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Non-Carcinogenic Genotoxic Drugs Could Be Used to Prevent and Treat COVID-19

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Abstract

Three-dimensional (3D) genome structure plays an important role in the regulation of gene expression. Alteration of 3D genome structure can change cell's gene expression pattern that causes cellular function change and thus could be used as a novel therapy for treating many diseases including COVID-19. Genotoxic drug is the only drug that could be used to alter 3D genome structure. Since at present no purpose-made non-carcinogenic genotoxic drugs for altering genome structure are available and fighting COVID-19 must be done without delay, it is possible to repurpose some old drugs as non-carcinogenic genotoxic drugs that can be used to reduce target cell's susceptibility to SARS-CoV-2 which causes COVID-19 and to modulate immune cell's response to SARS-CoV-2 infection through altering 3D genome structures in target cells and immune cells.

Subject Areas

Cell Biology, Molecular Biology, Pharmacology

Keywords

Three-Dimensional Genome Structure, Non-Carcinogenic Genotoxic Drugs, Chloroquine, Hydroxychloroquine, SARS-CoV-2, Coronavirus Disease 2019 (COVID-19)

1. Introduction

In recent decades, a growing number of research evidence has demonstrated that three-dimensional (3D) genome structure plays an important role in the regulation of gene expression and abnormalities of 3D genome structure are associated with many diseases [1] [2], which indicates that altering 3D genome structure by drugs could be a novel therapy for treating a wide range of diseases that have no

cure at present.

Thirty-four years ago, we proposed a hypothesis that oncogenesis might be linked to abnormalities of 3D genome structure and as such restoration of normal 3D genome structure could be a novel strategy for treating cancer [3]. Literature search results demonstrate that our paper may be the first published paper that indicates the possibility of treating diseases through altering cell's 3D genome structure.

Starting from December of 2019 [4], the COVID-19 pandemic has now killed more than half million people worldwide. Since no vaccine and effective drugs available, many countries still remain under lockdown, which has caused huge social and economic problems. In this paper, we present that alteration of cell's 3D genome structure by non-carcinogenic genotoxic drugs could be a novel strategy for preventing and treating COVID-19.

2. Genotoxic Drug Is the Only Drug That Can Alter 3D Genome Structure

It has been common sense for a long time that drug genotoxicity is a type of drug side effects, but now we think that genotoxic drug is the only drug that could be used to alter 3D genome structure. Carcinogens belong to genotoxic agents, but not all genotoxic agents are carcinogens. Therefore, it is possible to develop a novel drug class: non-carcinogenic genotoxic drugs that can temporarily alter 3D genome structure when being used for a short period of time, but will not cause permanent damage to genome structure, *i.e.* the altered genome structure will return to normal after drug withdrawal. This novel class drugs are different from genotoxic anticancer drugs that cause cancer-cell death through damaging DNA or genome structure [5]. It is also possible to repurpose some old drugs as non-carcinogenic genotoxic drugs, for example, chloroquine (CQ) and its derivative hydroxychloroquine (HCQ) could be used as non-carcinogenic genotoxic drugs to alter 3D genome structure [6].

Recently, whether CQ and HCQ can be used in the prevention and treatment of COVID-19 remains unsolved. The underlying reason perhaps is because the mechanisms of CQ's diverse therapeutic actions are unclear. Different from mainstream views, we recently proposed that CQ or HCQ might exert their diverse therapeutic actions through targeting 3D genome structure [6]. Gene expression pattern in a cell type is determined by the cell type 3D genome structure, and even a slight alteration in the 3D genome structure will cause a wide-range change in gene expressions, in which probably hundreds or thousands of genes will be either up-regulated or down-regulated, leading to cellular function changes including response to environmental changes.

The reason why a virus can infect its target cells is because the target cell's gene expression pattern is suitable for the viral invasion. Therefore, if the target cell's gene expression pattern is temporarily changed through altering 3D genome structure in the target cells by short-time administration of non-carcinogenic genotoxic drugs, the target cell's susceptibility to the virus will be reduced. This

is the mechanism of antiviral action of genotoxic drugs. Many diseases are linked to abnormalities of gene expression patterns that are caused by abnormal 3D genome structure. In theory, to treat these diseases, normal gene expression pattern should be restored through altering 3D genome structure by specific genotoxic drugs, but unfortunately, no such drugs are available at present. Although non-specific genotoxic drugs cannot be used to restore normal gene expression pattern through altering 3D genome structure, they could be used to interfere existing abnormal gene expression patterns through non-specifically altering 3D genome structure and thus to improve patient conditions. Therefore, in addition to inducing antiviral effects, altering 3D genome structure by non-specific genotoxic drugs could be a cure-all strategy for treating many diseases that have no cure at present. We can hereby draw a conclusion that any agents shown to have cure-all properties must be non-specific genotoxic agents.

