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Drug Resistance in Malaria Parasites: Does "Specific Antidrug Substance" Exist?

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Abstract

Development of drug-resistant lines in rodent malaria parasites left us a deep impression on antidrug specificity of antimalarial drug-resistant lines, which is similar to antigen-induced antibody. Based on this comparison, "specific antidrug substance" was proposed to explain antidrug specificity of drug-resistant lines. If "specific antidrug substance" refers to a protein that is quite like antibody, the concept of "specific antidrug substance" is wrong because no such protein has been discovered. However, if "specific antidrug substance" refers to a "specific antidrug group of protein combinations", the concept of "specific antidrug substance" might be true. A detailed explanation of "specific antidrug substance" is presented in this paper.

Subject Areas

Drugs & Devices, Pharmacology

Keywords

Molecular Pharmacology, Drug Resistance in Malaria Parasite, "Specific Antidrug Substance", 3D Genome Architecture, "Specific Antidrug Group of Protein Combinations"

1. Introduction

Drug resistance, especially multidrug resistance, in malaria parasites has become the biggest obstacle that global eradication of malaria is facing [1] [2] [3]. Currently, studies on drug resistance in malaria parasites mainly focus on mutated gene hunting. Many drug resistance-associated genes have been discovered, such as mutated genes of *Pfdhfr* and *Pfdhps* in pyrimethamine and sulfadoxine resistance, mutated genes for chloroquine resistance including pfmdr1 and pfcrt, and mutated PfKelch-13 gene for artemisinin resistance [4]. Mutated genes are help-

ful for identification of drug resistant malaria, but will not solve the whole problem of drug resistance in malaria parasites.

The obvious phenomenon in drug resistance of malaria parasites is antidrug (antidrug = resistance to drugs that kill pathogens) specificity, *i.e.*, a drug-resistant line is most resistant to the drug or inducer that was used to develop the line, and slightly resistant to the drugs that are structurally similar to the inducer. Usually, the line has no resistance to drugs that are not structurally similar to the inducer. Behind this phenomenon, there may be an interesting mechanism. However, no such experimental researches have been reported recently.

In 1985, we first developed two piperaquine-resistant lines, which showed antidrug specificity after cross-resistance testing of several antimalarial drugs [5] [6]. This experienced practice made a deep impression on us. We thought that antidrug specificity in drug resistance of malaria parasites was quite similar to antigen-antibody relationship and therefore we published a hypothesis that drug-resistant malaria parasites, like lymphocyte producing specific antibody, may release certain "active antidrug substance" [7]. Later on, we published a paper entitled "Antagonism of serum of mice infected with chloroquine-resistant 'NS' line to the antimalarial action of chloroquine", which indicates that malaria parasites may produce "specific antidrug substance" [8].

Almost four decades have passed, rethinking of "specific antidrug substance" hypothesis seems worthwhile. "Specific antidrug substance" was proposed based on comparison between antigen-antibody specificity and antidrug specificity. This comparison could be wrong or right based on how to explain the "specific antidrug substance". If "specific antidrug substance" refers to a protein, the hypothesis is wrong because a protein against a drug molecule is uneconomical and also no such protein has been found. But if "specific antidrug substance" refers to a "specific antidrug group of protein combinations", the hypothesis is right. A theoretical explanation of this novel idea is presented in this paper.

2. Changes of Three-Dimensional (3D) Genome Architecture in Drug-Resistant Malaria Parasites

In 1986, we hypothesized that abnormalities of 3D genome architecture are linked to cancer formation [9]. Also in this article, we mentioned that different cells may have different 3D genome architectures which determine gene expression patterns. Recent researches on 3D genome architecture support our hypothesis [10] [11] [12]. Drug-resistant malaria parasites are different cell types compared to normal malaria parasites, therefore they should have different 3D genome architectures. Based on this logic and reason, we claimed that chloroquine resistance in malaria parasites is caused by abnormalities of 3D genome architecture or altered 3D genome architecture [13] [14]. Now we further point out that all antimalarial drug resistances are caused by altered 3D genome architectures which control drug resistance phenotypes including antidrug specificity.

