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Antiviral Theory Might Help to Develop Drug-Resistance-Free Antimalarial Drugs

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Abstract

Based on a novel antiviral theory, the reason why a virus can infect its target cells is because the gene expression pattern in the target cells is suitable for viral infection. Therefore, the alteration of the gene expression pattern in target cells means a reduced susceptibility to all viral infections. Analogously, the reason why sporozoites of malaria parasites can infect hepatocytes is because the gene expression pattern in hepatocytes is suitable for sporozoite infection. If a drug could be used to temporally alter the gene expression pattern in hepatocytes, the susceptibility to sporozoite liver infection will be reduced and thus could decrease or block infection of malaria. Since the drug only acts on hepatocytes, the malaria parasite will not develop resistance to this drug even after long-time repeated exposure.

Subject Areas

Virology, Malaria Prophylaxis

Keywords

Virus, Antiviral Theory, Malaria, Malaria Parasite, Sporozoite, Hepatocyte, Liver, Drug Resistance, Drug-Resistance-Free Antimalarial Drug

1. Introduction

Malaria remains a life-threatening disease in tropic and subtropical countries. According to the report of World Health Organisation, in 2021, there were an estimated 247 million cases of malaria and more than 600,000 malaria deaths. One of the challenges in malaria control is drug resistance in malaria parasites. The development of drug resistance and declining efficacy of combinations have been found in all antimalarial drugs, such as chloroquine [1], quinine [2], sulphadoxine-pyrimethamine [3] [4], amodiaquine [5], mefloquine [6], piperaquine

[7], pyronaridine [8] and artemisinin derivatives [9]. All these drugs are used to kill the erythrocytic forms of malaria parasites. Primaquine kills the intrahepatic forms and gametocytes of malaria parasites to prevent the relapses *of Plasmodium vivax* and *Plasmodium ovale* and its resistance in malaria parasite is also reported [10]. Obviously, any drugs that act on malaria parasites, either on the erythrocytic forms or on the intrahepatic forms, will eventually cause drug resistance in malaria parasites.

Malaria parasites develop resistance to all antimalarial drugs, which makes the situation of antimalarial chemotherapy worse and has put more pressure on the development of new antimalarial drugs. When a new drug is used in malaria treatment, malaria parasites will develop resistance to this drug some years later, and then another new drug needs to be developed again, leading to a vicious cycle. If drug-resistance-free antimalarial drugs are developed, the vicious cycle could be broken. These drugs could be used to prevent the infection of malaria for a long time or forever because no matter how long the drugs are repeatedly used, there will be no chance for malaria parasites to develop resistance to them.

The development of drug-resistance-free antimalarial drugs sounds ridiculous, but based on the novel antiviral theory proposed by us recently [11] [12], it is possible to develop drug-resistance-free antimalarial drugs. For this purpose, a hypothesis is presented in this paper.

2. A Novel Hypothesis for the Development of Drug-Resistance-Free Antimalarial Drugs

In order to prevent COVID-19 infection, we proposed a novel antiviral theory. The key points of this theory are: viral infection is cell-type specific, and the reason why a virus can infect its target cells is because the gene expression pattern in the target cells is suitable for viral infection. Therefore, the alteration of the gene expression pattern in target cells means a reduced susceptibility to all viral infections. We assume that genotoxic drugs (mainly referring to drugs with genotoxic side effects) could directly or indirectly alter genome architecture to change the gene expression pattern in host cells and therefore they could be used for preventing all viral infections including COVID-19 [11] [12]. Since the drugs only act on host cells, the viruses will not develop resistance to these drugs. A similar idea could be used to develop drug-resistance-free antimalarial drugs because the sporozoites of malaria parasites, like viruses, are cell-type specific and only invade hepatocytes when an infected female mosquito bites a human host. Therefore, the reason why sporozoites of malaria parasites can only infect hepatocytes is because the gene expression pattern in hepatocytes is suitable for sporozoite infection. If a drug could be used to temporally alter the gene expression pattern in hepatocytes, the susceptibility to sporozoite liver infection will be reduced. Since this drug does not act on malaria parasites, malaria parasites will not develop resistance to this drug even after a long time of repeated exposure.