3. Using Genotoxic Drug Combinations for Preventing and Treating COVID-19

Since we don't have ready-to-use non-carcinogenic genotoxic drugs at present, what we can only do is to find out some approved drugs with genotoxic side effects. These drugs could be repurposed as genotoxic drugs. However, drug side effects are not drug's main therapeutic effects, which means that to prevent and treat COVID-19, just using a single drug with genotoxic side effects is not enough. Therefore, we should use genotoxic drug combinations for preventing and treating COVID-19. No doubt, many approved drugs that are already used in clinical practice have more or less genotoxic effects. But we have no time to study each of them because fighting COVID-19 to save lives is so urgent that we need to quickly find out few promising old drugs that can be repurposed as genotoxic drugs for altering cell's 3D genome structure. There are many drug classes, from which the drugs with genotoxic side effects could be selected. Based on literature search and drug safety information, we have picked out 9 candidate drugs with genotoxic side effects from 5 drug classes (Table 1). Other drug classes also include drugs that could be used to alter 3D genome structure, such as anticancer drugs and hypomethylating agents etc., but due to high toxicity in

Table 1. Candidate drugs with genotoxic side effects.

Drug classes	Candidate drugs	Reference	Combinations
Antimalarials	CQ/HCQ	[7] [8]	
Antibiotics	Clarithromycin (CM)	[9]	HCQ + CM
	Ofloxacin (OX)	[10]	HCQ + OX
Glucocorticoids	Betamethasone (BM)	[11]	HCQ + BM
	Dexamethasone (DM)	[12]	HCQ + DM
Differentiation therapy drugs	Calcitriol (CT)	[13]	HCQ + CT
	ATRA	[14]	HCQ + ATRA
Vitamins	Vitamin C (VC)	[15]	HCQ + VC

humans, it is better not to choose them for treating COVID-19.

CQ or HCQ can intercalate into DNA duplex and bind to a possible genome architectural protein, Pfcrmp [6], and thus could lay a good foundation for further alteration of 3D genome structure by other genotoxic drugs, which suggests that to effectively alter 3D genome structure, using CQ or HCQ is necessary but not enough and as such CQ or HCQ must work together with other genotoxic drug. Besides, since HCQ is less toxic than CQ [16], it could be used as a key drug in the drug combinations for preventing and treating COVID-19. For this reason, 7 HCQ-containing drug combinations have been proposed (**Table 1**). To clarify the effectiveness of these drug combinations, urgent clinical trials are needed. However, since all the drugs included in the drug combinations are old drugs that are already used for treating other conditions in the clinical practice, the front-line doctors, depending on drug availability, can try to use any drug combinations shown in **Table 1** for treating their COVID-19 patients before clinical trials.

The purpose of these combination therapies is to reduce target cell's susceptibility to SARS-CoV-2 that causes COVID-19 and to modulate immune cell's response to SARS-CoV-2 infection through altering 3D genome structures in target cells and immune cells. One COVID-19 patient has been successfully cured by a combination therapy using CQ and clarithromycin [17]. Since clarithromycin has the property of genotoxicity [9], we think that this case report is a piece of evidence that supports our hypothesis. From our point of view, using CQ or HCQ plus azithromycin to treat COVID-19 might not be a good idea because azithromycin has no genotoxic potential [18].

4. Conclusions

The fighting COVID-19 strategy presented in this paper is to reduce target cell's susceptibility to SARS-CoV-2 and to modulate immune cell's response to SARS-CoV-2 infection through altering 3D genome structures in target cells and immune cells by genotoxic drugs. Since this strategy is not to precisely target one cell type genome structure, many cell type genome structures might be more or less altered. Therefore, the genotoxic drugs shouldn't cause permanent genome structure damage or cause cancer when being used for short period of time. This is why we call these drugs as non-carcinogenic genotoxic drugs.

No doubt, this strategy is a cure-all strategy that can be used for preventing and treating all viral infections and other diseases that have no cure at present, for example, it can be used to prevent and treat cancer because cancer associated genome structure could be altered by genotoxic drugs. Once cancer cell's genome structure is altered, cancer cell function will be changed, which will cause cancer cell to become less harmful or to be easily killed by immune system. We previously proposed that to prevent cancer, people could periodically receive a long course treatment of a low dose non-carcinogenic genotoxic agents because compared to normal cells, cancer cells are more susceptible to low dose genotoxic

agents due to their flexible genome structure [6] [19]. This cancer prevention theory is contrary to popular belief that to prevent cancer people should avoid taking any genotoxic substances.

In conclusion, our strategy for picking out drugs that might be used for preventing and treating COVID-19 is different from mainstream's virus-killing strategy. Since no purpose-made non-carcinogenic genotoxic drugs for altering genome structure are available at present and fighting COVID-19 must be done without delay, it is possible to repurpose some old drugs with genotoxic side effects as non-carcinogenic genotoxic drugs for preventing and treating COVID-19. Hopefully, our strategy will contribute to the battle against COVID-19.

Conflicts of Interest

The author declares no conflicts of interest regarding the publication of this paper. No any funding was received for this research.

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