity and reserve, suggesting that it disrupts normal aerobic glycolysis. Alasdair et al demonstrated that mitochondrial uncoupling upregulates pyruvate influx into mitochondria and lowers the pentose phosphate pathway and phosphoglycerate activity dehydrogenase pathway.⁸⁷ Furthermore, it inhibits colon cancer cells' proliferation in vitro and suppresses the hepatic metastasis in vivo experiments. Most interestingly, Kumar et al revealed a novel antitumor mechanism of niclosamide in p53-defective cancers.⁸⁸ Their study demonstrated that niclosamide triggers intracellular calcium flux via mitochondrial uncoupling, thus disturbing the arachidonic acid metabolism in a p53 deficit-dependent manner. Moreover, their experiment revealed that an increased arachidonic acid level is responsible for the niclosamide-induced cytochrome c release and apoptosis. Yu et al showed that niclosamide induces apoptosis in

从这个方面来看, 无论自噬发挥什么作用, 完全抑制自噬可能是一种杀死癌细胞的实用方法。将 CQ、HCQ 或 MQ 与其他自噬抑制剂 (如 GSK690693 或 Autophinib) 相结合, 可能是抑制癌症的有效组合。关于自噬诱导剂, 我们认为未来的探索应该更多地集中在其癌症免疫调节作用上。虽然自噬被认为对免疫反应有复杂的影响, 但它提高了抗原呈递细胞 (APC) 和细胞毒性 T 淋巴细胞 (CTL) 的有效性, 而它们是癌症免疫的主要参与者。同样, 虽然自噬上调了肿瘤微环境中的许多细胞因子, 但大多数是免疫反应性的。这样, 值得尝试将自噬诱导剂与免疫疗法相结合, 如 CAR-T (嵌合抗原受体 T 细胞) 疗法或其他过继细胞免疫疗法。

抗寄生虫药物的线粒体破坏作用

线粒体损伤是抗寄生虫药物抗癌特性中另一个值得注意的机制 (表 3)。一般来说, 针对线粒体可能产生两种结果。首先, 直接损伤线粒体会触发内在凋亡途径, 导致细胞死亡。其次, 作为能量工厂, 线粒体功能障碍会严重扰乱细胞正常代谢, 导致能量不足, 降低生存能力。

最近的研究不断加深我们对 CQs 作用机制的认识。Liang 等发现 CQ 通过诱导线粒体损伤 (以线粒体结构异常为特征) 来影响三阴性乳腺癌 (TNBC) 癌症干细胞样细胞的侵袭和迁移能力。这种线粒体损伤导致线粒体膜去极化和细胞色素 c 的释放。CQ 还抑制细胞色素 c 氧化酶活性, 将电子从细胞色素 c 转移到氧气, 导致 ROS 水平升高。这样, CQ 诱导的 ROS 导致以 γ -H2AX 积累为特征的 DNA 双链损伤。除了诱导 DNA 损伤外, CQ 还会削弱 TNBC 癌细胞的 DNA 修复能力, 从而进一步加剧其 DNA 相关损伤。自噬抑制、线粒体损伤和下游 ROS 产生都可能导致癌细胞死亡。值得注意的是, Vessoni 等指出

虽然 CQ 诱发了所有这些病理过程, 但只有线粒体膜电位的损失才是癌细胞对 CQ 敏感的原因。他们的实验表明, 虽然 CQ 确实诱导了嘌呤氧化, 但是当 MMP 的损失已经可检测到时, 不会发生 DNA 双链损伤, 这表明 DNA 损伤发生在 MMP 的损失和 CQ 诱导的细胞死亡之后。结合这两项研究, 我们可以得出结论, ROS 的产生和 DNA 双链损伤都是 CQ 诱导线粒体损伤的下游事件, 而 CQ 相关的癌细胞死亡更多地依赖于 MMP 的损失。甲氟喹在诱导线粒体损伤随后产生 ROS 方面表现出类似的机制。总之, 这些研究强烈表明, 以线粒体为靶点的策略在 CQ 的抗癌特性中起着关键作用。

氯硝柳胺作为一种驱虫药, 主要作为线粒体解偶联剂发挥作用, 在治疗剂量下抑制氧化磷酸化, 减少 ATP 的产生, 但在体外较高剂量下也能抑制人体线粒体功能。基于这样的药理机制, 科学家们想到将其重新定位为抗癌药。近年来, 许多研究集中在其对癌细胞线粒体氧化磷酸化的抑制作用上。这种对线粒体的抑制会干扰细胞代谢。上官等在体内和体外都验证了氯硝柳胺对卵巢癌细胞的抑制作用。他们发现氯硝柳胺扰乱了卵巢癌细胞的线粒体呼吸并诱导线粒体去极化。通过这种方式, 氯硝柳胺促进糖酵解并降低糖酵解的能力和储备, 表明它破坏了正常的有氧糖酵解。Alasdair 等人证明, 线粒体解偶联上调丙酮酸流入线粒体, 降低戊糖磷酸途径和磷酸甘油酸活性脱氢酶途径。此外, 它抑制结肠癌细胞体外增殖, 抑制体内实验中的肝转移。最有趣的是, Kumar 等人揭示了氯硝柳胺在 p53 缺陷癌症中的一种新的抗肿瘤机制。他们的研究表明, 氯硝柳胺通过线粒体解偶联触发细胞内钙通量, 从而以 p53 缺陷依赖的方式扰乱花生四烯酸代谢。此外, 他们的实验表明, 花生四烯酸水平升高是氯硝柳胺诱导的细胞色素 c 释放和细胞凋亡的原因。Yu 等人表明, 氯硝柳胺诱导

thyroid cancer cells in vitro and inhibits tumor growth in vivo.⁸⁹ Further, they observed mitochondrial membrane potential change and activation of Bax and inhibition of Bcl-2 in niclosamide-treated cells, suggesting that the intrinsic mitochondrial pathway mediates niclosamide-induced apoptosis. Altogether, these studies revealed that niclosamide targets mitochondria as its primary anticancer mechanism.

Scientists did not discover the inhibitory effect of ivermectin on mitochondria in cancer cells until 2016. In 2016, Liu et al revealed that ivermectin induces proliferation inhibition and apoptosis in both glioblastoma and endothelial cells, thus exhibit antitumor effect and anti-angiogenesis effect.⁹⁰ Furthermore, they showed that it induces mitochondrial dysfunction and oxidative stress in glioblastoma and endothelial cells, which correlates with the inhibition of the Akt/mTOR pathway.⁹⁰ Scientists revealed similar phenotypes, including mitochondrial dysfunction and oxidative stress induction in ivermectin-treated chronic myeloid leukemia cells and in renal cell carcinoma correspondingly.^{91,92} Interestingly, in Wang's study, ivermectin exhibits renal cancer cell inhibitory effect while sparing the normal kidney cells, suggesting it potent in further clinical treatment.⁹² In Zhang's experiment, they demonstrated that ivermectin-induced mitochondrial damage leads to increased Bax/Bcl-2 ratio, which leads to cytoplasm c release and caspase-mediated cancer cell apoptosis.⁹³ Altogether, these studies demonstrated that ivermectin targets mitochondrion and induces its dysfunction, leading to its antitumor effect.

Nitazoxanide (NTZ) and its bromo-derivative RM4819 also target mitochondria to inhibit cancer cells.^{94,95} Tantawy et al demonstrated that NTZ influences the Bcl-2 family and results in mitochondria dysfunction characteristic of cytochrome-c release.⁹⁴ In another study, Ripani et al revealed that while both NTZ and RM4819 exhibit mitochondria uncoupling effect, only RM4819 shows mitochondria complex III inhibitory effect.⁹⁵ Due to such pharmaceutical target difference, RM4819 is far more effective than NTZ in disrupting mitochondria function. Their experiment further revealed that these 2 agents have minimal effect on the normal enteral epithelium. Altogether, these results suggest that NTZ and RM4819 could be potent anticancer agents, and further in vivo exploration may be needed.

