



NON-CARCINOGENIC GENOTOXIC DRUGS (NCGDS): A NEW CONCEPT OF OLD DRUGS WITH GENOTOXIC SIDE EFFECTS

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Abstract

We first proposed that non-carcinogenic genotoxic drugs (NCGDs) can alter gene expression patterns through affecting 3D genome structure, which makes NCGDs be able to prevent viral infections. The NCGDs exclusively refer to old drugs that are non-carcinogenic but have genotoxic side effects that influence 3D genome structure. Some old drugs that induce expression of many genes, but no obvious genotoxicity is tested out, also belong to NCGDs. In a word, any old drugs with genotoxic side effects that are non-carcinogenic but can alter expression of many genes are named as NCGDs. One feature of NCGDs is cure-all properties, leading them to be able to treat many diseases. In this paper, a mini review on history and function of NCGDs is presented.

Keywords: Non-Carcinogenic Genotoxic Drugs (NCGDs), Antiviral Theory, Alteration of 3D Genome Structure, Gene Expression Patterns, X-Ray Irradiation, Non-Antigen-Based 'Vaccine'.

INTRODUCTION

COVID-19 pandemic started in 2019 but become worse worldwide in 2020 [1]. To quickly discover drugs for prevention of COVID-19 infection, the scientists of most countries are focussing on development of drugs. Unfortunately, till now, no prophylactic drugs for viral infections are discovered. In 2020, we first published a paper that proposed an antiviral theory which can quickly find prophylactic drugs for viral infections [2]. The theoretic foundation of the novel antiviral theory is that the reason why a virus can infect viral target cells in human, or animals is because the gene expression patterns in viral target cells are suitable for viral infection. If the gene expression patterns in viral target cells are altered by non-carcinogenic genotoxic drugs (NCGDs), the susceptibility of viral targets cells to viral infection will be reduced, making the virus difficult to enter the cells or cannot survive after entering the cells. In this way. The NCGDs might be prophylactic drugs for viral infections. To prevent COVID-19 infections worldwide, we proposed that taking paracetamol and vitamin C or ibuprofen and vitamin C every day could be a simple way to prevent COVID-19 infection [3]. These drug combinations used as prophylaxis of viral infection are cheap, safe and can be used for long time. We are looking forward to getting scientific evidence for this antiviral theory, but no scientists have done such research. The scientists published many virus papers about COVID-19 virus infection and human genetic factors, monoclonal antibodies, anti-SARS-CoV-2 agents including nirmatrelvir-ritonavir, remdesivir and molnupiravir, etc [4]-[9], but none of them are linked to discovery of new prophylactic drugs for preventing COVID-19 infection, which were urgently needed during the COVID-19 pandemic.

In 2023, scientific evidence supporting our theory came out. Embryonated eggs pretreated with hyoscyamine sulphate showed up regulation and down regulation of many genes,

resulting in a significant decrease in the viral load in both chorioallantois membrane and brain tissues at 48 and 96 hours post infection [10]. The results of this experiment indicated that alteration of gene expression patterns in viral target cells can reduce susceptibility to viral infections, which has perfectly supported the novel antiviral theory. If the scientific evidence could be obtained to support our opinion that paracetamol and vitamin C (both are NCGDs) could decrease the viral load in viral target cells, the drug combinations could have been used as prophylactic drugs for mass drug administration worldwide, which might have saved at least a million lives over the world.

Since we have known the concept and origin of viruses, we still have not known how to prevent viral infections. Even today, the prevention of viruses remains physical protection because no theory can help us to find medicine. The novel antiviral theory we proposed is a practical theory which might help us to find medicine to prevent all viral infections. This theory presents a breakthrough idea on preventing and treating all viral infections including COVID-19, which will be proved as a milestone in the antiviral strategies of human history. The drugs for prevention of viral infections are NCGDs, and in this paper, the history and function of NCGDs are presented.

