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Research Article

NON-CARCINOGENIC GENOTOXIC DRUGS (NCGDS) AND CANCER PREVENTION AND TREATMENT

***Gao-De Li**

Chinese Acupuncture, Liverpool, UK

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Abstract

Based on our carcinogenesis theory, cancer cell formation might be a cell transformation, that is a normal cell type being transformed into cancer-cell type. Cancer cell's chromatin configuration has been named as cancer- associated chromatin configuration (CACC) that could be cancer-cell-type chromatin configuration. Under long-time carcinogen exposure, a cell that may have many gene mutations but without CACC will not be cancerous. Only cells that have CACC are cancerous. Non-carcinogenic genotoxic drugs (NCGDs) are old drugs that have genotoxicity but are non-carcinogenic when safe dose and course are used or might modulate the expression of many genes through directly or indirectly affecting 3D genome structure. We believe that NCGDs are the best drugs for preventing all viral infections including transmitted viruses and cancer-causing viruses, but also good drugs for preventing and treating cancer. Besides, antioxidants that support anticancer activity belong to NCGDs, indicating that NCGDs might improve immune system. We encourage researchers to use NCGDs as a tool to study 3D genome structure and transcriptome, which will help to rapidly discover good medicines like NCGDs for treating variety of difficult diseases including cancer.

Keywords: Cancer, Carcinogenesis, Cancer-Associated Chromatin Configuration (CACC), Non-Carcinogenic Genotoxic Drugs (NCGDs), Antioxidants, Cancer Prevention, Cancer Treatment.

INTRODUCTION

Non-carcinogenic genotoxic drugs (NCGDs) were proposed in 2020 for preventing and treating COVID-19 [1]. NCGDs refer to old drugs that have genotoxicity but will not cause cancer. Later, the concept of NCGDs is defined as old drugs that are non-carcinogenic but can regulate expression of many genes through interfering 3D genome structure [2]. It is difficult to check what type of 3D genome structure is interfered by NCGDs, which makes regulation of many gene expressions become the basic content of concept of NCGDS. Therefore, a new concept for NCGDs is defined as old drugs that have genotoxicity but are non-carcinogenic when safe dose and course are used or might modulate the expression of many genes through directly or indirectly affecting 3D genome structure. NCGDs exist in many products such as medicine, Chinese herbs, plant extracts. cooking spice, tea, coffee, tobacco and illegal drugs [3]. Since NCGDs' main function is alteration of gene expression patterns in various cells, they can treat many diseases. We think that many good drugs might be linked to randomly changing gene expression patterns. It is unbelieved that a drug that solely blocks a pathway could be used to treat a disease without affecting gene expression patterns. This is the reason why we proposed that drug development should focus on gene expression pattern changes, all old and new drugs must have this data [4].

NCGDs are important in the prevention and treatment of cancer. It is possible that cancer is caused by genotoxic drugs or substances but could be prevented and treated by genotoxic drugs like NCGDs [1][5]. Antioxidant supplements are widely used for maintaining good health of our body, especially in supporting prevention and treatment of cancer [6]. But we confidently assert that all antioxidants belong to NCGDs, which we will talk about below. In this paper, cancer formation mechanism and NCGDs' role in the prevention and treatment of cancer will be discussed.

Corresponding Author:** ***Gao-De Li,
Email: gaode_li@yahoo.co.uk

OUR THEORY OF CARCINOGENESIS

In 1986, we proposed that abnormal chromatin configuration might cause cancer cell formation [7]. But due to no technology available at that time, researchers had no chance to study 3D genome architecture. It was in 2002 that chromosome conformation capture technique was invented [8]. Few years later, many researchers have proved that 3D genome architecture is involved in gene regulation, cell differentiation and carcinogenesis [9]-[11]. We believe that cancer cell formation is a cell transformation, that is a normal cell type being transformed into cancer-cell type. In human body, there are about 200 types of cells, which indicates that there are about 200 types of chromatin configuration. Cancer-cell type appearance is because there is a redundancy in chromatin configuration. Without this redundancy, there will be no cancer in human body. Cancer cell's chromatin configuration was named as cancer-associated chromatin configuration (CACC)[12]. Later, we proposed a hypothesis of cell- type-associated chromatin configuration [13], suggesting that CACC is cancer- cell-type chromatin configuration. Hallmarks of cancer are controlled by CACC [14]. If a cell has been exposed to carcinogens (physical, chemical and biological) for a long time, the cell that may have many gene mutations but without CACC will not be cancerous. Only cells that have CACC are cancerous. We think that flexible CACC might be the reason why cancer is difficult to cure, and cancer cells might be very sensitive to genotoxic drug compared to normal cells because of flexible CACC [15].