Immunoregulating Effect of Antiparasitic Agents

Interestingly, several antiparasitic drugs exhibit immunoregulatory effects as anticancer mechanisms (Table 4). Immunoregulatory effects include directly affecting some specific immune cells and regulating the cancer microenvironment as a whole. Immunoregulation may further enhance the antitumor effect of these agents, which is worth discussing.

In the past five years, scientists dramatically deepened the understanding of ARTs immunoregulatory effects. Many of these studies focus on how ARTs affect immune cells. Cao et al demonstrated that ART upregulates the proportion of CD4+ IFN- γ + T cells and Granzyme B + cytotoxic T lymphocyte while abolishing the immunosuppressive effect of Treg cells and MDSCs (myeloid-derived suppressor cells).⁹⁶ In another study, Qian et al revealed that ARS enhances the cytotoxicity of $\gamma\delta$ T cells via upregulating the expression of granzyme B in $\gamma\delta$ T cells.⁹⁷ However, current research on how ARS affects $\gamma\delta$ -T cell immunity is far not sufficient. In the future, we may focus on the detailed mechanism of how ARS upregulates the granzyme B level, and if other mechanisms exist in ARS-induced $\gamma\delta$ -T cell enhancement. Considering further application, since ARS enhances $\gamma\delta$ T cell function, combining ARS with $\gamma\delta$ -T related immunotherapies (like CAR $\gamma\delta$ -T therapy) would be worth of trying.⁹⁸ NK cells are also targets of ARTs. Houh et al revealed that ART enhances the cytotoxic effect of NK cells and stimulates the granule exocytosis.⁹⁹ Although it does not interfere with the NK activating receptors' expression level, it modulates their downstream proteins, including Vav-1 and ERK1/2.⁹⁹ Similarly, Lu et al reported that ART sensitizes cancer cells to NK cell-induced cytotoxicity manifested by enhancing conjugation between NK cells and tumor cells.¹⁰⁰ Further exploration revealed that ART enriched apoptotic genes in cancer cells, making them more susceptible to NK cell-mediated lysis. In the future, combining ART with NK cell immunotherapies (adoptive NK transfer, CAR-NK, etc.) in animal experiments would be interesting. Besides directly acting on immune cells, ART also regulates the immunoreactive mediators' expression level (T-bet, IFN- γ and TNF- α).^{96,97} While cancer cells may secrete immunosuppressive mediators to inhibit T cells' cytotoxicity, both ART and ARS help cancer cells regain sensitivity to $\gamma\delta$ T cells via inhibiting TGF- β secretion.^{97,101} These results suggested that ARTs may help construct a more stressful microenvironment for cancer

体外研究发现, 氯硝柳胺可抑制甲状腺癌细胞, 并在体内抑制肿瘤生长。此外, 他们还观察到氯硝柳胺处理的细胞中线粒体膜电位变化、Bax 激活和 Bcl-2 抑制, 这表明内在线粒体途径介导氯硝柳胺诱导的细胞凋亡。总之, 这些研究表明, 氯硝柳胺以线粒体为主要抗癌机制。

直到 2016 年, 科学家们才发现伊维菌素对癌细胞线粒体的抑制作用。2016 年, 刘等人发现伊维菌素在胶质母细胞瘤和内皮细胞中均能诱导增殖抑制和凋亡, 从而表现出抗肿瘤和抗血管生成作用。此外, 他们还发现伊维菌素在胶质母细胞瘤和内皮细胞中诱导线粒体功能障碍和氧化应激, 这与 Akt / mTOR 通路的抑制有关。科学家们在伊维菌素治疗的慢性粒细胞白血病细胞和肾细胞癌中也发现了类似的表型, 包括线粒体功能障碍和氧化应激诱导。有趣的是, 在王的研究中, 伊维菌素表现出肾癌细胞抑制作用, 同时保留了正常肾细胞, 这表明其在进一步的临床治疗中具有潜力。张教授的实验表明, 伊维菌素引起的线粒体损伤会导致 Bax/Bcl-2 比值升高, 进而导致细胞质 c 释放和 caspase 介导的癌细胞凋亡。总之, 这些研究表明伊维菌素靶向线粒体并诱导其功能障碍, 从而发挥抗肿瘤作用。

硝唑尼特 (NTZ) 及其溴衍生物 RM4819 也靶向线粒体来抑制癌细胞。Tantawy 等人证明 NTZ 影响 Bcl-2 家族并导致线粒体功能障碍, 这是细胞色素 c 释放的特征。在另一项研究中, Ripani 等人发现, 虽然 NTZ 和 RM4819 都表现出线粒体解偶联作用, 但只有 RM4819 表现出线粒体复合物 III 抑制作用。由于这种药物靶标差异, RM4819 在破坏线粒体功能方面比 NTZ 更有效。他们的实验进一步表明, 这两种药物对正常肠上皮的影响微乎其微。总之, 这些结果表明 NTZ 和 RM4819 可能是有效的抗癌药物, 可能需要进一步进行体内探索。

抗寄生虫药物的免疫调节作用

有趣的是, 一些抗寄生虫药物表现出免疫调节作用作为抗癌机制 (表 4)。免疫调节作用包括直接影响某些特定的免疫细胞和整体调节癌症微环境。免疫调节可能进一步增强这些药物的抗肿瘤作用, 值得讨论。

在过去的五年中, 科学家们对 ART 的免疫调节作用的认识大大加深, 其中许多研究集中于 ART 如何影响免疫细胞。Cao 等的研究发现 ART 可以上调 CD4+IFN- γ +T 细胞和颗粒酶 B+细胞毒性 T 淋巴细胞的比率, 同时消除 Treg 细胞和 MDSC (髓系抑制细胞) 的免疫抑制作用。在另一项研究中, Qian 等发现 ARS 通过上调 $\gamma\delta$ T 细胞中颗粒酶 B 的表达来增强 $\gamma\delta$ T 细胞的细胞毒性。然而, 目前关于 ARS 如何影响 $\gamma\delta$ -T 细胞免疫的研究还远远不够。未来我们可重点研究 ARS 上调颗粒酶 B 水平的具体机制, 以及 ARS 诱导的 $\gamma\delta$ -T 细胞增强中是否存在其他机制。考虑到进一步的应用, 由于 ARS 增强了 $\gamma\delta$ T 细胞的功能, 将 ARS 与 $\gamma\delta$ -T 相关的免疫疗法 (如 CAR- $\gamma\delta$ -T 疗法) 相结合是值得尝试的。NK 细胞也是 ART 的靶点。Houh 等人发现 ART 增强了 NK 细胞的细胞毒作用并刺激颗粒胞吐。虽然它不干扰 NK 活化受体的表达水平, 但会调节其下游蛋白, 包括 Vav-1 和 ERK1/2。同样, Lu 等人报道 ART 使癌细胞对 NK 细胞诱导的细胞溶解敏感, 表现为增强 NK 细胞与肿瘤细胞之间的结合。进一步的探索发现 ART 在癌细胞中富集了凋亡基因, 使它们更容易受到 NK 细胞介导的溶解。未来, 在动物实验中将 ART 与 NK 细胞免疫疗法 (过继性 NK 转移、CAR-NK 等) 相结合将会很有趣。除了直接作用于免疫细胞外, ART 还调节免疫反应介质 (T-bet、IFN- γ 和 TNF- α) 的表达水平。虽然癌细胞可能分泌免疫抑制介质来抑制 T 细胞的细胞毒性, 但 ART 和 ARS 均通过抑制 TGF- β 分泌帮助癌细胞重新获得对 $\gamma\delta$ T 细胞的敏感性。这些结果表明 ART 可能有助于为癌症构建更具压力的微环境