SYNOPSIS OF NCGDS

The old drugs with genotoxic side effects that are non-carcinogenic are named as NCGDs, which is a new concept appearing first in 2020 [2]. The NCGDs exclusively refer to old drugs that have genotoxic side effects but will not cause cancers. NCGDs can alter gene expression patterns by influencing 3D genome structure. This alteration is gentle and reversible and will not cause genome permanent damage [2]. NCGDs are non-carcinogenic which can be known in advance by Google search. Old drugs that have genotoxicity are usually called drugs with genotoxic side effects. The genotoxicity can be tested by genotoxicity assays [11][12]. Therefore, genotoxicity is a key element of NCGDs because genotoxic side effects will play a main role in alteration of gene

expression patterns. Some old drugs have not obvious genotoxicity but can induce expression of many genes, which are also NCGDs because genotoxicity assays may not be suitable to check their genotoxicity. Therefore, we conclude that old drugs that are non-carcinogenic and can induce expression of many genes are called NCGDs.

Traditionally, we were told that drugs with genotoxic side effects are toxic and cannot use them too much. But the reality is that many drugs with genotoxic side effects are successfully used in medical practice. The NCGDs do not cause cancers within the use of their dose allowance and are non-carcinogenic. NCGDs change gene expression patterns but will not cause permanent genome damage or cancers. What types of genes are involved by NCGDS, what genomic sites are interacted with NCGDs and what molecular mechanism NCGDs used to change gene alterations, all of which are the mystery of therapy of NCGDs. Without computer assistance, it is difficult to solve this mystery. Fortunately, we can use NCGDs to prevent viral infections even we don't know the mystery. Discovery of NCGDs, a class of drugs for viral infection prevention, is a great achievement which needs further research. Picking up NCGDs for preventing viral infections is simple and safe, scientists can conduct simple experiment to validate them, such as, testing if a drug of NCGDs can change gene expression patterns in viral target cells and then studying decrease of viral load in these cells.

Many good drugs have genotoxic side effects, such as vitamin C, aspirin, paracetamol, chloroquine, mefloquine, artemisinins, metformin, ivermectin, niclosamide, polyphenols, cannabidiol, ursodeoxycholic acid (UDCA), and theophylline, etc. [13][14]. We can say that good drugs including traditional Chinese medicinal herbs belong to NCGDs. We revealed that alteration of gene expression patterns in human is the mystery of treatment of Chinese medicinal herbs [15]. Many Chinese medicinal plant extracts have significant health benefits. but some medicinal plant extracts can be toxic, genotoxic, mutagenic, or carcinogenic [16], which means that many Chinese medicinal herbs have genotoxicity, indicating that the main ingredients of herbs belong to NCGDs. A drug that has genotoxic side effects is good for the drug's main effects which have been forgotten in medical practice for long time. We propose NCGDs as new concept for old drugs with genotoxic side effects, NC (non-carcinogenic) refers to old drugs that are non-carcinogenic, and GD (genotoxic drug) refers to ability for alteration of gene expression patterns through affecting 3D genome structure. Recently, we published a paper asking focussing on gene expression alteration when developing new and old drugs [15]. In a word, a drug without genotoxic side effects might not be a good drug. Hopefully, NCGDs can subvert the negative effect of genotoxic side effects.

FUNCTION OF NCGDS

Prevention of viral infections

The main points of our antiviral theory are that viral infection is cell-type specific, and that the reason why a virus can specifically infect its target cells is because the gene expression patterns in the viral target cells are suitable for viral infection. Alteration of 3D genome structure by NCGDs can change the gene expression patterns in viral target cells, which will reduce susceptibility of the target cells to viral

infections [2]. We once proposed that taking vitamin C and paracetamol, or vitamin C and berberine can prevent COVID-19 infection because these drugs belong to NCGDs, they can change gene expression patterns that is the reason why they can prevent COVID-19 infection and other viral infections [2][3]. If NCGDs can change gene expression patterns in liver cells, they can prevent hepatitis. If NCGDs can change the gene expression patterns in neural cells, they can prevent virus encephalitis. If NCGDs can change the gene expression patterns in CD4 T lymphocytes, HIV infection could be prevented. Of course, different NCGDs could be tested and screened for preventing different viral infections. Scientists can carry out experimental research to validate them.