Malaria parasites have two stages of schizogony in human hosts. The sporo-

zoites are injected into the skin of the human host by infected female mosquito bites and then invade the liver where they develop for days to weeks to mature into schizonts which rupture and release merozoites. This stage is called exo-erythrocytic schizogony. The released merozoites will infect red blood cells and undergo asexual multiplication in the erythrocytes, which is the point where the clinical symptoms of malaria are manifested. This stage is called erythrocytic schizogony. In short, if exo-erythrocytic schizogony is blocked by a drug that changes gene expression pattern in hepatocytes, the erythrocyte schizogony will not happen because no merozoites are produced in hepatocytes, and thus infection of malaria is prevented (Figure 1). Since this drug only acts on hepatocytes, the malaria parasite will not develop resistance to this drug.

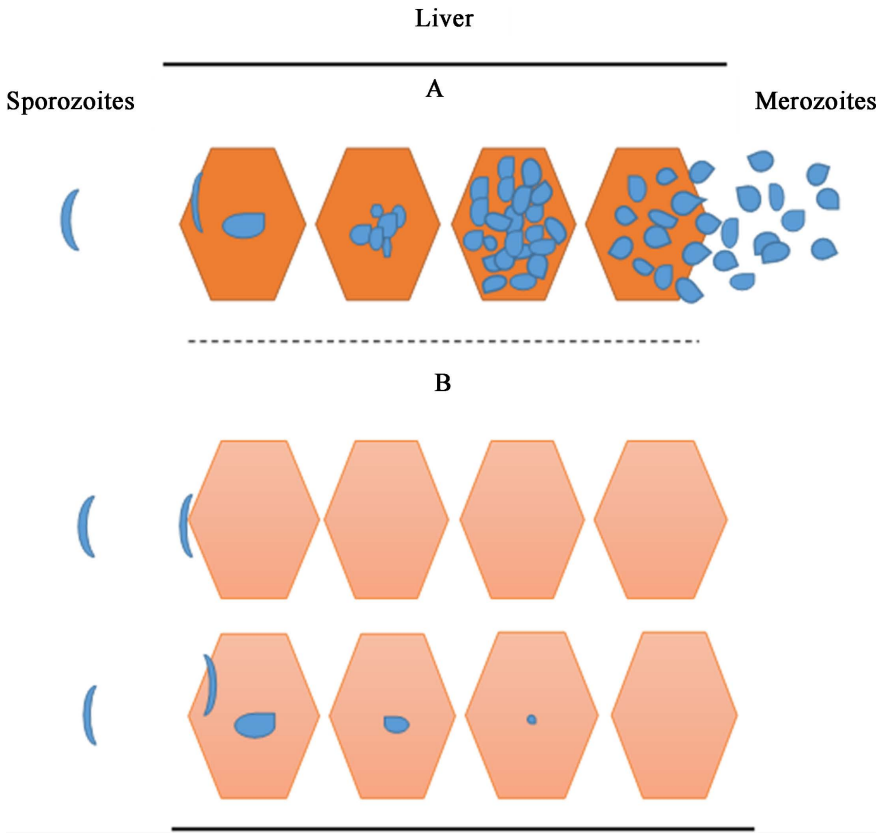

Figure 1. Schematic diagram for exo-erythrocytic schizogony. A = Normal hepatocytes: sporozoites mature into schizonts which rupture and release merozoites; B = Hepatocytes with gene expression pattern changes: sporozoites cannot enter cells or can enter cells but cannot survive.

Taken together, the hypothesis for developing drug-resistance-free antimalarial drugs for preventing infection of malaria might be feasible.

3. Hypothesis Testing

3.1. Reliability of Antiviral Theory

The antiviral theory is a hypothesis, but the foundation of this theory is reli-

able. The reason why a virus can infect its target cells is because the gene expression pattern in the target cells is suitable for virus infection. Recent research has indicated that host genetic factors determine COVID-19 susceptibility and severity [13] [14]. Therefore, it is reasonable that alteration of gene expression pattern in viral target cells means a reduced susceptibility to all viral infections including SARS-CoV-2. Since gene expression pattern is determined by genome architecture, and a slight alteration of genome architecture can cause the expression of a large number of genes [11]. We assume that drugs with genotoxic side effects could alter the gene expression pattern by affecting genome architecture.

Using drugs with genotoxic side effects to prevent viral infection is practicable because many drugs with genotoxic side effects are commonly used in clinical practice for a long time. Nearly all antimalarial drugs are drugs with genotoxic side effects. Even commonly used aspirin, vitamin C and paracetamol, etc., are drugs with genotoxic side effects [15] [16]. Drugs with genotoxic side effects might cause cancer, but can treat cancer as well [17]. Besides, drugs with genotoxic side effects can treat many diseases because the genotoxic side effects in the drugs can modulate the expression of many genes in different cell types through alteration of genome structure [12].