Table 4 Immuregulating Effect of Antiparasitic Agents

Drug	Mechanism	Reference
Artemisinin	Upregulates the proportion of CD4+ IFN- γ + T cells and Granzyme B + cytotoxic T lymphocyte while abolishes the immunosuppressive effect of Treg cells and MDSCs	[96]
	Regulates the expression level of immune mediators by upregulating the T-bet, IFN- γ , TNF- α while downregulating the TGF-b	
	Enhances the cytotoxic effect of NK cells and stimulates the granule exocytosis	[99]
	Modulates their downstream proteins of NK activating receptors including Vav-1 as well as ERK1/2	
	Sensitizes cancer cells to NK cell-induced cytotoxicity by enhancing conjugation between NK cells and tumor cells	[100]
Artesunate	Enhances the cytotoxicity of $\gamma\delta$ T cells via upregulating the expression of granzyme B in $\gamma\delta$ T cells	[97]
	Helps HepG2 cancer cells regain sensitivity to $\gamma\delta$ T cells via inhibiting TGF-b secretion	[101]
Chloroquine	CQ-induced autophagy inhibition enhances the immunogenicity of cancer cells, thus enhances DC maturation and T cell response by inducing autophagy inhibition	[102]
	Promotes cancer cell killer CD8+T cell and downregulates immunosuppressive cells in vivo	[104]
	Suppresses TGF-b production of the cancer cells in vitro and in vivo	
	Downregulates the Immunol response via upregulating the FoxP3 positive Treg cells and reducing the T cytotoxic cells	[105]
Hydroxychloroquine	Sensitizes CML cell to V γ 9V δ 2 T cell-mediated lysis in an autophagy-independent way	[103]
Pyrimethamine	Suppresses Treg cells as well as TH-17 associated immune response, while enhances the cytotoxicity of CD8 + T cells via promoting exocytosis	[107]

cells, and its potential application in cancer-related immune regulation is worth of exploring in the future.

Several pieces of research focused on CQs' immunoregulatory effect. Autophagy inhibition, the original impact of CQs, may contribute to such an immunoregulatory effect. A recent study revealed that CQ-induced autophagy inhibition enhances cancer cells' immunogenicity, thus enhancing dendritic cell (DC) maturation and T cell response.¹⁰² Their experiment showed that combining 5-FU with CQ significantly induces carcinoembryonic antigen (CEA) family protein expression, which leads to enhanced immunogenicity and promotes DC maturation. As it is known that apoptotic cells are usually weak in immunogenicity, such a difference in immunogenicity probably correlates with autophagy-inhibition induced apoptosis, as it is different from physiological apoptosis. Although to some degree, there is insufficient evidence proving that such enhancement in immunogenicity directly correlates with CQ-induced autophagy blockage, their study is still inspirational, and further investigations should focus more on the exact mechanism of how such

CQ-induced immunogenicity enhancement is mediated. The immunoregulatory effect of CQ can also be autophagy inhibition-independent. Han et al revealed that, although HCQ does inhibit autophagy of CML cancer cells, it sensitizes CML cell to V γ 9V δ 2 T cell-mediated lysis in an autophagy-independent way.¹⁰³ Further exploration demonstrated that HCQ induces UL16 Binding Protein 4 (ULBP4), the NKG2D ligand, on the CML cells' surface. The enhanced connection between ULBP4 and NKG2D augments the recognition capability of V γ 9V δ 2 T cells on CML cells. Interestingly, HCQ does not directly alter the production or degradation of ULBP4. Instead, it facilitates the translocation of ULBP4 from the cytoplasm to the cell membrane.¹⁰³ In another study, Zhang et al demonstrated that CQ promotes cancer cell killer CD8+T cell and downregulates immunosuppressive cells, including tumor-associated macrophages, myeloid-derived suppressor cells, and Tregs in breast cancer in vivo.¹⁰⁴ Notably, it suppresses TGF-b production of the cancer cells in vitro and in vivo, suggesting that it functions as a cancer microenvironment regulator.¹⁰⁴ While most studies revealed that CQ

表 4 抗寄生虫药物的免疫调节作用

Drug	机制	参考
青蒿素	上调 CD4+ IFN- γ + T 细胞和 Granzyme B + 细胞毒性 T 淋巴细胞的比例，同时消除 Treg 细胞和 MDSC 的免疫抑制作用	[98]
	通过上调 T-bet、IFN- γ 、TNF- α 和下调 TGF- β 来调节免疫介质的表达水平	
	增强 NK 细胞的细胞毒作用，刺激颗粒胞吐	[99]
	调节 NK 激活受体的下游蛋白，包括 Vav-1 以及 ERK1/2	
	通过增强 NK 细胞与肿瘤细胞之间的结合，使癌细胞对 NK 细胞诱导的细胞溶解敏感	[100]
青蒿琥酯	通过上调 $\gamma\delta$ T 细胞中颗粒酶 B 的表达，增强 $\gamma\delta$ T 细胞的细胞毒性	[97]
	通过抑制 TGF- β 分泌帮助 HepG2 癌细胞恢复对 $\gamma\delta$ T 细胞的敏感性	[101]
氯喹	CQ 诱导的自噬抑制增强了癌细胞的免疫原性，从而通过诱导自噬抑制增强了 DC 成熟和 T 细胞应答	[102]
	促进癌细胞杀伤性 CD8+T 细胞并下调体内免疫抑制细胞	[104]
	抑制体内和体外癌细胞的 TGF- β 产生	
	通过上调 FoxP3 阳性 Treg 细胞和减少 T 细胞毒性细胞来下调免疫反应	[105]
羟氯喹以自噬非依赖的方式	增强 CML 细胞对 V γ 9V δ 2 T 细胞介导的裂解的敏感性	[103]
乙胺嘧啶	抑制 Treg 细胞以及 TH-17 相关免疫反应，同时通过促进胞吐增强 CD8 + T 细胞的细胞毒性	[107]

细胞，其在癌症相关免疫调控中的潜在应用值得未来探索。

有几项研究关注 CQ 的免疫调节作用。自噬抑制是 CQ 的最初影响，可能有助于这种免疫调节作用。最近的一项研究表明，CQ 诱导的自噬抑制可增强癌细胞的免疫原性，从而增强树突状细胞 (DC) 成熟和 T 细胞反应。他们的实验表明，5FU 与 CQ 结合可显著诱导癌胚抗原 (CEA) 家族蛋白表达，从而增强免疫原性并促进 DC 成熟。众所周知，凋亡细胞的免疫原性通常较弱，这种免疫原性的差异可能与自噬抑制诱导的细胞凋亡有关，因为它不同于生理性细胞凋亡。虽然在某种程度上，没有足够的证据证明这种免疫原性的增强与 CQ 诱导的自噬阻断直接相关，但他们的研究仍然很有启发性

