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REVIEW ARTICLE

RECENT ADVANCEMENT IN THE DEVELOPMENT OF ANTI-CANCER DRUGS

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ABSTRACT

Cancer is a group of disease characterized by the property of uncontrolled cell division caused by activation of proto-oncogenes, and potential to evade or spread to the other part of the body. It is second most cause of dead in a world. There are several types of cancer associated with a high rate of mortality, and initiation of cancer is highly dependent upon unhealthy lifestyle, genetic composition of an individual or environmental factors. Therefore, many cancers can be prevented by maintaining a healthy life and avoid smoking. During cancer progression, overexpression of proto-oncogenes directly related to the loss of the functions of tumor suppressor genes. Nowadays, there are several types of treatment available depending upon the type of cancer and individual itself, but among all, chemotherapy is the most commonly and widely used. In chemotherapy, a different type of drugs used for the treatment of cancer, and are commonly known as anticancer drugs. There are several types of drugs which includes plants or chemically synthesized compound. Metals have unique features that include redox activity, variable coordination modes, and reactivity towards organic substrates. There are several metal ion complexes available being used for cancer treatment, such as cisplatin, Carboplatin, Aroplatin, Auranofin, NAMI-A, and KP1019 so on. This article focused on selected metal ion complexes that have gained a huge interest in the treatment of cancer.

INTRODUCTION

In the recent decades, a large number of people died due to cancer, the most solemn and threatening disease. Cancer leads to the uncontrolled growth and cell division cell with the potential to invade other parts of the body. The continuous and uncontrolled cell division leads to the development of abnormal cell mass called "tumor".[1] The tumor can be of a benign type, precancerous type, and cancerous or malignant type. About 14.1 million different cases of cancer arisen globally (other than melanoma) in 2012. In the same year, about 165,000 children under 15 years of age were diagnosed with cancer. It caused about 8.2 million deaths or 14.6% of the total human death. The most common types of cancer in males are lung cancer, prostate cancer, colorectal cancer and stomach cancer, whereas, in the females, most common are breast cancer, colorectal cancer, lung cancer and cervical cancer. In children, acute lymphoblastic leukemia and brain tumors are most common, except in Africa, where non-Hodgkin lymphoma occurs more often, [2] however, the incidence of cancer increases significantly with an increase in the age and daily lifestyle.

As the incidences of cancer increases worldwide, people have developed several approaches to combat with the demises caused by cancer. Among different types of treatment available, chemotherapy is most commonly and widely used approach for the cancer treatment. During chemotherapy, anti-cancer drugs (chemotherapeutic agents) are used as a part of standardized routine chemotherapy, and they are administered either intravenously, orally, applied to the skin or by injection, depending upon the type of cancer.[3] The heavy metals used in the anti-cancer drugs are highly cytotoxic, inhibit the process of cell division, and selectively block the extracellular growth signals of the cancer cells (i.e. blockers of signal transduction). These drugs act nonspecifically, in most cases, they also interfere with the normal cell division and function, as a result, develops many side effects. This review will focus on recent development in the platinum, gold and copper complexes based drugs as anticancer agents, their limitations, and another possible way to cure cancer.

Unique Properties of Metal Ions and Metal-Based Complexes

The metal complex is a structure consisting of a central atom or ion bonded with anions (ligands). Compounds that contain a coordination complex are called coordination compounds.[4] The activity of bio-metals is attained through the formation of complexes with different bio-ligands and the mode of

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biological action for complexes depends upon the thermodynamic and kinetic properties. Metals or metal complex depends not only on the metal itself, but also on its oxidation state, number and types of ligands bound, and the coordination geometry of the complex. Metals have a positive charge which helps to bind with negatively charged molecules of the ligand lead to the formation of complexes. The transition metal ion has partially filled' orbitals and oxidation state which is very important in the design of anticancer agents[5] and it allows in the participation in biological redox chemistry and plays a significant role in optimal dose and bioavailability of the agent controlled.[6,7] Metals are ubiquitous and some are important for cellular processes. Depending on their convenience, metals were designated during the process of evolution to improve biochemical function involved in cellular processes.[8]

Deficiency or accumulation of some metal ions can lead to disease. As for the anticancer activity, ligands of compound also play an important role in the binding to metal.[9] Furthermore, when designing of metal-based drugs take place, one is not restricted only by metals selected but also can take advantage of the unique properties of nonessential metals, and metals that can impart additional utility not found naturally.[10]