In the 1986's paper, we assumed that reverting abnormal chromatin configuration back to normal state would make cancer cells become normal cells[7]. A cancer reversion therapy has been proposed to be a paradigm shift from cancer

cell killing therapies [16]. Reversion switch in the transition of colorectal tumorigenesis has been reported recently [17]. The master transcriptional regulators control the transition and knockdown of these master regulators can revert colorectal cancer cells into normal-like enterocytes [18]. All these recent results have supported our assumption, indicating our carcinogenesis theory has been validated.

NCGDS INVOLVED IN PREVENTION AND TREATMENT OF CANCER

Current cancer treatments include chemotherapy, radiotherapy, surgery and immunotherapy. The common problem of these treatments is when they first touch the cancer cells, some cancer cells might release dormant or metastasis signal to the population of cancer cells and few years later, the cancer will come back. Clinical results have showed that chemotherapy treatment is harsh and can induce malignancy and metastasis that could be the main cause of the death [19]. NCGDs are cure-all drugs that could help to treat cancer through alter gene expression patterns [2]. NCGD treatment is soft because it will not kill cancer cells but changes CACC, making cancer cells appear as abnormal cells that are early destructed by immune system. Compared with chemotherapy, NCGD treatment might not give more stress to cancer cells and thus no metastasis occurs. Berberine belonging to NCGDs has potential in the prevention and treatment of various types of cancer including prostate, bladder, kidney, liver, colon, pancreas, gastric, bile duct, oesophagus, lung, oral, cervix, endometrial, ovarian, breast, thyroid, lymphoma, bone, leukaemia, myeloma, glioblastoma, and melanoma [20], indicating that berberine can alter gene expression patterns in most of the tissue and cell types, leading to prevent all viral infections including transmitted viruses and cancer-causing viruses, which indicates that NCGDs might prevent some types of cancer. To prevent cancer, we also proposed that people could periodically receive a long course NCGD treatment [5][1].

It has been reported that malaria drug resistance can make drug-resistant parasites grow more slowly than drug-sensitive cells , and cancer drug resistance has the same phenomenon [21-24]. We could use berberine (belong to NCGDs) to treat cancer until drug resistance in cancer happening and keep use the drug to maintain the drug resistance level, which will slow down the growth of cancer cells, giving us more time to deal with the cancer. Following treatment could be done with different NCGDs such as metformin that has the potential in treatment of many types of cancer [25]. Compared with chemotherapy, there are lot of NCGDs that have low toxicity and could improve immune system might be selected. Hopefully, this treatment could cure cancer. If cancer is not cured, it might become a manageable chronic disease, making cancer patients live a long life [26].

ALL ANTIOXIDANTS BELONG TO NCGDS

Antioxidants are substances that neutralize free radicals and reduce oxidative stress, protecting human body from damage of cell membrane, DNA, protein and lipids that are linked to multiple illnesses like diabetes, heart disease and cancer. There are many different antioxidants in fruits, seeds, foods, and natural products [27]. Few antioxidants are presented here: phenolics, flavonoids, polyphenols. Phenolics, curcumin, phenols, ferulic acid β- carotene, lycopene, vitamin C, vitamin D, vitamin A, vitamin E, manganese, zinc, selenium. Honestly, all antioxidants including nature or synthetic form belong to NCGDs because they all have genotoxicity at high dose or might modulate the expression of many genes through directly or indirectly affecting 3D genome structure, leading to treatment of few to many diseases depending on interfering power and patterns. Antioxidants may be used to support anticancer treatments [28], indicating that NCGDs might improve immune system. When NCGDs are used to protect our body, the dose of NCGDs should be within the safe range. If antioxidant-contained foods are taken by people, many diseases like cancer could be prevented. It has been reported that the high prevalence of undiagnosed prostate cancer was found at autopsy. The men aged 70-79, prostate cancer was found 36% in Caucasians and 51% in African Americans [29]**.** Positively view about this is that these men probably took enough antioxidants, making their cancer become non-cancer treated chronic disease.

