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The Mechanism of Drug Resistance in Cellular Pathogens: A Hypothesis

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Abstract

Drug resistance in pathogens including cancer cells, bacteria, protozoa, fungi and viruses remains the major global health challenge. To deal with drug resistance in pathogens, an understanding of drug resistance development is of great importance. Recently, we published a hypothesis that drug resistance in malaria parasites could be determined by the altered 3D genome architecture which regulates many normal genes in malaria parasites to form a "specific antidrug group of protein combinations" (SAGPC). Like a "specific antidrug substance" or an "antibody", SAGPC might specifically resist the efficacy of drugs. In this paper, we further assume that drug resistance in cellular pathogens excluding non-cellular viruses might share the mechanism we proposed for drug resistance development in malaria parasites.

Subject Areas

Pharmacology

Keywords

Drug Resistance in Cellular Pathogens, Specific 3D Genome Architecture, Specific Antidrug Group of Protein Combinations (SAGPC), Specific Antidrug Substance

1. Introduction

Drug resistance in pathogens including cancer cells, bacteria, protozoa, fungi and viruses has become one of the biggest global health challenges in clinical practice. Understanding the mechanism of drug resistance in all pathogens is of fundamental importance for solving this increasingly severe challenge. Recently, we published a paper in which drug resistance in malaria parasites might be caused by the altered 3-Dimensional (3D) genome architecture in malaria parasites which regulates many normal genes to form a "specific antidrug group of

protein combinations" (SAGPC). Like a "specific antidrug substance" or an "antibody", SAGPC might specifically resist the efficacy of drugs [1] [2]. Currently, the mechanisms of drug resistance in pathogens are complicated, which includes altered drug metabolism, epigenetic changes, drug target changes, DNA repair enhancement, limiting drug uptake, active drug efflux, and so on [3] [4]. Only recently, the relationship between 3D genome architecture and drug resistance formation has been studied. Several researchers have verified that the altered 3D genome architecture in pathogens plays an important role in drug resistance development [5] [6] [7], which indirectly support our idea about drug resistance in malaria parasites. Furthermore, we hypothesize that drug resistance in other cellular pathogens excluding non-cellular viruses might share the mechanism we proposed for drug resistance in malaria parasites. To support this hypothesis, more explanations are presented in this paper.

2. The Mechanism of Drug Resistance in Cellular Pathogens

The mechanism of drug resistance in cellular pathogens is a hypothesis that might unify all the mechanisms of drug resistance in cellular pathogens into one mechanism. Cellular pathogens refer to cancer cells, bacteria, protozoa, and fungi. We propose that each drug that includes anticancer, antibacterial, antiprotozoal, and antifungal drugs will change the 3D genome architecture in a cellular pathogen into an altered 3D genome architecture after long-time drug pressure. Now we change the "altered" into "specific". The specific 3D genome architecture in each cellular pathogen will regulate many normal genes to form SAGPC. More like a "specific antidrug substance" or an "antibody", SAGPC might specifically resist the efficacy of the drug (**Figure 1**).

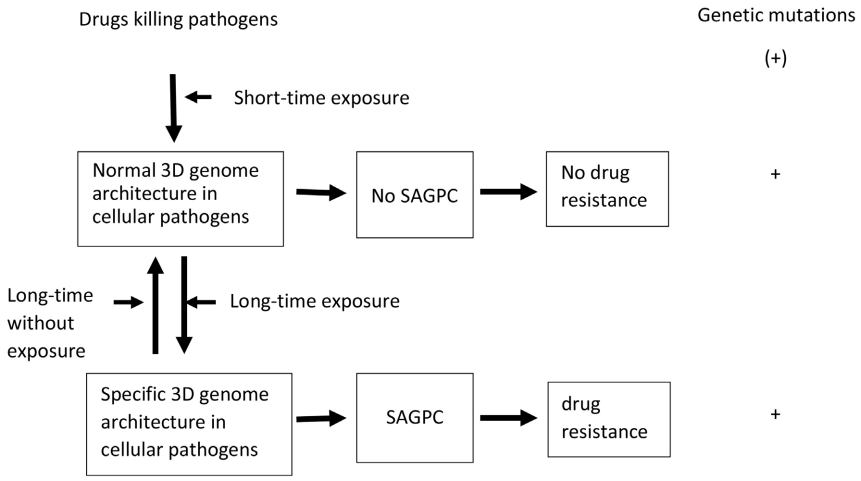

Figure 1. The mechanism of drug resistance in cellular pathogens. Long-time drug exposure on a pathogen might change 3D genome architecture into a specific 3D genome architecture which regulates many normal genes to form a "specific antidrug group of protein combinations" (SAGPC) for specifically resisting the efficacy of drugs. The specific 3D genome architecture might return to normal state if the drug has not been used for a long time. Only genetic mutations that occur after the formation of drug resistance could be used to detect drug resistance.