Platinum-Based Analogs in Cancer Therapy

More than 90% of currently permitted clinical drugs are organic compounds. However, the percentage of metal-containing drugs is very low. In cancer chemotherapy, however, platinum compound is widely used but coordination compounds represented by cisplatin and its derivatives are essential anticancer agents with verified effects against a variety of tumors (such as testicular cancer, epithelial ovarian cancer, gestational trophoblastic tumors). The cytotoxicity of cisplatin originates from its binding to DNA and the formation of covalent cross-links. Binding of cisplatin to DNA causes significant distortion of helical structure and results in inhibition of DNA replication and transcription [11](Figure 1). The drug becomes activated once it enters the cytoplasm, where the chlorine atoms on cisplatin are displaced by water molecules. This aquated product is a potent electrophile that can react with any nucleophile, including the sulfhydryl groups on proteins and nitrogen donor atoms on nucleic acids. The most prevalent cisplatin-induced DNA adducts is an intrastrand crosslink in which the platinum is covalently bound to the N7 positions of the imidazole ring of two adjacent guanines.[12] Platinum compounds continue to be synthesized and designed through several different methods in order to increase the therapeutic effects and to overwhelm the disadvantages of current platinum-based drugs. Further, several other metallo-drugs with least side effects are already in clinical trials. It is commonly considered as a cytotoxic drug which kills cancer cells by damaging DNA and inhibiting DNA synthesis.[13,14] Because of the confirmed clinical submissions of these platinum-based drugs, the number of research initiatives to identify other metallo-drugs that can be used for cancer therapy has increased considerably in the field of inorganic biochemistry. Numbers of platinum compounds have been made and assessed as potential chemotherapeutic agents, while few have entered clinical use.[15] Binding of platinum-based compounds, to which molecule various signal transduction pathways are activated, which interfere with different cellular processes including transcription and DNA replication, thereby triggering cell death.[16] Poor solubility and low bioavailability of clinically approved platinum compounds are two important considerations that provoked the search for novel platinum-based coordination compounds with emphasis on oral administration.[17] There are few cancer cells which show chemoresistance against cisplatin such as endometrial cancer cell (KLE) which shows resistance by forming isoform of Akt i.e. Akt2 and Akt3 but Hela and HEC-1 cancer cell do not show resistance. These are regulated by PDK1 and PDK2 whereas Akt2 is ubiquitous in nature but overexpression leads to human ovarian, breast carcinomas and Akt3 express mainly in brain, heart, and kidney and cause breast cancer.[18, 19] Secondly, Nasopharyngeal carcinoma (NPC) can develop cisplatin-resistant by high expression of Brain-expressed X-linked 3 (BEX3), a CD271 receptor-associated protein.[20]

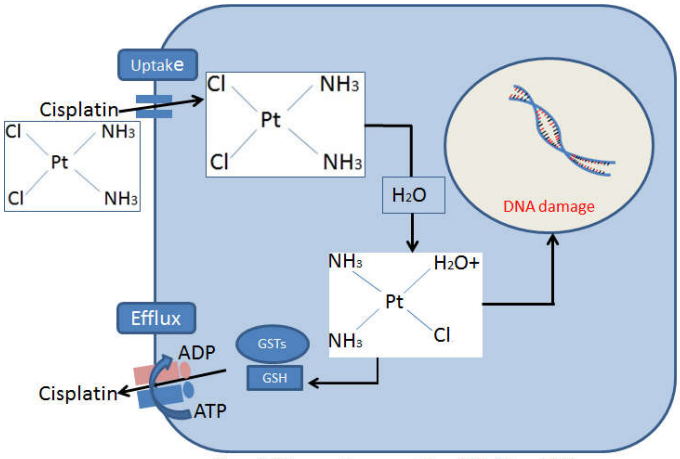

Figure 1: Diagrammatic representation of Cisplatin on DNA.

Gold

In comparison to cisplatin, the primary target of gold (I) complexes is not DNA but the alteration of mitochondrial function as well as inhibition of protein synthesis which help in DNA cross-link [21] whereas cisplatin exerts its anti-tumor activity by interacting with DNA.[22] Gold has rich coordination chemistry and show high oxidation state these properties make dramatic changes in their physicochemical and thus biological properties. Oxidation state, as well as ligand, bound and coordinate geometry is also very important for the proper function.[23] A number of automatous studies with auranofin identified that it has potent biological targets of anti-inflammatory and anti-cancer activities. One of the first studies suggested that auranofin has properties to inhibits DNA, RNA, and protein synthesis[24] while later It has found that the ability of auranofin to generate reactive oxygen species (ROS) in leukemia and ovarian cancer cells.[25, 26]Auranofin also inhibits mitochondrial thioredoxin reductase (TrxR) and cathepsin B.[27, 28]

Auranofin and other gold (I) compounds are able to induce mitochondrial swelling, membrane potential decrease and stimulation of respiration dependent on transition of mitochondrial membrane in presence of calcium ions.[29] Auranofin and a number of its equivalents showed potent cytotoxic activity against melanoma and leukemia cell lines in vitro and anti-tumor activity against leukemia in vivo but, these complexes were completely inactive against solid tumors.[30] Some other gold (III) complexes play an important role in the

reduction in growth of tumor cell. Recent studies show that Gold (III) complexes have high anticancer towards cancer cell and least side effect as compared to Gold (I) complexes.[31] This is different from Gold (I) complexes by reducing the growth of cancer cell (such as breast cancer cell) through inhibition of Ubiquitin-proteasome pathway[32] (Figure 2).

