

A brief history of artemisinin: Modes of action and mechanisms of resistance

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Available online 20 May, 2019

[ABSTRACT] The cornerstone of antimalarial treatment, artemisinin, has reduced malaria associated morbidity and mortality worldwide. However, *Plasmodium falciparum* parasites with reduced sensitivity to artemisinin have emerged, and this threatens malaria control and elimination efforts. In this minireview, we describe the initial development of artemisinin as an antimalarial drug, its use both historically and currently, and our current understanding of its mode of action and the mechanisms by which malaria parasites achieve resistance.

[KEY WORDS] Artemisinin; Resistance; Malaria

[CLC Number] R284, R965 **[Document code]** A **[Article ID]** 2095-6975(2019)05-0331-06

Introduction

Malaria remains one of the most prevalent and serious infectious diseases in the world, and there is little indication that current prevalence reducing strategies are working. Alarmingly, there was an increase of five million cases from 2015 to 2016^[1]. Artemisinin and its derivatives (ARTs), have been widely used globally as the first-line drug class for the

treatment of malaria, but there is currently concern over the emergence of parasite resistance against these drugs.

Artemisinin (ART, also known as “Qinghaosu”) is a sesquiterpene lactone extracted from *Artemisia annua* L. (Sweet Annie, or Sweet Wormwood), a plant employed in Chinese traditional medicine. The drug was developed in 1967 in China by a nationwide program known as Project 523, which involved the work over 500 scientists from ~60 different laboratories and institutes within the country^[2]. The remit of the project was to identify new antimalarial drugs through the screening of compounds used in traditional Chinese medicine. Of over 2000 types of traditional Chinese herbs that were investigated, one plant, *Artemisia annua*, exhibited significant inhibitory properties against malaria parasites. This effect was enhanced further when the active ingredient, artemisinin, was extracted using ether at low temperatures, rather than ethanol; a discovery which led to the awarding of part of the 2015 Nobel Prize in Medicine to TU You-You of the China Academy of Traditional Chinese Medicine.

Since the initial purification of artemisinin from *Ar-*

[Received on] 13-Mar.-2019

[Research funding] This work was supported by the National Natural Science Foundation of China (Nos. 81601790 and 81603080), the Natural Science Foundation of Jiangsu Province (No. BK20150001), the Jiangsu Provincial Department of Science and Technology (Nos. BE2016631 and BM2018020), and the Jiangsu Provincial Project of Invigorating Health Care through Science, Technology and Education (Nos. CXTDA2017031 and wk018-004).

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These authors have no conflict of interest to declare.

temisia annua, many derivatives have been synthesized, including dihydroartemisinin (DHA) (also initially synthesized by TU You-You), artesunate, and artemether, which offer improved bioavailability and efficacy compared to ART^[3].

The impact of the (re)discovery of artemisinin and its derivatives on the treatment of malaria in the developing world has been immense. Since the late 1990s, ART and its derivatives have been the frontline treatment for uncomplicated *P. falciparum* malaria throughout the tropical world, and they are also increasingly recommended for the treatment of malaria caused by *Plasmodium vivax*. They have saved countless lives and have led to a net reduction in malaria prevalence in many countries.

Compared to other antimalarial drugs, ART and its derivatives are particularly fast-acting against the intra-erythrocytic asexual blood-stage parasites, rendering them highly effective for the treatment of severe malaria^[4-5]. However, due to their very short *in vivo* half-lives, (~1 hr in humans)^[4,6], ARTs are commonly co-administered with longer half-life partner drugs such as lumefantrine, amodiaquine, piperaquine, mefloquine or sulphadoxine-pyrimethamine in ART-based combination therapies (ACTs).

The use of ART in combination with another drug to prevent recrudescence and the development of resistance was first proposed by Prof. LI Guo-Qiao of Guangzhou College of Traditional Chinese Medicine, based on the results of two clinical studies^[7-8]. Soon afterwards, Professor Nicholas White of the Oxford Nuffield Department of Medicine began studying the efficacy of ARTs and confirmed their rapid activity and the need for a partner drug to prevent recrudescence^[9-10]. ACTs are now the standard first-line treatment for uncomplicated falciparum malaria worldwide.