NCGDS ARE TOOL DRUGS FOR INVESTIGATION OF CANCER AND ORTHER DISEASES

Many diseases like cancer have abnormalities in genome structure, leading to abnormal expression of many genes. To study this problem, the gene expression patterns, and related 3D genome structure must be completely investigated. NCGDs might be the best drugs to do so. Without using gene editing, NCGDs can alter gene expression patterns through interfering 3D genome structure. Each NCGD might cause different transcriptome and 3D genome structure results that could be saved in a database. Combinations of different NCGDs could be used to do the similar research. We are confident that some combinations of NCGDs , especially from plant extracts, could cure cancer if a great number of NCGGs are investigated. There is no need to design and produce new drugs because the drugs, NCGDs, are there.

Looking at today's biological research, many projects are study of many pathways, finding druggable target or receptor, and if something new is found, the researchers need to design drugs accordingly. Development of new drug takes a long time. We might not believe that a drug's function is just through blocking a pathway or binding receptor or hitting the target because communication signals in cells are so complicated that even an epigenic change might alter gene expression patterns. It is sure that the drug might alter gene expression patterns even if the drug was originally called receptor-binding drug or target-hitting drug. Molnupiravir is an antiviral drug that functions as a ribonucleoside analog to treat COVID-19 by inducing lethal mutagenesis in the virus. But Google search showed that molnupiravir has low risk of genotoxicity, indicating that molnupiravir belongs to NCGDs. Ursodeoxycholic acid (UDCA) has genotoxicity and can regulate more than 440 genes in rat hepatocytes [30], suggesting that UDCA is a NCGD. Recent research has shown that UDCA can prevent COVID-19 infection through the reduction of ACE2 [31]. It seems that nearly all good drugs have multiple functions for treating disease through changing gene expression patterns. Any drugs claimed to solely target a gene or receptor without affecting gene expression patterns might not exist, which encourages me to publish a paper of focusing on gene expression alterations and giving up the mechanisms of action of drugs when developing drugs [4]. Collectively, using the tool of NCGDs to study 3D genome

structure and transcriptome might be the best project for discovering good medicines like NCGDs that could be used to treat variety of difficult diseases including cancer.

CONCLUSION

Forty years ago, we proposed a hypothesis that abnormal chromatin configuration might cause cancer, which has been proven by the results of 3D genome structure. We assumed that reverting the abnormal chromatin configuration back to normal state will cure the cancer. Recent cancer reversion therapy has indirectly supported this assumption. Now, we clearly conclude that cancer cell formation is a cell transformation, that is a normal cell type being transformed into cancer-cell type. NCGDs are the best drugs for preventing all viral infections including transmitted viruses and cancer-causing viruses, but also good drugs for preventing and treating cancer. In this paper, we first point out that all antioxidants including nature or synthetic form belong to NCGDs. Antioxidants could be used to support anticancer treatments, suggesting that NCGDs might improve immune system. Our good health is kept by NCGDs even if we are not told by doctors. When talking about NCGDs, people always believe that avoiding genotoxic drugs could be important for preventing cancer or other illnesses. However, we are using NCGDs every day, for example, many products contain NCGDs, such as many medicines, cooking spices, plant extracts, nuts, seeds, tea, coffee, tobacco. Besides, in medical research, NCGDs could be used as a tool to study gene expression pattern changes. If a great number of NCGDs, especially from plant extracts, are studied, the medicines like NCGDs for curing cancer and other diseases could be rapidly discovered.

CONFLICTS OF INTEREST

The author declares no conflicts of interest.

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