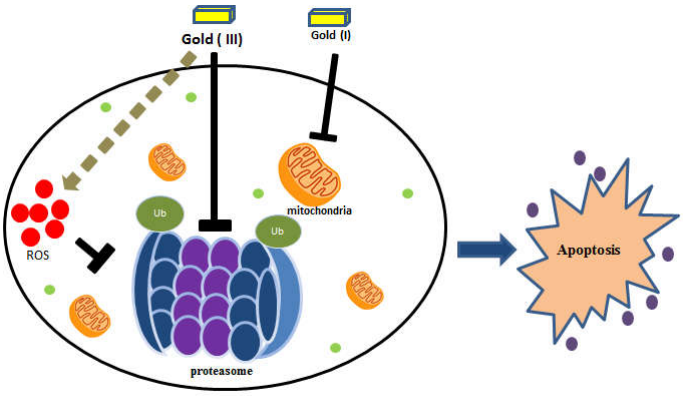

Figure 2: Diagrammatic representation of inhibition of Mitochondria and 26S proteasome by gold(III)and gold (I).

Copper

Copper is a crucial element found in all living organisms and it is very necessary for the function of several enzymes and proteins involved in energy metabolism, respiration and DNA synthesis, notably cytochrome oxidase, superoxide dismutase (SOD), ascorbate oxidase and tyrosinase.[33] The major functions of copper compounds involve oxidation-reduction reactions in which copper containing molecules react directly with molecular oxygen to produce free radicals.[34, 35]

It has been found that copper is efficient to induce DNA double-strand break and oxidation of bases by producing ROS.[36, 37] It also has properties to bind to different ligands very effectively and performed anti-angiogenesis effects and proteasomes inhibitor. [38, 39, 40] It is important to note that not all copper binding compound has both proteasome-inhibitory and apoptosis-inducing capability.[41] Anticancer activity of copper complex compounds is related to their ability to produce reactive oxygen species (ROS). One of the key mechanisms proposed to explain copper complexes induced cellular toxicity comes from the tendency of free copper ions to participate in the formation of ROS. Cupric and cuprous copper ions can participate in oxidation and reduction reactions. In the presence of superoxide (O_2^-) or reducing agents such as ascorbic acid or glutathione (GSH), Cu(II) can be reduced to Cu(I), which is capable of catalyzing the formation of hydroxyl radicals ($OH^•$) from hydrogen peroxide (H_2O_2) via the Haber-Weiss reaction.[42]

$$Cu^{2+} + O_2^{*-} \longrightarrow Cu^{+} + O_2$$

$$Cu^{+} + H_2O_2 \longrightarrow Cu^{2+} + OH^{*} + OH^{-}$$

$$O_2^{*} + H_2O_2O_2 + \longrightarrow OH^{*} + OH^{-}$$

Hydroxyl radical is a highly reactive and able to bind with any biological molecule by abstracting the hydrogen from an amino bearing carbon to form a carbon-centered protein radical and from an unsaturated fatty acid to form a lipid radical (Figure 3). This results in oxidative damage of cells.[43] In another way ROS lead to the formation of another type of reactive oxygen species - the hydroxyl radical (OH•). Formation of radical is the main factor which causes DNA damage in cells under oxidative stress.[44, 45]

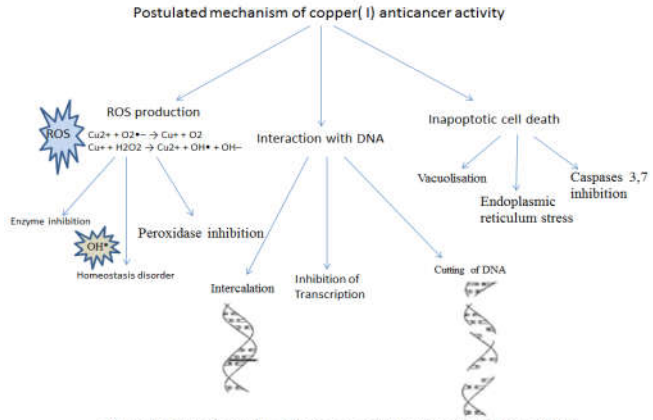

Figure 3: Selected examples of anticancer activity and mode of action of Cu(I) complexes.

CONCLUSION

The continuous research and urge to improve the life of a cancer patient have made the discovery of more than 50 chemotherapy drugs, including widely used cisplatin, gold, and copper-based drugs discussed earlier. Recent advances in the field of inorganic chemistry give us significant advantages for the utilization of metal complexes in the development of different anticancer drugs. Platinum complexes, i.e., cisplatin have confirmed to be a highly effective chemotherapeutic agent for treating various types of cancers. Besides these, gold complexes also exhibit anticancer property by inhibiting the proteasome. However, most chemotherapeutic drugs available today are cytotoxic in nature, interfere with the ability of normal and cancerous cells to grow or multiply, and therefore, causes various side effects. Therefore, it is an urgent requirement for the development of new drugs with less or no side effects. Recently, it has been found that higher concentration of copper is a common trademark of many human tumors, and therefore, targeting the copper content of tumor cells with copper chelating agents emerged as an exciting new approach in cancer therapy. The success achieved in this area will certainly improve the lifestyle of cancer patients in the future.

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