Emergence of Resistance to Artemisinin

One of the major rationales for the exclusive use of ARTs in combination with other drugs was to protect against the emergence of drug resistance in malaria parasites. It was initially argued that resistance against ART was unlikely to emerge, due to its short half-life and ability to kill gametocytes^[11-12]. This was not the case, however, and ART “resistant” *P. falciparum* is now a major concern in Southeast Asia. Just one year after ACTs were recommended as the first line treatment for uncomplicated falciparum malaria by the WHO, parasites with reduced sensitivity to ART were reported close to the Thailand-Cambodia border, a phenomenon which manifested itself phenotypically in parasite strains which were cleared from the blood at a reduced rate following the standard ACT treatment protocol^[6,13]. There is some controversy regarding whether parasites with this reduced sensitivity to ARTs are truly “resistant”^[14], as resistance to all other antimalarial drugs is defined by clinical treatment failure and reduced *in vitro* sensitivity. However, for the remainder of this review, we will use the term “ART resistant” to describe parasites with decreased sensitivity to ARTs as defined by

increased survival rates as assessed by the *in vitro* Ring Survival Assay (RSA).

Since these first reports, the documented prevalence of ART resistance has expanded widely; the clinical phenotype having been documented across the Greater Mekong Sub-region (GMS) of Southeast Asia, from the coast of Vietnam in the East to India in the West^[15-17]. There are also reports of parasites resistant to ART from China^[18] and, of particular concern, from Equatorial Guinea^[19] and Uganda^[20] in Africa. Equatorial Guinea, situated in Central Africa, was a relatively early adopter of ACTs as a first line treatment for malaria, having switched from sulphadoxine pyrimethamine (SP) to Artesunate and Amodiaquine combination (AS + AQ) in 2004^[21]. In Africa, where malaria exerts its greatest burden, ART resistance could have a devastating effect on malaria control programmes, analogous to the consequences of the spread of chloroquine resistance towards the turn of the century^[22]. There are currently no alternative drugs available to replace artemisinin should resistance render it obsolete.

Mechanisms of Parasite Resistance to Artemisinin

All artemisinin-containing drugs are metabolized in the body to dihydroartemisinin (DHA)^[23], a sesquiterpene lactone endoperoxide. It is this endoperoxide which mediates parasite killing, through the production of free radicals following its cleavage. In order for ART to be activated (which involves the release of carbon-centered radicals that are able to disrupt parasite proteins), the endoperoxide bond undergoes reductive scission catalyzed by the reduced Fe²⁺ form of iron^[24-26]. The major source of this iron probably comes from imported host hemoglobin, proteolysis of which produces highly reactive heme species. Most of this heme is sequestered into hemozoin crystals, but a small proportion will remain free and available to activate ART. Other iron sources such as the low steady-state labile iron pool maintained in parasites may also be utilized in ART activation^[25,27]. Finally, there is some evidence to suggest that in very early rings, biosynthetic heme produced by the parasite may also activate ART^[28-29]. This dependence on free Fe²⁺ for activation offers an explanation for why ARTs are active against blood stage parasites^[30] but are not active against mature gametocytes^[31] or liver stages^[32].

The mode of action of ART against parasites involves the destruction of proteins by carbon centered radicals released upon activation of the drug. These radicals target a wide range of proteins, lipids and membrane components, and cause extensive and widespread cellular damage^[28,33]. This action is radically different to other antimalarial drugs which typically target one enzyme or pathway. There is also evidence to suggest that DHA causes proteostatic stress through inhibition of the proteasome, and both damages existing proteins and prevents the correct folding of newly synthesized proteins^[34]. This multi-pronged attack on an array of proteins leads to ER stress and attenuation of translation, which in turn leads

to a lethal buildup of polyubiquitinated damaged proteins^[34].

ART resistance is characterized by a reduction in early ring-stage parasite susceptibility and slow parasite clearance^[6, 13]. Multiple studies have confirmed the association of polymorphisms in the *P. falciparum* Kelch 13 propeller protein with ART resistance, and parasites carrying various single nucleotide polymorphisms in the gene encoding it (*PfK13*) display varying parasite clearance rate phenotypes^[35-36]. At present, parasites carrying *PfK13* mutations including F446I, N458Y, M476I, Y493H, R539T, I543T, P553L, R561H and C580Y, have been shown to be associated with slow clearance in clinical studies and reduced *in vitro* drug sensitivity, and while *PfK13* is now generally accepted as a valid marker for artemisinin resistance, around a further twenty reported polymorphisms remain to be characterized phenotypically for their effects on parasite sensitivity to ARTs^[37].