Tough diseases could be treated with NCGDs

The feature of NCGDs is cure-all properties [2][14] because they can only prevent viral infections but also treat many diseases due to alteration of gene expression patterns in several types of cells. Many aging-related diseases, such as cancers, diabetes, cardiovascular disease, and neurodegenerative are linked to abnormalities of gene expression patterns, which can be treated by NCGDs. I published a paper about treating cancer using NCGDs to alter cancer-associated chromatin configuration [14]. In my clinic, if cancer patients don't want to use chemotherapy, I always recommend them to use NCGDs, such as vitamin C and berberine, which might help them to live longer because berberine has anticancer effects on many types of cancers [17].

Type 2 diabetes is a commonly incurable disease because the cause of the disease is unknown. Recently, we proposed a hypothesis that high- or hyper-absorbing cells for carbohydrates in small intestine might be the cause of type 2 diabetes [18], which indicates that the gene expression patterns in high- or hyper-absorbing cells are different from those of normal cells. Certain drugs of NCGDs might regulate expression of many genes in high- or hyper-absorbing cells, which could relieve type 2 diabetes. Another problem of type 2 diabetes is the resistance of human cells to insulin, which likes the mechanism of drug resistance in cellular pathogens and the resistance is caused by altered genome structure [19]. Therefore, certain drugs of NCGDs might help to alleviate insulin resistance in type 2 diabetes.

Cure-all properties of NCGDs does not mean that every drug of NCGDs has these properties. It is depended on what kind of genes they have altered and what type of cells are involved. But it can be sure that drugs with cure-all properties exist within NCGDs. A drug that has not genotoxic effects and cannot change gene expression patterns will never become a drug with cure-all properties.

Derivative of NCGDs: X-ray irradiation could be a non-antigen-based 'vaccine'

Based on this antiviral theory, X-ray irradiation can change gene expression patterns like NCGDs and thus could be used as a non-antigen-based 'vaccine' to prevent all viral infections [20]. It is also possible that X-ray irradiation of whole liver could prevent all malaria infections. There are five species of malarial parasite that can infect humans. The sporozoites are injected into humans by infected mosquitoes and then they invade hepatocytes. Blockade of sporozoite infection of hepatocytes is the key to preventing malaria infections. The

reason why sporozoites of the five species of malarial parasite can infect hepatocytes is because the gene expressions patterns in hepatocytes are suitable for sporozoite infections. Therefore, alteration of gene expression patterns in hepatocytes will reduce the susceptibility to sporozoite infections. Perturbation of 3D genome architecture could change gene expression patterns. Many research findings have shown that X-ray irradiation can change the 3D genome architecture, leading to alteration of gene expression patterns [21][22][23]. Thus, we assume that a low-dose X-ray irradiation of the whole liver might protect people from malaria infections for a long time (hopefully, more than one year). Of course, this theory needs experimental and clinical trials to prove. In conclusion, the X-ray irradiation of the whole liver could be a non-antigen-based cure-all 'vaccine' to prevent all malaria infections, which may contribute a lot to malaria eradication.

CONCLUSION

NCGDs are a new concept, but the function of NCGDs is important in the prevention of viral infections and treatment of many diseases. Viral infection success is because gene expression patterns in viral target cells are suitable for viral infections. Therefore, using NCGDs to randomly change gene expression patterns in viral target cells might reduce susceptibility of viral target cells to viral infections. People who can do Google search could easily find an old drug with genotoxic side effects to be a drug of NCGDs and use it to prevent viral infections. Researchers can test if drugs can alter gene expression patterns in viral target cells and whether they could prevent viral infections. NCGDs have cure-all properties, which helps people to use NCGDs for treatment of many tough diseases linked to abnormalities in expression of genes. NCGDs are new concept of old drugs with genotoxic side effects, which are safe and non-carcinogenic because pre-checking on their toxicities could be searched in Google. Since NCGDs are non-carcinogenic, we can use them to do many things, for example, preventing viral infections, treating cancer, diabetes, and prolonging life, etc. In a word, NCGDs are not bad drugs, but could be promising drugs in the prevention and treatment of many diseases.

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