而 CQ 增强免疫原性的具体机制尚待进一步研究。CQ 的免疫调节作用也可以不依赖于自噬抑制。Han 等的研究发现，虽然 HCQ 确实抑制了 CML 癌细胞的自噬，但它能以不依赖于自噬的方式使 CML 细胞对 V γ 9V δ 2 T 细胞介导的裂解敏感。进一步的研究表明，HCQ 诱导了 CML 细胞表面的 NKG2D 配体 UL16 结合蛋白 4 (ULBP4)。ULBP4 和 NKG2D 之间增强的连接增强了 V γ 9V δ 2 T 细胞对 CML 细胞的识别能力。有趣的是，HCQ 并不直接改变 ULBP4 的产生或降解。相反，它促进 ULBP4 从细胞质转移到细胞膜。在另一项研究中，Zhang 等人证明 CQ 促进癌细胞杀伤性 CD8+T 细胞并下调乳腺癌中的免疫抑制细胞，包括肿瘤相关巨噬细胞、髓系抑制细胞和 Treg。值得注意的是，它在体外和体内抑制癌细胞的 TGF- β 产生，表明它作为癌症微环境调节剂发挥作用。虽然大多数研究表明 CQ

enhances tumor-related immune response, Masuelli et al demonstrated a different result, suggesting that CQ may be an immune inhibitor.¹⁰⁵ Their study revealed that while CQ enhances curcumin (CUR) in vitro and nude mice, it reduces the antitumor effect of curcumin in immunocompetent mice. Further investigation suggests that CQ downregulates the immune response via upregulating the FoxP3 positive Treg cells and reducing the T cytotoxic cells. Moreover, a higher expression level of HIF-1 α in the CQ + CUR group is observed. The authors hypothesized that the immunosuppressive effect of CQ probably correlates with its damage-associated molecular pattern (DAMP)-inducing effect or the immune-suppressive cytokines released due to higher HIF-1 α . Currently available results are still insufficient to conclude whether CQ/HCQ functions as an immune enhancer or inhibitor in the cancer microenvironment. Future studies should focus more on the exact mechanism of how CQ boosts or inhibits immune response in immunocompetent mice models via analyzing the expression level of DAMP molecules, including HIF-1 α , the cytokine levels, and the response of different types of immune cells to determine the overall effect of CQs on the cancer-related immune response.

In 2011, Takakura et al firstly demonstrated that pyrimethamine (Pyr) functions as a STAT3 inhibitor in polycystic kidney disease models.¹⁰⁶ However, such STAT3 inhibitory effect had not been studied in the cancer field until 2018. In this year, Khan et al validated the STAT3 inhibitory effect of Pyr in breast cancer.¹⁰⁷ Such inhibition on STAT3 suppresses the proliferation and invasion of breast cancer cells in vitro. Interestingly, Pyr also exhibits an immunoregulatory effect via inhibiting STAT3. Their experiments demonstrated that administration of Pyr suppresses Treg cells as well as TH-17 associated immune response, while enhancing the cytotoxicity of CD8⁺ T cells via promoting exocytosis. It has been fully demonstrated that STAT3 plays a critical role in carcinogenesis in various types of cancers. Future studies should explore the STAT3 inhibitory effect of Pyr in other cancers, especially in which STAT3 plays an important role in immunoregulation.

Metabolic Disrupting Effect of Antiparasitic Agents

Cancer cell metabolism is characterized by aerobic glycolysis, known as the Warburg effect. Disrupting glycolysis can significantly disturb the normal metabolism of cancer

cells. The past several years witnessed progress in understanding the glycolysis disrupting effect of antiparasitic agents, and we will discuss them in detail.

Artemisinins function as glycolysis inhibitors. In 2015, Mi et al revealed that DHA downregulates the glycolysis metabolism level characteristic with decreased ATP and lactate levels in non-small cell lung carcinoma (NSCLC).¹⁰⁸ Further exploration suggests that it inhibits the mTOR pathway and downregulates the expression level of GLUT1, resulting in reduced glucose uptake and decreased glycolysis metabolism.¹⁰⁸ Similarly, in esophageal carcinoma, Li et al observed that DHA suppresses glycolysis via inhibiting the expression level of pyruvate kinase M2.¹⁰⁹ In prostate cancer cell line LNCaP, DHA reduces the glucose uptake, ATP level, and lactate level.¹¹⁰ Western blotting revealed that the expression of a series of glycolysis-related proteins, including GLUT1, hexokinase 2, platelet-type fructose phosphate kinase, pyruvate kinase M2, and lactate dehydrogenase are decreased.¹¹⁰ Furthermore, they demonstrated that DHA suppresses the expression of HIF-1 α , which is the upstream regulator of glycolysis, via regulating the PI3K/Akt/mTOR pathway.¹¹⁰ Similarly, scientists also observed the glycolysis inhibitory effect of ARS in B cell lymphoma.¹¹¹ Benzimidazole derivatives also exhibit a glycolysis-disrupting effect. Zhou et al reported that albendazole inhibits the expression of HIF-1 α in NSCLC cells.¹¹² Such suppression on HIF-1 α results in glycolysis inhibition.¹¹² Under the hypoxia condition, albendazole inhibits glycolytic enzymes, including HK, PK, and LDH, while reducing lactate.¹¹² Altogether, this experiment suggests that albendazole may disrupt hypoxia-induced glycolysis via suppressing the expression level of HIF-1 α . Fenbendazole, another benzimidazole derivative, also disturbs the glycolytic metabolism. It inhibits the glucose uptake and the activity of hexokinase 2, thus significantly attenuating glycolysis. The in-silico analysis revealed that fenbendazole probably interferes with hexokinase II by mimicking the structure of glucose or G6P, thus binding to the enzyme's active site and disrupting its normal function.¹¹³

Disturbance of glycolysis would profoundly interfere with the survival ability of cancer cells in hypoxia conditions. Notably, although radiotherapy or TACE (transcatheter arterial chemoembolization) are both potent therapy against the tumor, they are not effective enough for the cancer cells that are hypoxia-resistant. In this way, combining these agents with radiotherapy or TACE should be considered. Several studies combine ARTs or

增强肿瘤相关免疫反应, Masuelli 等人得到了不同的结果, 表明 CQ 可能是一种免疫抑制剂。他们的研究表明, 虽然 CQ 在体外和裸鼠中增强了姜黄素 (CUR) 的作用, 但它降低了姜黄素在免疫功能正常的小鼠中的抗肿瘤作用。进一步的研究表明, CQ 通过上调 FoxP3 阳性 Treg 细胞和减少 T 细胞毒性细胞来下调免疫反应。此外, 在 CQ + CUR 组中观察到更高的 HIF-1a 表达水平。作者推测 CQ 的免疫抑制作用可能与其损伤相关分子模式 (DAMP) 诱导作用或由于较高的 HIF-1a 而释放的免疫抑制细胞因子有关。目前现有的结果仍然不足以断定 CQ/HCC 是否在癌症微环境中起到免疫增强剂或抑制剂的作用。未来的研究应更多地关注 CQ 如何通过分析 DAMP 分子 (包括 HIF-1a) 的表达水平、细胞因子水平和不同类型免疫细胞的反应来增强或抑制免疫功能正常的小鼠模型中的免疫反应的确切机制, 以确定 CQ 对癌症相关免疫反应的整体影响。

2011 年, Takakura 等人首次证明乙胺嘧啶 (Pyr) 在多囊肾模型中起 STAT3 抑制剂的作用。然而, 这种 STAT3 抑制作用直到 2018 年才在癌症领域得到研究。今年, Khan 等人在乳腺癌中验证了 Pyr 对 STAT3 的抑制作用。这种对 STAT3 的抑制在体外抑制了乳腺癌细胞的增殖和侵袭。有趣的是, Pyr 还通过抑制 STAT3 表现出免疫调节作用。他们的实验表明, 施用 Pyr 可抑制 Treg 细胞以及 TH-17 相关的免疫反应, 同时通过促进胞吐增强 CD8 + T 细胞的细胞毒性。已经充分证明了 STAT3 在各种类型癌症的致癌作用中起着关键作用。未来的研究应探索 Pyr 在其他癌症中的 STAT3 抑制作用, 特别是在 STAT3 在免疫调节中起重要作用的癌症中。