The K13 protein is thought to be a substrate adapter of an

E3 ligase which binds to phosphatidylinositol-3-kinase (PI3K) and marks it for proteosomal degradation by ubiquitin ligase. Mutations in the K13-propeller protein destabilize this interaction, resulting in decreased proteolysis of PI3K and increased levels of its lipid product phosphatidylinositol-3-phosphate (PI3P), which in turn makes the parasite more resistant to ART-mediated oxidative damage^[35]. Supporting this hypothesis, artificially increased levels of PI3P also confer ART resistance^[35] (Figure 1). K13 co-localizes with PI3P in vesicles found in the endoplasmic reticulum (ER) parasitophorous vacuole and the apicoplast^[38]. PI3P maintains the export of essential proteins from the parasite's ER to host erythrocytes at the early ring stage^[35]. Mutations in K13 are associated with increased numbers PI3P vesicles, and it has been hypothesized that this leads to increased stimulation of autophagy, allowing the removal of greater quantities of misfolded/toxic protein aggregates induced by ART^[39].

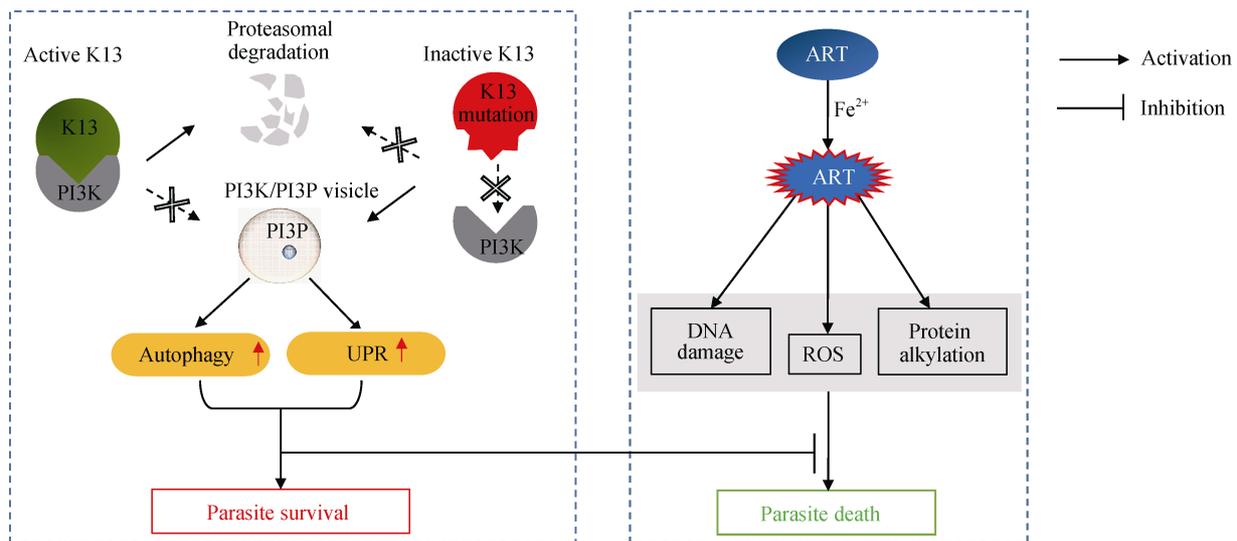


Fig. 1 Hypothesized mechanism of artemisinin resistance in *Plasmodium falciparum* involving decreased proteolysis of phosphatidylinositol-3-phosphate (PI3P). Ferrous ions within malaria parasites activate ARTs, causing DNA damage, the generation of reactive oxygen species (ROS) and the alkylation of multiple proteins, ultimately leading to parasite death. Mutations in Kelch 13 (K13) result in decreased proteolysis of phosphatidylinositol-3-kinase (PI3K) and increased levels of its lipid product PI3P. Increased PI3P may stimulate autophagy, engaging the unfolded protein response (UPR) to mount a stress response, thus promoting parasite survival.