According to malaria treatments and drug-resistant line developments, the levels of antimalarial drug resistance could be divided into 3 types: reversible re-

sistance, stable resistance and permanent resistance, all of which are controlled by altered 3D genome architecture (Figure 1). The reversible resistance is not hereditary and will lose drug resistance if no drug pressure is given. However, the drug resistance can quickly come back if drug pressure is given again. The mechanism is that altered 3D genome architecture can return to normal if no drug pressure is given. The stable resistance is "temporally" hereditary and even without drug pressure, the drug resistance can pass few generations. The mechanism is that epigenetic changes may temporarily "fix" altered 3D genome architecture. The permanent resistance is hereditary and drug resistance will not lose even without drug pressure. The mechanism is that mutated genes can permanently fix altered 3D genome architecture. The mutated proteins may affect their own original functions but are not as important as mutated genes in formation of permanent drug resistance. The appearance of mutated genes is probably caused by alterations of 3D genome architecture [15].

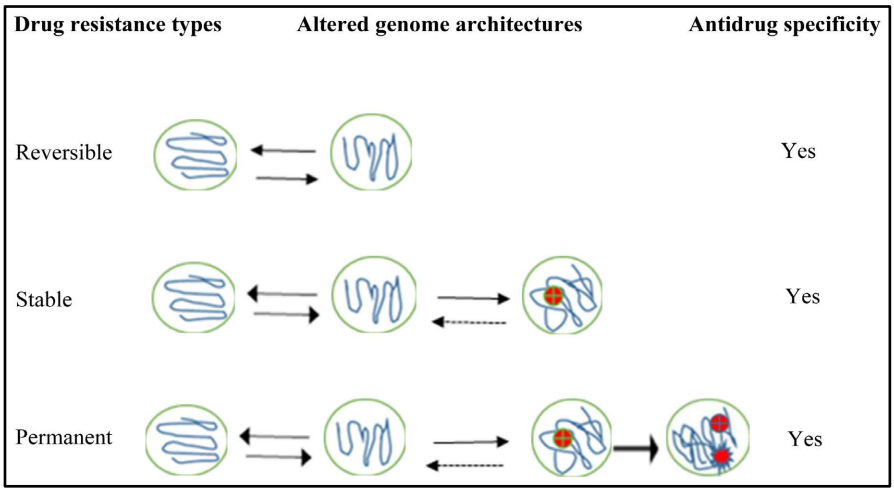

Figure 1. Reversible, stable and permanent drug resistances in malaria parasites. The nucleus of malaria parasite = ; Epigenetic change sites = ; Mutated genes = . Drug-resistant lines developed in laboratory are usually reversible in drug resistance, but antidrug specificity in these lines has been confirmed after cross-resistance testing of different drugs.

From Figure 1, antidrug specificity is first seen in reversible resistance, which means that epigenetic changes and mutated genes have nothing to do with antidrug specificity because reversible resistance that has no epigenetic changes and mutated genes holds on to antidrug specificity. Altered 3D genome architecture manipulates a large number of normal gene expressions so that drug resistance is drug-specific. The conclusion can be drawn that antidrug specificity in malaria parasites is controlled by many normal genes.

3. "Specific Antidrug Substance" and "Specific Antidrug Group of Protein Combinations"

Since many normal genes are involved in formation of antidrug specificity, it is

confirmed that "specific antidrug substance" is not a protein, but combination of many proteins. The proteins involved in antidrug specificity could be named as "antidrug specificity-associated protein", all of which work together for forming "specific antidrug group of protein combinations" in each drug-resistant line (Figure 2).