破坏糖酵解会严重干扰癌细胞的正常代谢。过去几年来, 人们对抗寄生虫药物破坏糖酵解作用的认识取得了进展, 我们将对此进行详细讨论。

青蒿素具有糖酵解抑制剂的作用。2015 年, Mi 等发现 DHA 可下调非小细胞肺癌 (NSCLC) 的糖酵解代谢水平, 以 ATP 和乳酸水平降低为特征。进一步的研究发现, 其可能通过抑制 mTOR 通路, 下调 GLUT1 的表达水平, 导致葡萄糖摄取减少, 糖酵解代谢降低。同样, 在食管癌中, Li 等观察到 DHA 通过抑制丙酮酸激酶 M2 的表达水平来抑制糖酵解。在前列腺癌细胞系 LNCaP 中, DHA 可降低葡萄糖摄取、ATP 水平和乳酸水平。Western 印迹显示, 一系列与糖酵解相关的蛋白, 包括 GLUT1、己糖激酶 2、血小板型果糖磷酸激酶、丙酮酸激酶 M2 和乳酸脱氢酶的表达均降低。此外, 他们还发现 DHA 通过调控 PI3K/Akt/mTOR 通路, 抑制糖酵解上游调控因子 HIF-1a 的表达。同样, 科学家们也在 B 细胞淋巴瘤中观察到了 ARS 对糖酵解的抑制作用。苯并咪唑衍生物也表现出了糖酵解干扰作用。Zhou 等报道阿苯达唑抑制了 NSCLC 细胞中 HIF-1a 的表达。这种对 HIF-1a 的抑制导致了糖酵解的抑制。在缺氧条件下, 阿苯达唑抑制糖酵解酶, 包括 HK、PK 和 LDH, 同时降低乳酸。总之, 本实验表明阿苯达唑可能通过抑制 HIF-1a 的表达水平来干扰缺氧诱导的糖酵解。另一种苯并咪唑衍生物芬苯达唑也会干扰糖酵解代谢。它抑制葡萄糖的摄取和己糖激酶 2 的活性, 从而显著减弱糖酵解。计算机分析显示, 芬苯达唑可能通过模仿葡萄糖或 G6P 的结构来干扰己糖激酶 II, 从而与酶的活性位点结合并破坏其正常功能。

糖酵解紊乱会严重影响癌细胞在缺氧条件下的生存能力。值得注意的是, 虽然放射治疗或 TACE (经导管动脉化疗栓塞) 都是有效的抗肿瘤治疗方法, 但对于耐缺氧的癌细胞, 效果不够好。因此, 应考虑将这些药物与放射治疗或 TACE 结合起来。一些研究将 ART 或

抗寄生虫药物的代谢干扰作用

癌细胞代谢的特点是有氧糖酵解, 即所谓的瓦堡效应

benzimidazole derivatives with radiotherapy and showed that these agents do exhibit radiosensitizing effects.^{114,115} In this way, it would be interesting to carry on clinical trials that combine radiotherapy with these agents. Regarding TACE, no animal experiment is available and future investigations would be needed to explore whether such strategy is effective.

Pyrimethamine (Pyr) functions as a plasmodium dihydrofolate reductase (pDHFR) inhibitor in fighting against malaria.¹¹⁶ It inhibits the transformation from dihydrofolate to tetrahydrofolate, resulting in nucleic acid synthesis dysfunction. Interestingly, a recent study revealed that pDHFR has a similar structure with human dihydrofolate reductase (hDHFR), and pyrimethamine does exert an inhibitory effect on hDHFR by directly binding to it, thus inhibiting tumor cell proliferation and metastasis.¹¹⁷ Moreover, researchers demonstrated that compared with methotrexate, another hDHFR inhibitor, Pyr additionally inhibits epithelial–mesenchymal transition, metastasis, and invasiveness of cancer cells. Further, they revealed that thymidine phosphorylase is another target of Pyr, which can explain such a difference in the inhibitory effect on cancer cells. Since it may interfere with DNA synthesis and metabolism, considering combining it with radiotherapy is reasonable. An *in vitro* experiment suggested that administration of Pyr on glioblastoma cells before chemoradiotherapy would enhance their anticancer effect.¹¹⁸ In the future, more exploration in animal experiment and in more cancer cell types would be necessary.

Dark Side: Limitations and Future Directions

Although *in vitro* and animal experiments suggest that these agents are potent cancer killers, limitations that slowed their pace into clinical application emerge at the clinical trial stage. We analyze the results of the clinical trials and explore the limitations of these agents. Finally, we manage to provide possible solutions to overcome these limitations and give our opinions on the future directions of these agents. The data of the clinical trials are obtained from www.clinicaltrials.gov.

Artemisinins

We summarized the ongoing and completed clinical trials which apply ARTs in cancer treatment. (Table S1) Two completed Phase I trials published their results. Considering the medication tolerability, 18 mg/kg given

on days 1 and 8 of a 21-day cycle or 200 mg/d orally are both tolerable dosage regimens.^{119,120} The major observed DL-AE (Dose Limited-Adverse Event) is anemia, which is also commonly seen in malaria ARS therapy and is acceptable and well tolerated. However, as previous animal studies aroused concerns about the potential ototoxicity of ARS, intermittent vertigo, ongoing tinnitus, or subclinical hearing loss is observed in several patients (4/23).^{119–121} Thus, future clinical trials should continue to pay attention to the possible ototoxicity, especially in long-term surveillance. In these two clinical trials, drug efficacy is kind of disappointing. No complete or partial remission was observed. A possible reason lies in its pharmacokinetic property. Pharmacokinetic analysis suggested that the concentration of ARS rapidly declined in the first 20 mins ($T_{1/2}=7-8$ mins), although its active metabolite DHA exists much longer ($T_{1/2}=0.5-3.5$ h). This suggests that future investigations *in vitro* should focus more on DHA instead of ARS. Besides, considering modifying the chemical structure of ARS that may slow down its transformation into DHA would be another way out. In the clinical trials, the plasma concentration of DHA (1.46 μM) is far not high enough to reach the IC_{50} concentration of the preclinical trials (8–100 μM) in the acceptable dosage (18 mg/kg given on days 1 and 8 of a 21-day cycle).¹¹⁹ These pharmacokinetics data suggested that future *in vivo* or *in vitro* studies should focus on DHA's anticancer effect at a low dose, and we would better consider it as a combination therapy medication. Currently, there are no completed Phase II/III clinical trials, and the ongoing ones focus on colorectal carcinoma. Previous *in vitro* and *in vivo* experiments suggested that ARS has an anticancer effect on various cancers, including head and neck carcinoma, breast cancer and lymphoma, etc.^{27,111,122} Thus, it would be meaningful to carry on clinical trials of ARS on these cancer types after the pharmacokinetic issue is solved.

