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A Review on : Transition Metal Complexes as Anticancer Agent

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Metals are essential cellular components selected by nature to function in several indispensable biochemical processes for living organisms. Metals are endowed with unique characteristics that include redox activity, variable coordination modes, and reactivity towards organic substrates. Due to reactivity, metals are tightly regulated under normal conditions and aberrant metal ion concentrations are associated with various pathological disorders, including cancer. For these reasons, coordination complexes, either as drugs or prodrugs, become very attractive probes as potential anticancer agents. The discovery of cisplatin, cis-$[Pt^{II}(NH_3)_2Cl_2]$, was a defining moment which triggered the interest in platinum (II)- and other metal-containing complexes as potential novel anticancer drugs. This review article highlights selected metals that have gained considerable interest in both the development and the treatment of cancer.

In 1960 the anti-tumor activity of an inorganic complex cis-diammine-dichloroplatinum (II) (cisplatin) was discovered. Cisplatin has developed into one of the most frequently used and most effective cytostatic drug for treatment of solid carcinomas. Other metal like gallium, germanium, tin, bismuth, titanium, ruthenium, rhodium, iridium, molybdenum, copper, gold were shown effective against tumors in man and animals.

Platinum based anticancer drugs

Platinum (II) complexes has been used as anti cancer drugs since long, among them cisplatin has proven to be a highly effective chemotherapeutic agent for treating various types of cancers. Cisplatin moves into the cell through diffusion and active transport. Inside the cell it causes platination of DNA, which involves interstrand and intrastrand cross-linking as well as formation of adducts, usually through guanine, as it is the most electron rich site and hence, easily oxidized. Formation of cisplatin DNA adducts causes distortion and results in inhibition of DNA replication. Cisplatin DNA Adducts also serve as binding site for cellular proteins such as repair enzymes, histones, transcription factors and HMG-domain proteins. Drugs like cisplatin does not specifically affect cancer cells but it also effect the rapidly dividing cells of certain normal tissues, such as those found in hair follicles, bone marrow, and lining of the gastrointestinal tract. Pt. (II) and Pt (IV) complexes are photo reactive. Irradiation of cis-platin modified DNA with UV light can induce cross-links with the protein HMG, which can inhibits RNA

transcription. Like many other anticancer drugs, cisplatin also faces the same problem called "Drug Resistance". It is major complication in cancer chemotherapy because of decreased intercellular accumulation of cisplatin, it cannot form adduct with DNA. Pt (II) complexes have been conjugated to molecules like porphyrin ring. The porphyrin enchances the tumor tissue specificity of the Pt (II) complexes. Porphyrins are used as photodynamic therapeutic agents and can offer additional antitumor activity by photo-induced mechanism. The clinical use of cisplatin is limited because of the toxicity to the normal cells and drug resistance, therefore, new platinum based anticancer drugs has also been synthesized such as carboplatin, oxaplatin, nedaplatin etc.

Non-platinum anticancer agents

Platinum is not the only transition metal used in the treatment of cancer, various other transition metals have been used in anticancer drugs. Titanium complexes such as Titanocene dichloride has been recognized as active anticancer drug against breast and gastrointestinal carcinomas. Gold complexes also show anti-cancer activity, these complexes act through a different mechanism as compared to cisplatin. The target site of Au complexes is mitochondria not DNA. Certain gold complexes with aromatic bipyridyl ligands have shown cytotoxicity against cancer cells. Many of Ru complexes exhibit anti-estrogen properties similar to that observed for novel anti-estrogen Tamoxifen. Complexes of transition metal like Iron have shown remarkable anti-proliferative properties. The ferrocene derivates having hydroxyl group in phenyl ring and have high affinity for estrogen receptor. Many organometallic anlaogues of tamoxifen used as a vehicle for introducing other cytotoxic agents to the cancer cells. Normally, cancers are diagnosed at a stage of the disease when some anatomical changes occur in the body in the form of well defined tumors.

Copper is another essential trace metal that has been selected by nature to be a driving for in many biochemical processes including chemical redox reactions, cellular growth, development. and angiogenesis. Under biological conditions, copper exists in both (Cu^{+}) and (Cu^{2+}), which allows it to serve as a cofactor in redox reactions, such as cytochrome c oxidase (involved in the mitochondrial electron transport chain) and superoxide dismutase (involved in the detoxification of reactive oxygen species. The acquisition and distribution of copper is a tightly regulated process to assure proper uptake, distribution, and to avoid unnecessary binding to biomolecules.

Zinc is an indispensable trace element that plays a critical role in a wide range of cellular processes including cell proliferation, differentiation, and defense against free radicals. Zinc acts as a key structural component in many proteins and enzymes, including transcription factors, cellular signaling proteins, and DNA repair enzymes.

It has also been well established that zinc plays a critical role in the regulation of apoptosis in mammalian cells, However the precise role of zinc in modulating this response appears to be cell specific, highly complex, and lacking firm conclusion. IN

many cell types, including prostate epithelial, glial cells, ovarian epithelial cells, others, zinc has been reported to induce apoptosis. However, in breast cells, lung epithelial cells, renal cells, macrophages, and Hela cells, zinc exhibits antiapoptotic effects.

Conclusion

The critical role that metals play in the functioning and maintenance of life highlights the extensive role that nature plays in regulating these vital components. The clinical success of cisplatin provided the "proof of concept" for investigating metals, essential or nonessential, and their coordination complexes as potential anticancer agents. Since the discovery of cisplatin, thousands of platinum analogs have been synthesized, with only carboplatin and oxaliplatin achieving widespread clinical use. Design strategies of novel platinum complexes have been under intense investigation to address shortcomings of previous generation platium compounts. Targeting the ubiquitin-proteasome pathway with metal-based compounds is an emerging concept in developmental theraeutics. These include, but are not limited,, copper-, zinc- and gold-containing complexes which have made significant progress in the pursuit of developing novel anticancer drugs.

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