Polymorphisms in the K13-propeller protein have also been found to be linked to increased expression of “the unfolded protein response” (UPR) pathway involving two major chaperone complexes, the *Plasmodium* reactive oxidative stress complex (PROSC) and the T-complex protein-1 ring complex (TRiC)^[40]. The two molecular pathways of artemisinin-resistance may be consolidated into a single model, in which increased PI3P results in vesicle expansion that increases engagement with UPR^[41].

ART-resistant *P. falciparum* lines have been generated in the laboratory that do not possess mutations in K13, and multiple other genes contributing to resistance have been pro-

posed^[42-43], indicating the genetic background of strains may influence the development of resistance mechanisms.

Discussion

Despite the worrying emergence of parasites with apparent reduced sensitivity to ARTs, ACTs remain the most effective treatment for uncomplicated falciparum malaria. The definition of artemisinin resistance is ‘partial/relative resistance’; there is an increase in parasite clearance time, but treatment is still effective^[14, 44]. To date, there is little evidence that higher degrees of artemisinin resistance have emerged, and partial artemisinin resistance has not resulted in

increased morbidity or mortality in the GMS [37]. It is important that public health policy makers and medical practitioners understand this situation accurately, and so avoid changes to treatment policies that may be counter-productive.

Based on current WHO recommendations, treatment policies do not require radical changes as long as the partner drug in ACTs continues to be effective [37]. The principle of partner drug selection is very important; longer half-life partner drugs should be selected in order to reduce the risks of re-exposure in highly endemic areas, and two or more drugs of different class combinations should be considered, as these may have a synergistic action and act against multiply resistant strains.

The development of compounds which can overcome artemisinin resistance and achieve high efficacy against malaria parasites has become more urgent. For example, a novel synthetic trioxolane; Artefenomel (OZ439), has recently been developed and appears to be a potential effective antimalarial drug that warrants further investigation [45].

The threat posed to public health by the continued selection of ART resistant parasites should not be ignored. To ensure that ACTs remain effective, routine monitoring should be carried out in endemic areas. As PI3P appears to be an important mediator of ART resistance, development of a simple PI3P analysis method may be useful for ART resistance surveillance and could complement detection of genetic markers such as mutations in *PfK13*.

In low malaria transmission areas, control programmes may move from control to elimination, and surveillance is a key component of this. China's "1-3-7" surveillance and response strategy is a valuable and simple methodology which could be adopted in other low transmission areas [46]. China has achieved great success in malaria control, and is close to its aim of eliminating malaria by 2020. The "1-3-7" surveillance and response strategy limits the time of case reporting, investigation and focused investigation, and public health action to within one, three, and seven days, respectively. This strategy could be further improved through obtaining additional information regarding the outcome of drug treatment, which would allow the monitoring of drug sensitivity. Imported cases, such as migrant workers from malaria-endemic countries could then be useful sources of information regarding the efficacy of ART in parasites obtained globally, which would benefit assessment of the spread of ART resistance around the world.

Conclusion

In summary, artemisinin is currently the bedrock of malaria chemotherapy worldwide, although its mode of action, and the mechanisms behind the development of parasite resistance require further investigation. Despite the fact that

ARTs are currently only ever used in combination with other drugs, *P. falciparum* parasites with reduced sensitivity to the drug have emerged. The mechanism of this resistance appears to involve two molecular pathways, and mutations in *PfK13* are the primary molecular markers. Artemisinin 'resistance' as currently defined remains partial, and the drug remains clinically efficacious.

Abbreviations

ARTs: Artemisinin and its derivatives;
 ART: Artemisinin;
 DHA: Dihydroartemisinin;
 GMS: Greater Mekong Sub-region;
 SP: Sulphadoxine pyrimethamine;
 RSA: Ring Survival Assay;
 ER: Endoplasmic reticulum;
 ROS: Reactive Oxidative Stress;
 UPR: Unfolded protein response;
 PROSC: *Plasmodium* reactive oxidative stress complex;
 TRiC: T-complex protein-1 ring complex;
PfK13: *P. falciparum* Kelch 13;
 PI3K: Phosphatidylinositol-3-kinase;
 PI3P: Phosphatidylinositol-3-phosphate

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Cite this article as: LU Feng, HE Xin-Long, Richard Culleton, CAO Jun. A brief history of artemisinin: Modes of action and mechanisms of resistance [J]. *Chin J Nat Med*, 2019, **17**(5): 331-336.