Benzimidazole Derivatives

We may first discuss the pharmaceutical properties of benzimidazole derivatives according to several previous clinical trials, although they are not correlated with cancer. In 2010, a clinical trial explored the maximum tolerated dose of albendazole and revealed that up to 2400 mg/d is tolerable.¹²³ Moreover, the pharmacokinetic analysis showed that ABZ is rapidly metabolized into albendazole sulfoxide (ABZ-SO), the major active metabolite of ABZ. ABZ-SO. The mean maximum plasma concentration of ABZ-SO reaches 2.7 ± 2.1 (0.80–4.7) $\mu\text{g/mL}$, which is

苯并咪唑衍生物与放射治疗联合使用，并表明这些药物确实具有放射增敏作用。因此，开展将放射治疗与这些药物相结合的临床试验将会很有趣。关于 TACE，目前还没有动物实验，未来需要进行研究来探索这种策略是否有效。

乙胺嘧啶 (Pyrimethamine, Pyr) 是一种疟原虫二氢叶酸还原酶 (pDHFR) 抑制剂，可抑制二氢叶酸转化为四氢叶酸，导致核酸合成障碍。有趣的是，最近的一项研究表明，pDHFR 与人类二氢叶酸还原酶 (hDHFR) 具有相似的结构，而乙胺嘧啶确实通过直接与 hDHFR 结合发挥抑制作用，从而抑制肿瘤细胞增殖和转移。此外，研究人员证明，与另一种 hDHFR 抑制剂甲氨蝶呤相比，Pyr 还能抑制癌细胞的表皮-间质转化、转移和侵袭性。此外，他们还发现胸苷磷酸化酶是 Pyr 的另一个靶点，这可以解释对癌细胞的抑制效果的这种差异。由于它可能会干扰 DNA 的合成和代谢，因此考虑将其与放射治疗相结合是合理的。体外实验表明，在放化疗之前给胶质母细胞瘤细胞施用 Pyr 可增强其抗癌作用。未来还需要在动物实验和更多癌细胞类型中进行更多探索。

18 mg/kg (21 天周期的第 1 天和第 8 天) 或口服 200 mg/d 都是可以耐受的给药方案。观察到的主要 DL-AE (剂量限制不良事件) 是贫血，这在疟疾 ARS 治疗中也很常见，并且是可以接受的，耐受性良好。然而，正如之前的动物研究引起人们对 ARS 潜在耳毒性的担忧一样，在几名患者中观察到了间歇性眩晕、持续性耳鸣或亚临床听力损失 (4/23)。

121 因此，未来的临床试验应继续关注可能的耳毒性，尤其是在长期监测中。在这两项临床试验中，药物疗效令人失望。没有观察到完全或部分缓解。可能的原因在于其药代动力学特性。药代动力学分析表明，ARS 的浓度在前 20 分钟内迅速下降 ($T_{1/2}=7-8$ 分钟)，尽管其活性代谢物 DHA 存在的时间更长 ($T_{1/2}=0.5-3.5$ 小时)。这表明未来的体外研究应该更多地关注 DHA 而不是 ARS。此外，考虑修改 ARS 的化学结构以减缓其转化为 DHA 将是另一种出路。在临床试验中，DHA 的血浆浓度 ($1.46 \mu\text{M}$) 远远不足以达到临床前试验的 IC_{50} 浓度 ($8-100 \mu\text{M}$)，剂量为可接受剂量 (18 mg/kg，第 1 天和第 8 天给药，21 天周期)。这些药代动力学数据表明，未来的体内或体外研究应侧重于低剂量 DHA 的抗癌作用，我们最好将其视为一种联合治疗药物。目前，尚未完成 II/III 期临床试验，正在进行的临床试验主要针对结直肠癌。先前的体外和体内实验表明 ARS 对多种癌症具有抗癌作用，包括头颈癌、乳腺癌和淋巴瘤等。因此，在药代动力学问题得到解决后，对这些癌症类型进行 ARS 的临床试验将很有意义。

黑暗面：局限性和未来方向

尽管体外和动物实验表明这些药物是有效的癌症杀手，但在临床试验阶段，它们出现的局限性减缓了其临床应用的步伐。我们分析了临床试验的结果，并探讨了这些药物的局限性。最后，我们设法提供了克服这些局限性的可能解决方案，并对这些药物的未来发展方向发表了意见。临床试验数据来自 www.clinicaltrials.gov。

青蒿素

我们总结了正在进行和已完成的 ART 癌症治疗临床试验 (表 S1)。两项已完成的 I 期试验公布了结果。考虑到药物耐受性

苯并咪唑衍生物

我们首先可以根据之前的几项临床试验讨论苯并咪唑衍生物的药理特性，尽管它们与癌症无关。2010 年的一项临床试验探讨了阿苯达唑的最大耐受剂量，结果显示最高耐受剂量为 2400 mg/d。此外，药代动力学分析表明，ABZ 迅速代谢为阿苯达唑亚砷 (ABZ-SO)，这是 ABZ 的主要活性代谢物。ABZ-SO 的平均最大血浆浓度达到 2.7 ± 2.1 ($0.80-4.7$) $\mu\text{g/mL}$ ，

much higher compared with its IC₅₀ value in cell experiments.^{124,125} Currently, there are no ongoing or finished clinical trials applying ABZ to treat cancers. Based on the promising antitumor effect of ABZ in vitro and in vivo experiments, carrying out more clinical trials applying ABZ to treat cancers is necessary. Moreover, the pharmacokinetic properties of ABZ suggested that future in vitro studies should focus more on the antitumor characteristics of ABZ-SO since ABZ remains only a short time in the plasma and ABZ-SO is the major active metabolite. Regarding MBZ, Guerini et al have summarized the pharmacokinetic properties of MBZ in detail.¹²⁶ The maximum plasma concentration of MBZ under the tolerated dose is higher than the IC₅₀ value in vitro experiments. There are several clinical trials applying mebendazole in treating cancers (Table S2). However, most of them are at the “Recruiting” stage and currently there are no available results. A terminated clinical trial suggested that MBZ may not be effective enough to inhibit cancer progression in GI cancer patients. However, no detailed results are available. The ongoing trials focus more on brain tumors and it is worth waiting for further results.

Ivermectin

Currently, there are no available clinical trials that apply ivermectin in treating cancers. Several recently published reviews focused on the antitumor pharmacokinetic properties of ivermectin.^{127,128} The pharmacodynamic evaluations revealed that the highest approachable plasma concentration of ivermectin in humans is higher than the average effective concentration in animal experiments. Moreover, several recent clinical trials which use ivermectin to treat other diseases again confirm that its side effect and toxicity are relatively acceptable.^{129,130} In constant with the previous authors' conclusion, we strongly suggest carrying out more clinical trials using ivermectin to treat cancers.

Chloroquine Derivatives

For chloroquine derivatives, there are more clinical trials compared with other antiparasitic agents (Tables S3 and S4). CQ's anticancer potential in brain tumors is attracting scientists' attention (NCT02496741, NCT01894633, NCT01727531, NCT02378532, NCT02432417, NCT00224978). It is a pity that not all of these trials have published data. A clinical trial (n=30) published in 2006 suggested that additional CQ to chemotherapy may improve the mid-term survival of glioblastoma multiforme

(GBM) patients.¹³¹ Another completed clinical trial (NCT02378532) which started in 2015 combines chloroquine with chemoradiation in GBM patients. Unfortunately, no published result is available. An ongoing clinical trial (NCT02432417) combines CQ with temozolomide and radiotherapy in GBM patients.¹³² Previous studies suggested that upregulation of EGFRVIII would help cancer cells survive stress conditions by inducing autophagy in GBM cancer cells.¹³² In the future, whether CQ-induced autophagy-inhibition may improve the overall survival of GBM patients, especially those with EGFRVIII-positive subtype, should be investigated. The result of this clinical trial is worth waiting for.

Niclosamide

The available clinical trials are summarized in Table S5. As mitochondrial uncoupler, it has a natural potent to harm other cells like cardiac or muscular cells. Whether such cytotoxic effect would limit its clinical application in treating cancer is attracting scientists' attention. A recent study focused on this problem and investigated how cardiac cells would react to mitochondrial uncouplers including niclosamide.¹³³ Gao et al demonstrated that while high-level niclosamide does exhibit cardiotoxicity, it exerts a cardio-protective effect by activating the STAT3 pathway at lower concentration (so-called “mild mitochondrial uncoupling”).¹³³ According to previous preclinical experiments, the minimum clinically meaning dose is about 163.5 ng/mL (combined with enzalutamide), which equals approximately 0.5 μ M. At such a concentration, niclosamide induces about 5% cardiac cell death and a 20% loss of membrane potential (MMP), which may disturb the normal cardiac function. Cardiac cell protection or targeted delivery to cancer cells could be the way out. No matter which approach is selected, cardiotoxicity monitoring should be included in clinical trials. Currently, there is no available study focusing on whether niclosamide would affect muscle cells, and investigations on this issue would be necessary. Another barrier to the clinical application of niclosamide is whether it can achieve targeted concentration in vivo. A published clinical trial suggested that at the maximum tolerated dose (500 mg TID), only 1/3 of the patients reach 163.5 ng/mL.¹³⁴ Scientist thought of improving the delivery system and several nanobased-agents were invented, which may improve its bioavailability.¹³⁵ In the future, scientists may explore these agents in clinical trials.