We assume that epigenetic changes and genetic mutations might be involved in the formation of the specific 3D genome architecture. Drug-caused genetic mutations are environmental-factor-joined mutagenesis which is a special gene regulation that regulates gene product quality not gene product quantity [8]. This special gene mutation will quicken the process of "fixing" the altered 3D genome architecture that helps the pathogens to survive the harmful environment for a longer time. Under long-time drug pressure, genetic mutations might occur in an attempt at any stage of the drug resistance development. Both epigenetic changes and genetic mutations might "fix" the specific 3D genome architecture so that the drug resistance in the pathogens could be inherited. As for the detection of drug resistance phenotype with mutated genes, the timing of genetic mutation occurring is important. If the mutations in a gene occur before drug resistance formation, the mutated gene might not be able to detect drug resistance. If the mutations in a gene occur after drug resistance formation, the mutated gene could be used to detect drug resistance. Normally, the mutated gene used for detecting drug resistance is the gene that has a higher mutation rate after drug resistance formation. Therefore, the mutated genes alone might not cause drug resistance, and could only be used to indirectly and roughly detect drug resistance.

The specific 3D genome architecture in cellular pathogens is induced after long-time drug usage, which is beneficial to the survival of the pathogens. However, if no drug has been used for a long time, the specific 3D genome architecture in cellular pathogens might return to a normal state because the specific 3D genome architecture is the burden for the normal growth of pathogens. The returning reason could be explained with an "epigenetic-change U-turn" or back mutation [9]. Collectively, the drug resistance development in cellular pathogens seems a cellular defense mechanism and might have nothing to do with so-called "evolution". The intracellular defense mechanism in cellular pathogens could be named "genome-modulated intracellular acquired immunity".

3. Supporting Evidence for the Hypothesis

In theory, drug resistance in cellular pathogens is a response to genome-regulated expressions of many normal genes because the drugs that kill pathogens might endanger the lives of pathogens and to survive this fatal disaster, whole genes in cellular pathogens must work together. Some proteins of genes might work as efflux proteins to pump drugs out of cellular pathogens, and others might help to repair or overcome malfunctions in cellular pathogens which are caused by drugs. Different drugs can cause different malfunctions in cellular pathogens and that is the reason why SAGPC should be produced for specifically resisting the efficacy of drugs. SAGPC is more like an "antibody" that binds antigen and similar antigens, leading to cross immune reactions. But SAGPC's "binding specificity" is formed by various protein combinations, which leads the "binding specificity" to be less strict so that SAGPC is not only resistant to the drugs that cause the resistance and cross-resistant to structure-similar drugs but also cross-resistant to structure-different drugs if their actions on pathogens are

within SAGPC's "binding specificity". Drug resistance and cross-resistance are common features in all drug-resistant pathogens, which we named antidrug specificity. Any mechanisms that cannot be used to explain the antidrug specificity might not be right.

Many differential gene expression analyses or transcriptome analyses between drug-sensitive and drug-resistant lines or strains have suggested that many normal genes are involved in the formation of drug resistance, which also indicates the existence of SAGPC. A few examples are presented here: in multidrug-resistant gastric carcinoma cells, a transcriptome analysis showed that 156 genes were significantly regulated in the multidrug-resistant cell line compared with the sensitive line [10]; regarding the levofloxacin-resistant mycobacterium tuberculosis, transcriptome analysis demonstrated that 953 differentially expressed genes were identified with 514 and 439 genes were downregulated and upregulated in the levofloxacin-resistant group and control group, respectively [11]; as for artemisinin-resistant *Plasmodium falciparum*, a research identified at least 156 genes that may contribute to artemisinin resistance [12]; with regard to drug resistance in fungi, transcriptome analysis revealed that 541 upregulated and 453 downregulated genes in the resistant—*Candida auris* strain compared with the sensitive strain [13].

In 1986, we proposed a hypothesis in which 3D genome structure determines gene expression patterns or gene expression patterns depending on 3D genome structure [14]. Therefore, we could confirm that drug resistance might be determined by the specific 3D genome architecture or by SAGPC. Comparing the different types of SAGPC among drug-resistant pathogens, it is possible to find that some protein combinations might be able to distinguish different types of drug resistance. If immunoassay chips are made with these protein combinations, we could specifically and reliably detect drug resistance in cellular pathogens. If drug resistance in cellular pathogens is determined by the specific 3D genome architecture, we would have a good foundation for fighting drug resistance, which might include intermittent use of different drugs, usage of drug combinations, and addition of adjuvants to block epigenetic changes or slow down the dynamic changes of 3D genome structure.

4. Conclusion

Drug resistance in cellular pathogens might be determined by the specific 3D genome architecture. The formation of the specific 3D genome architecture needs several factors: long-time drug usage is of paramount importance; epigenetic changes and genetic mutations are necessary; even mutations in non-coding DNA sequences might be involved as well. Currently, it is difficult to test the whole of a specific 3D genome architecture in a drug-resistant pathogen, but we might predict the existence of specific 3D genome architecture by SAGPC because gene expression patterns depend on 3D genome structure. Each drug changes the 3D genome structure in cellular pathogens into a specific 3D genome architecture

which regulates many normal genes to form SAGPC. More like a "specific antidrug substance" or an "antibody", SAGPC specifically resists the efficacy of drugs, which could be used to explain the antidrug specificity. Besides, the novel mechanism of drug resistance might help to create a specific and reliable method for detecting drug resistance and develop new approaches to combat drug resistance in cellular pathogens.

Conflicts of Interest

The author declares no conflicts of interest.

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