



Novel anti-cancer drug candidates with immunotherapeutic potentials

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Cite this study: Aslan, Ş. M., & Ayaz, F. (2022). Novel anti-cancer drug candidates with immunotherapeutic potentials. 3rd Advanced Engineering Days, 67-68

Keywords

Phenothiazine
Derivatives
Anti-cancer activity
Immune system
Colon Cancer
Macrophages

Abstract

Cancer is a group of diseases that occurs when cells grow rapidly and uncontrollably, divide and metastasize to the other tissues and organs. In addition, it was stated that the total number of cases worldwide in 2018 was 18.1 million, while the death rate was 9 million. In cancer therapy, treatment is done by using radiotherapy, chemotherapy, surgical intervention and various other anti-cancer drugs. These methods damage normal cells as well as cancerous cells, and their side effects are versatile and severe. It is important to do research and develop the potential specific drug candidates with fewer side effects. In addition, the immune system is of great importance because of its effects in the emergence and development of cancer and in preventing its spread to the other tissues. It is known that cancer cells have an interplay with the immune system cells which eventually leads to the suppression of the anti-tumor activity. Therefore, various immunomodulation methods as part of cancer immunotherapy have been developed and utilized in the field. Phenothiazine derivatives, which have a wide range of uses, are very important because of our ability to generate novel varieties with different functions as anti-cancer drug candidates. In our study we are aiming to generate and characterize novel phenothiazine derivatives and decipher their anti-cancer as well as immunomodulatory activities.

Introduction

Colon cancer ranks third among the cancer types in terms of the mortality [1]. Colon cancer is diagnosed with more than 1 million new patients annually in the world and its incidence is third among other cancer types [2]. It has been reported that an average of 600,000 people die annually due to the colon cancer. Colon cancer occurs more frequently in men than in women [3]. Various treatment methods are used, but they cannot be cured completely. Various drug candidates are being investigated in these treatment methods. Phenothiazine derivatives form the basis of drugs in different fields, some of which are used in drugs for diseases such as Schizophrenia, Parkinson's, Alzheimer's, and migraine. In addition, it is used as anti-helminthic (insecticidal), insecticides [4], as a sedative, antispasmodic, anti-bacterial and anti-fungal, etc. It has also been used in alleviating the side effects of chemotherapy and its anti-tumor activity against different cancer cell lines have been studied.

Results

Cancer is one of the diseases that causes the most deaths in the world, and since the side effects of the methods used for treatment are very high, new agents with minimal side effects should be investigated. Chemotherapy, one of the techniques used in the treatment of cancer, is also known as drug therapy. It aims to cause damage by preventing cancer cells from growing and multiplying. The purpose of the chemotherapy drugs is directly destroying the cancer cells without harming normal cells in the body. But one of the biggest problems in this

treatment method is that it seriously damages normal cells and chemotherapy agents cause very severe side effects. For these reasons, researchers are still working on the production and design of new agents. In the synthesis of widely used phenothiazines, a change in the skeletal structure causes a wide variety of changes in their biological activities. These derivatives are used both in the industrial and medical fields. Therefore, it attracts attention in many areas and is used in drugs for the treatment of different diseases. It has been previously investigated in many studies that phenothiazine derivatives have anti-oxidant, anti-cancer, anti-tumor, antifungal, and anti-bacterial activities [5,6].

Macrophages, one of the most important cells of the immune system, form the first immune response of the innate immune system against the infections. Macrophages are one of the most important cell types in terms of being cells of both the hereditary immune system and the adaptive immune system, by functioning as antigen-presenting cells and producing pro-inflammatory cytokines [7,8]. Macrophages have many tasks, they can perform phagocytosis, provide wound repair, produce enzymes, cytokines and reactive oxygen species. As a result of excessive stimulation of these cells, inflammation occurs, pro-inflammatory cytokines are produced and lead to chronic inflammatory diseases and autoimmune diseases. Macrophage cells provide defense by synthesizing inflammatory mediators, namely cytokines and reactive oxygen species, and activating the immune system against tumor cells. Cytokines are non-structural protein or peptide molecules that establish communication between cells. These molecules take different names according to the tissues that they are produced and their functions change accordingly. Some of them can be listed as interleukins, interferons, tumor necrosis factors, chemokines. It is known that macrophages partially support cancer after a certain stage due to the suppressive messages they get from the tumor cells.

Pro-inflammatory cytokine production is provided by activating macrophage cells stimulated by LPS. Due to the relationship between macrophage cells and cancer, colon cancer treatment is provided in the presence of phenothiazine derivatives, while its effect on the immune system cells is also important to determine its immunomodulatory hence cancer immunotherapy potentials.

Discussion

According to literature reviews, the methods used in the cancer treatment led to damage to the other healthy cells in the body, and it is very important to develop novel and better methods. Since the drugs used in chemotherapy, which is one of these methods, cause too many side effects, it is necessary to develop a more effective drug candidate [9]. The activities of phenothiazine derivatives, known for their anti-tumor effects on the cancer cells and many other drug activities, on colon cancer cells and the immune system cells should be examined more extensively to determine their drug potentials [5,6]. The ability to develop drug candidates for cancer therapy and other diseases is critical, therefore new and more effective agents must be designed and tested more rigorously.

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