远高于细胞实验中的 IC50 值。目前，尚无正在进行或已完成的临床试验应用 ABZ 治疗癌症。基于 ABZ 在体外和体内实验中良好的抗肿瘤作用，开展更多应用 ABZ 治疗癌症的临床试验是必要的。此外，ABZ 的药代动力学特性表明，未来的体外研究应更多地关注 ABZ-SO 的抗肿瘤特性，因为 ABZ 在血浆中仅停留很短时间，并且 ABZ-SO 是主要活性代谢物。关于 MBZ，Guerini 等人详细总结了 MBZ 的药代动力学特性。耐受剂量下 MBZ 的最大血浆浓度高于体外实验中的 IC50 值。有几项临床试验应用甲苯咪唑治疗癌症（表 S2）。然而，它们中的大多数处于“招募”阶段，目前尚无可用结果。一项终止的临床试验表明，MBZ 可能不足以有效抑制胃肠道癌症患者的癌症进展。但目前还没有详细结果，正在进行的试验更多针对脑肿瘤，值得等待进一步的结果。

伊维菌素

目前，尚无伊维菌素用于治疗癌症的临床试验。最近发表的几篇综述主要关注伊维菌素的抗肿瘤药代动力学特性。药效学评价表明，伊维菌素在人体中最高可达血浆浓度高于动物实验中的平均有效浓度。此外，最近几项使用伊维菌素治疗其他疾病的临床试验再次证实，其副作用和毒性相对可接受。与前几位作者的结论一致，我们强烈建议开展更多使用伊维菌素治疗癌症的临床试验。

氯喹衍生物

对于氯喹衍生物，与其他抗寄生虫药物相比，临床试验更多（表 S3 和 S4）。CQ 在脑肿瘤中的抗癌潜力正在引起科学家的关注（NCT02496741、NCT01894633、NCT01727531、NCT02378532、NCT02432417、NCT00224978）。遗憾的是，并非所有这些试验都已发表数据

2006 年发表的一项临床试验 (n=30) 表明，在化疗中添加 CQ 可能会提高多形性胶质母细胞瘤 (GBM) 患者的中期生存率。另一项已完成的临床试验 (NCT02378532) 于 2015 年开始，将氯喹与放疗相结合治疗 GBM 患者。不幸的是，没有公布结果。正在进行的临床试验 (NCT02432417) 将 CQ 与替莫唑胺和放疗相结合治疗 GBM 患者。先前的研究表明，EGFRVIII 的上调可通过诱导 GBM 癌细胞的自噬来帮助癌细胞在压力条件下生存。未来，应研究 CQ 诱导的自噬抑制是否可以提高 GBM 患者的整体生存率，尤其是 EGFRVIII 阳性亚型患者。这项临床试验的结果值得期待。

氯硝柳胺

可用的临床试验总结在表 S5 中。作为线粒体解偶联剂，它具有损害其他细胞（如心脏或肌肉细胞）的天然潜能。这种细胞毒作用是否会限制其治疗癌症中的临床应用正引起科学家们的关注。最近的一项研究集中于这个问题，并研究了心脏细胞对包括氯硝柳胺在内的线粒体解偶联剂的反应。Gao 等人证明，虽然高浓度氯硝柳胺确实表现出心脏毒性，但它通过在较低浓度（所谓的“轻度线粒体解偶联”）下激活 STAT3 通路发挥心脏保护作用。根据之前的临床前实验，临床上有意义的最低剂量约为 163.5 ng/mL（与恩杂鲁胺结合），相当于约 0.5 μ M。在这样的浓度下，氯硝柳胺会诱导约 5% 的心脏细胞死亡和 20% 的膜电位 (MMP) 损失，这可能会扰乱正常的心脏功能。保护心脏细胞或靶向递送至癌细胞可能是出路。无论选择哪种方法，临床试验都应包括心脏毒性监测。目前，尚无关氯硝柳胺是否会影响到肌肉细胞的研究，因此有必要对此问题进行调查。氯硝柳胺临床应用的另一个障碍是它是否能在体内达到目标浓度。一项已发表的临床试验表明，在最大耐受剂量 (500 mg TID) 下，只有 1/3 的患者达到 163.5 ng/mL。科学家想到了改进递送系统，并发明了几种纳米基药剂，这可能会提高其生物利用度。未来，科学家可能会在临床试验中探索这些药剂。

Pyrimethamine

Only 2 ongoing clinical trials are available on www.clinicaltrials.gov. (Table S6). In one of the trials, the researchers have published some of the results.¹³⁶ Their investigation suggested that in the maximum dose cohort (50 mg/d), the plasma concentration of Pyr reached 6.17 μM , which has not reached the target concentration (10 μM) for maximum STAT3 inhibition. However, there is no dose-related toxicity observed at such dose, suggesting that a higher dosage may be tolerable. Researchers observed the STAT3 inhibition in CLL cells in some of the treated patients. Interestingly, their research suggested that it may be possible to predict whether the CLL cells would respond to Pyr in vivo by treating the CLL cells in vitro and evaluate the post-treatment STAT3 expression change. Moreover, a rebound of STAT3 expression at the progression stage of the treatment. In this way, it is worthy to consider combining Pyr with other STAT3 inhibitors in future exploration.

Nitazoxanide

Currently, there is only one clinical trial applying nitazoxanide (NTZ) in cancer treatment (NCT02366884), and the result is still unavailable. There are also insufficient in vitro and in vivo experiments to evaluate the detailed anticancer mechanism of nitazoxanide. Based on previous studies, colorectal cancer cells seem to be more sensitive to nitazoxanide (For HCT116 cell line: $\text{IC}_{50}=11.2 \mu\text{M}$) compare with glioblastoma (IC 50: around 400 μM).^{73,94} According to the reported clinical trials, the maximum plasma concentration of NTZ at 1g/d dosage is 10.2 $\mu\text{g/mL}$ (equals 33.2 μM).¹³⁶ Moreover, a previous study suggested that up to 4g/d NTZ is tolerated in humans.¹³⁶ In this way, future exploration may focus on evaluating the highest tolerated dose of NTZ in human and analysis its pharmacokinetic property.

Conclusion

Drug redirection is increasingly attracting the attention of both researchers and pharmaceutical companies. Repositioning anti-parasitic agents to kill cancer cells could be a feasible way to develop cancer medications, and investigations on the detailed mechanisms and related clinical trials are continuing to accumulating. We summarized the recent advance in exploring the antiparasitic drugs' anticancer properties. Most of these agents target multiple biological procedures and exhibit inspiring anticancer potential. Their pharmaceutical effects also provide ideas for novel

drug design and development. However, there is also a dark side in this field. Several limitations that may block their final clinical application still exist and is worthy of noticing. For most of these agents, whether the target plasma concentration is achievable under the tolerated dose is the major issue. Drug combination or pharmacokinetic property improvement by modifying the chemical structure or applying the delivery systems may be the way out. Future in vitro or animal experiments should also focus more on the pharmaceutical properties of these agents at the range of achievable plasma concentration. Hopefully, some of these anti-parasitic agents may emerge as clinically applicable anticancer medications in the future.