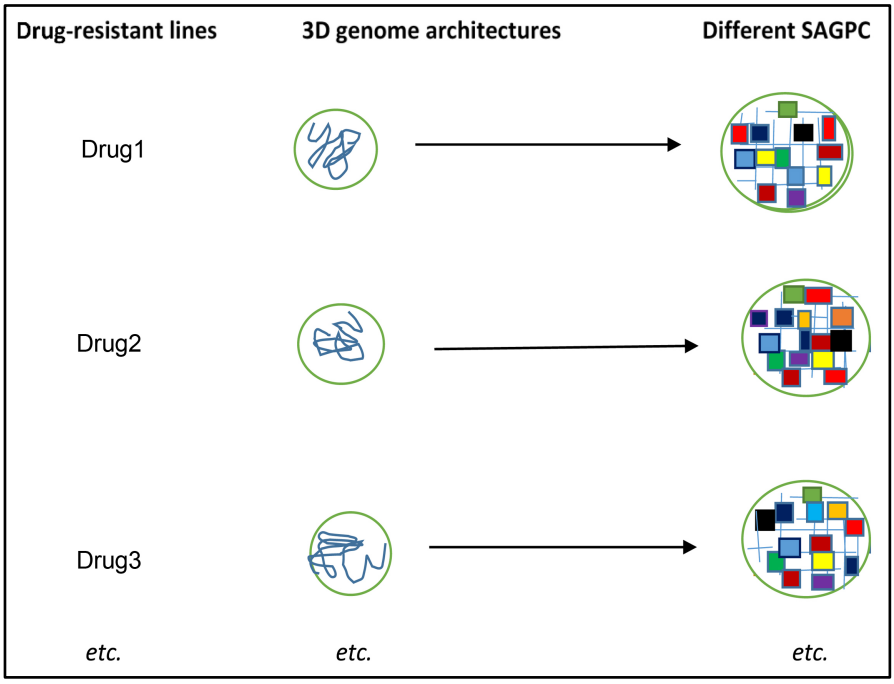

Figure 2. Different drug-resistant lines that produce different variety of "specific antidrug group of protein combinations" (SAGPC). The grids in the circles represent hundreds and thousands of "antidrug specificity-associated protein" (one grid = one protein); coloured squares represent different expression levels of protein (same colour = same expression level of different proteins).

It is obvious that "specific antidrug group of protein combinations" are the results of genes that are regulated by altered 3D genome architecture. If we check one "antidrug specificity-associated protein", we can't see any trace of linkage to antidrug specificity, but imagine what happens if all of "antidrug specificity-associated protein" are considered together. This is quite like doing a jigsaw puzzle. When we see a piece of jigsaw, we don't know the picture, but when all jigsaw pieces are put together, the real picture (antidrug specificity) appears.

Altered 3D genome architecture regulates gene transcriptions, some proteins might be down-regulated, others could be up-regulated. If there are hundreds and thousands of genes involved, the protein combination types could be as many as different antigen-types recognized by B lymphocyte. In other words, if there are many specific antibodies that are produced by immune cells, there will be many "specific antidrug group of protein combinations" that are produced by malaria parasites. Overall, this is the reason why antidrug specificity exists.

To prove whether antidrug specificity is controlled by "specific antidrug group of protein combinations", three things should be done: first, using differential gene expression analysis of drugs, genes of "antidrug specificity-associated protein" should be found out; second, protein levels of these genes should be measured; third, each drug should have a list of expression levels of all proteins, which is a "specific antidrug group of protein combinations". It may be expected that every drug-resistant line has a group of protein combinations which could be very close to a group of protein combinations of structure-similar drug. Obviously, if two drugs are structurally different, the two protein combinations will be different. In short, "specific antidrug group of protein combinations" could be considered as "specific antidrug substance" to understand antidrug specificity of drug-resistant malaria parasites.

4. Conclusions

Malaria parasites don't have acquired immune system, but their response to long-time drug pressure might be quite similar to acquired immune response. In this paper, we claim that all antimalarial drug resistances in malaria parasites are caused by altered 3D genome architectures and antidrug specificity is controlled by "specific antidrug group of protein combinations". Even though we only talk about drug-resistant malaria parasites in this paper, drug resistance formation in other pathogens, such as cancer cells and bacteria etc. could be the same as malaria parasites. In addition, to treat drug-resistant infections, a drug that causes changes in altered 3D genome architecture of drug-resistant pathogens could be used as an adjuvant.

The history of studies on drug resistance in malaria parasites has been more than 60 years, but except few mutated genes, many mysteries of drug resistance are still unknown. This paper suggests that many normal genes might be involved in formation of antidrug specificity, which requires further investigation. Revelation of secrets behind drug resistance is both interesting and important. Hopefully, more researches on drug resistance will focus on this area.

Conflicts of Interest

The author declares no conflicts of interest regarding the publication of this paper.

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