In order to check if the drugs that show anti-COVID-19 effects are the drugs with genotoxic side effects, we have carried out literature search and found that almost all these drugs have genotoxic side effects, such as chloroquine [18], mefloquine [19], artemisinins [20], metformin [21], ivermectin [22], niclosamide [23], polyphenols [24], cannabidiol [25], ursodeoxycholic acid (UDCA) [26], and theophylline [27] etc., which indirectly supports our assumption that drugs with genotoxic side effects could be used to prevent COVID-19 infection. Since the drugs cannot kill viruses, they are not appropriate for treating patients. Unfortunately, clinical trials using chloroquine, ivermectin and metformin, etc., to treat patients have suggested that no evidence supports the use of the trial drugs for the treatment or prevention of COVID-19 [28] [29] [30], which may be totally wrong because the drugs might be good at preventing COVID-19 infection.

A recent research indicates that UDCA can reduce FXR signalling and downregulate ACE2 in human lungs, concluding that UDCA can prevent COVID-19 infection through the reduction of ACE2 [31]. However, this research was only based on a study of one pathway (ACE2 production), and paid no attention to other functions of many altered pathways that are caused by UDCA which can modulate more than 440 genes in rat hepatocytes [32]. Therefore, UDCA's mechanism of viral prevention is changing the gene expression pattern in host cells, making the cells temporarily become unsuitable for COVID-19 infection (the virus is unable to enter cells and/or difficult to form virion after entering cells). In theory, the discovery of UDCA's efficacy in the prevention of COVID-19 infection fully supports our antiviral theory, but in practice, UDCA is not a good drug for preventing COVID-19 infection due to its toxicity.

Overall, the antiviral theory might be reliable, and thus based on this theory, the development of drug-resistance-free antimalarial drugs might be practical.

3.2. Screening of Drug-Resistance-Free Antimalarial Drugs

Like the prevention of viral infection, drug-resistance-free antimalarial drugs should be the drugs with genotoxic side effects. To screen drug-resistance-free antimalarial drugs, we can use a rodent malaria parasite model, such as *Plasmodium berghei* and *Anopheles stephensi* [33]. The drugs that alter the gene expression pattern could be tested on this model to see which drug can block infection of malaria through blockage of sporozoite liver infection, for example, normal mice could be divided into two groups with one group as a control, the treatment group is given a drug with genotoxic side effects and the control receives a placebo for 10 days, on the third day, let starved and infected A. *stephensi* females bite two groups for 1 hour. Observation of the two groups for 1 - 2 weeks to see which group has lower parasitemia or no infection of red blood cells. If one drug is found to completely block the infection of malaria, this drug could be a drug-resistance-free antimalarial drug because the drug does not act on malaria parasites but changes the pattern of gene expression in hepatocytes.

In theory, the above drugs with genotoxic side effects for viral prevention could be screened on this system, but UDCA has a great chance of success because UDCA can alter the expression of hundreds of genes in rat hepatocytes [32]. If UDCA is successful in the prevention of rodent malaria, it can be used in clinical trials. If UDCA is still successful in preventing infection of human malaria, it indicates that a novel resistance-free antimalarial drug is discovered. Then, we can screen less-toxic drug-resistance-free antimalarial drugs. Some drugs with genotoxic side effects are safe and affordable such as paracetamol, berberine, curcumin, theophylline, etc. Undoubtedly, these drugs cannot treat malaria, but they could become drug-resistance-free antimalarial drugs if they can alter the pattern of gene expression in hepatocytes.

4. Conclusion

During the COVID-19 pandemic, the discovery of a drug that can be used to kill SARS-CoV-2 is difficult, but based on our antiviral theory, finding drugs to prevent the COVID-19 pandemic is comparably easy. The mechanism of viral prevention is changing the gene expression pattern in viral target cells by taking old drugs with genotoxic side effects so that viruses cannot enter or cannot survive in the target cells. Since these preventive drugs only act on host cells, there will be no chance for viruses to develop resistance to these drugs. Likewise, we can use a similar idea to prevent sporozoites from infecting hepatocytes. Since the drugs only act on hepatocytes, malaria parasites will not develop resistance to these drugs. In conclusion, our antiviral theory might help to develop drug-resistance-free antimalarial drugs, which could play an important role in malaria control and elimination.

Conflicts of Interest

The author declares no conflicts of interest.

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