Abbreviations

ARTs, artemisinin derivatives; ART, artemisinin; ROS, reactive oxygen species; IRP, iron regulatory proteins; IRE, iron responsive element; ARS, artesunate; DHA, dihydroartemisinin; GSH, glutathione; GPX4, glutathione peroxidase 4; GS-SG, oxidized glutathione; Bcl-2, B-cell lymphoma 2; DSB, double-strand break; LC3-II, Microtubule-associated protein light chain 3-II; DAPK1, death-associated protein kinase 1; mTOR, mammalian target of the rapamycin; ATG7, autophagy related 7; ATG5, autophagy related 5; TRF2, TBP-related factor 2; Atg4b, autophagy-related 4B; TFEB, transcription factor EB; JNK, Jun N-terminal protein kinase; JNK/STAT3, pathway; EVA1A, Eva-1 homolog A; ATG16L1, Autophagy Related 16 Like 1; CQ, chloroquine; PPT-1, palmitoyl-protein thioesterase 1; HCQ, hydroxychloroquine; MQ, mefloquine; LAMP1/2, lysosomal-associated membrane protein 1/2; CAF, cancer-associated fibroblasts; HNSCC, head and neck squamous cell carcinoma; TNBC, triple-negative breast cancer; MMP, matrix metalloproteinase; ATP, adenosine triphosphate; Bax, BCL (B Cell Lymphoma)-Associated X; MDSCs, myeloid-derived suppressor cells; ERK1/2, extracellular signal-regulated kinases 1 and 2; DC, dendritic cell; 5-FU, 5-Fluorouracil; IFN- γ , interferon- γ ; TNF- α , tumor necrosis factor- α ; CEA, carcinoembryonic antigen; CML, chronic myeloid leukemia; ULBP4, UL16 Binding Protein 4; NKG2D, receptor natural killer group 2D; CUR, curcumin; FoxP3, forkhead box P3; HIF-1 α , hypoxia-inducible factor 1 α ; DAMP, damage-associated molecular pattern; TGF- β , transforming growth factor- β ; NSCLC, non-small cell lung carcinoma; GLUT1, glucose transporter type 1; LNCaP, lymph node carcinoma of the prostate; G6P, glucose-6-phosphate.

乙胺嘧啶

www.clinicaltrials.gov 上只有 2 项正在进行的临床试验。(表 S6)。在其中一项试验中, 研究人员发表了部分结果。他们的研究表明, 在最大剂量组 (50 mg/d) 中, Pyr 的血浆浓度达到 6.17 μM , 尚未达到最大 STAT3 抑制的目标浓度 (10 μM)。然而, 在这种剂量下没有观察到剂量相关的毒性, 这表明更高的剂量可能是可以耐受的。研究人员在一些接受治疗的患者中观察到了 CLL 细胞中的 STAT3 抑制。有趣的是, 他们的研究表明, 通过体外治疗 CLL 细胞, 可能可以预测 CLL 细胞是否会对体内 Pyr 作出反应, 并评估治疗后 STAT3 表达的变化。此外, 在治疗的进展阶段, STAT3 表达出现反弹。这样, 在未来的探索中, 值得考虑将 Pyr 与其他 STAT3 抑制剂结合起来。

硝唑尼特

目前, 仅有一项将硝唑尼特 (NTZ) 用于癌症治疗的临床试验 (NCT02366884), 且尚无结果。体外和体内实验也不足以评估硝唑尼特的详细抗癌机制。根据以前的研究, 与胶质母细胞瘤 (IC 50: 约 400 μM) 相比, 结直肠癌细胞似乎对硝唑尼特 (对于 HCT116 细胞系: IC50=11.2 μM) 更敏感。根据已报道的临床试验, 1g/d 剂量下 NTZ 的最大血浆浓度为 10.2 $\mu\text{g/mL}$ (相当于 33.2 μM)。此外, 先前的研究表明, 人类可以耐受高达 4g/d 的 NTZ。因此, 未来的探索可能集中在评估人类对 NTZ 的最高耐受剂量和分析其药代动力学性质上。

结论

药物重定向越来越受到研究人员和制药公司的关注。重新定位抗寄生虫药物以杀死癌细胞可能是开发癌症药物的可行方法, 有关其详细机制和相关临床试验的研究正在不断积累。我们总结了探索抗寄生虫药物抗癌特性的最新进展。这些药物中的大多数针对多种生物程序, 表现出令人鼓舞的抗癌潜力

它们的药理作用也为新型药物的设计和开发提供了思路。然而, 这一领域也有其阴暗的一面。一些可能阻碍其最终临床应用的限制仍然存在, 值得注意。对于大多数这些药物来说, 在耐受剂量下能否达到目标血浆浓度是主要问题。通过改变化学结构或应用递送系统进行药物组合或药代动力学性质改进可能是出路。未来的体外或动物实验也应该更多地关注这些药物在可达到的血浆浓度范围内的药理特性。希望这些抗寄生虫药物中的一些将来能成为临床适用的抗癌药物。

缩写

ARTs, 青蒿素衍生物; ART, 青蒿素; ROS, 活性氧; IRP, 铁调节蛋白; IRE, 铁反应元件; ARS, 青蒿琥酯; DHA, 双氢青蒿素; GSH, 谷胱甘肽; GPX4, 谷胱甘肽过氧化物酶 4; GS-SG, 氧化谷胱甘肽; Bcl-2, B 细胞淋巴瘤 2; DSB, 双链断裂; LC3-II, 微管相关蛋白轻链 3-II; DAPK1, 死亡相关蛋白激酶 1; mTOR, 雷帕霉素哺乳动物靶点; ATG7, 自噬相关 7; ATG5, 自噬相关 5; TRF2, TBP 相关因子 2; Atg4b, 自噬相关 4B; TFEB, 转录因子 EB; JNK, Jun N 末端蛋白激酶; JNK/STAT3, 通路; EVA1A, Eva-1 同源物 A; ATG16L1, 自噬相关 16 样 1; CQ, 氯喹; PPT-1, 棕榈酰蛋白硫酯酶 1; HCQ, 羟氯喹; MQ, 甲氟喹; LAMP1/2, 溶酶体相关膜蛋白 1/2; CAF, 癌相关成纤维细胞; HNSCC, 头颈部鳞状细胞癌; TNBC, 三阴性乳腺癌; MMP, 基质金属蛋白酶; ATP, 三磷酸腺苷; Bax, BCL (B 细胞淋巴瘤) 相关 X; MDSC, 髓系抑制细胞; ERK1/2, 细胞外信号调节激酶 1 和 2; DC, 树突状细胞; 5-FU, 5-氟尿嘧啶; IFN- γ , 干扰素- γ ; TNF- α , 肿瘤坏死因子- α ; CEA, 癌胚抗原; CML, 慢性粒细胞白血病; ULBP4, UL16 结合蛋白 4; NKG2D, 受体自然杀伤组 2D; CUR, 姜黄素; FoxP3, 叉头框 P3; HIF-1 α , 缺氧诱导因子 1 α ; DAMP, 损伤相关分子模式; TGF- β , 转化生长因子- β ; NSCLC, 非小细胞肺癌; GLUT1, 葡萄糖转运蛋白 1 型; LNCaP, 前列腺腺癌; G6P, 葡萄糖-6-磷酸。

Consent for Publication

The authors consent that the details of any images, videos, recordings, etc. can be published, and all the authors have been shown the article contents to be published.

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作者同意发布任何图像、视频、录音等的详细信息，并且已向所有作者展示了要发布的文章内容。

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披露

作者报告称此项工作没有利益冲突。

参考

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