International Journal of Engineering Science Invention
ISSN (Online): 2319 – 6734, ISSN (Print): 2319 – 6726
www.ijesi.org ||Volume 6 Issue 6|| June 2017 || PP. 125-130

Role of Metal Complexes in Drug Delivery and Anticancer Therapy

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Abstract
Metal complexes have become a significant category of therapeutic drugs in anticancer research because their special coordination chemistry and redox properties and their ability to interact with different cellular targets. The structural modifications of metal-based compounds enable developers to create products which provide better selectivity and enhanced stability and biologically active performance compared to traditional organic pharmaceuticals. This review explains how metal complexes function in anticancer treatment by describing their design elements and their operational systems and their application in current drug delivery technologies. The main pathways lead to cancer cell death through DNA binding and oxidative stress generation and enzyme inhibition and mitochondrial disruption. The use of metal complexes within nanocarriers and tumor-responsive delivery systems leads to better treatment results while reducing harmful effects on the body. The study identifies current challenges which include resistance development and clinical translation issues while presenting possibilities to create new metallodrugs.
Keywords:*Therapeutic Drugs, Anticancer Research, Organic Pharmaceuticals, Enzyme Inhibition, Tumor-Responsive Delivery Systems etc.*

I. Introduction

The medical field has made significant advancements through improved detection methods and surgical techniques and radiation therapy and chemotherapy, yet cancer remains one of its most challenging diseases to treat. Chemotherapy, which represents a standard cancer treatment, relies on small organic molecules that work by blocking either DNA replication or the process of cell division. The agents demonstrate effectiveness against multiple cancers, yet their clinical use faces major challenges because they exhibit untreated conditions of poor selectivity between cancerous tumor cells and normal cells, they produce harmful system-wide effects, their active components are not sufficiently absorbed, and patients develop resistance to multiple medications[1].

The rise in responsible concerns about future treatment development has created a need for treatment methods that provide better patient results through targeted therapies and medical treatments with new mechanisms of action. The field of metal complexes has developed into an effective category for developing anticancer treatments. Metal complexes display unique physical and chemical features that differ from organic drugs because they can change their oxidation states and their coordination structures and their ligand exchange rates and their ability to do redox reactions[2]. Metal-based compounds enable biological target interactions through the creation of multiple binding sites and the development of activation methods that respond to external stimuli, which traditional organic molecules cannot achieve.

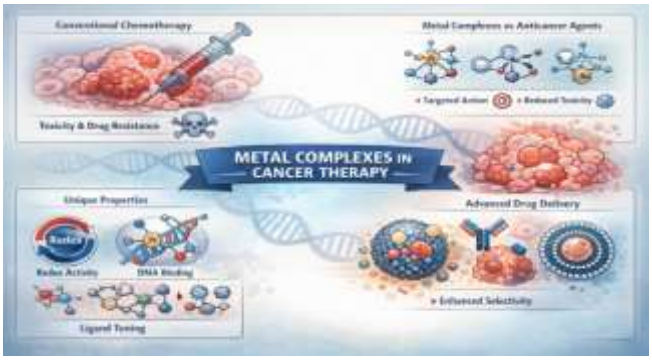

Figure 1: Meral in Cancer Therapy, Source: Author Generated

[1]Rosenberg, B., VanCamp, L., Trosko, J. E., & Mansour, V. H. (1969). Platinum compounds: A new class of potent antitumour agents. Nature, 222(5191), 385–386. https://doi.org/10.1038/222385a0
[2]Kelland, L. (2007). The resurgence of platinum-based cancer chemotherapy. Nature Reviews Cancer, 7(8), 573–584. https://doi.org/10.1038/nrc2167

The efficiency of most of the early metal-based chemotherapeutics aslways demonstrated that metals provide here in effective cancer treatment solutions. This discovery has led researchers to investigate unconventional metal complexes which demonstrate better therapeutic results and reduced harmful effects. The pharmacokinetic advantages and tumor targeting abilities of drug delivery systems can be enhanced through modifications of metal centers and their respective coordinating ligands. The use of metal complexes in advanced drug delivery systems enables the development of both nanoparticles and ligand-targeted carriers which enhance therapeutic performance.

This review provides a detailed investigation of how metal complexes function in drug delivery and their role in cancer treatment. The study focuses on metal-based anticancer drug delivery systems which include design elements and weapon systems while identifying the current obstacles and potential advancements for the development of future metallodrugs.

Design & Classification of Anticancer Metal Complexes

The metal ions and coordinating ligands dictate how coordination chemistry-derived anticancer metal complexes show their biological functions and drug selectivity and drug absorption properties. The three-dimensional structures of metal complexes enable them to interact with biological systems in a different way than organic drugs, which helps scientists' study how they bind to biological targets. The rational design process seeks to find optimal equilibrium between medication distribution throughout the body and medication effectiveness in tumor microenvironments[3].

Categories of Metal Ions

Scientists use transition metals in anticancer drugs because these metals can exist in more than one oxidation state and have flexible coordination systems. Platinum is the main metal that makes square-planar complexes that bind to DNA bases through covalent interactions to cause apoptosis. Researchers now know that ruthenium complexes can exist in more than one oxidation state and that the compounds tend to build up in tumor cells through iron-transport pathways. Researchers have looked into gold, copper, and iron complexes a lot[4]. These studies have shown that they can work in many ways, such as by stopping enzymes from working, cycling redox reactions, and breaking up mitochondria. The metals can do redox reactions, which means they can make reactive oxygen species that only attack cancer cells.

Strategies for Ligand Design

Chelating ligands make them more stable in terms of thermodynamics, and bioactive ligands work with them to make them more effective against cancer. Researchers use functional ligands that have peptides, sugars, and vitamins in them to make cells take in more and target tumors more effectively[5]. Scientists can control ligand exchange rates very carefully to make prodrug systems that work in acidic or reductive tumors but not in healthy tissue.

Coordination Geometry and Chemical Modification

The coordination geometry—whether square planar, octahedral, or tetrahedral—directly affects the interaction of metal complexes with biomolecules. The ligand exchange rates of octahedral compounds show a tendency to decrease, which results in reduced nonspecific toxicity of these compounds[6]. The precise control of coordination geometry enables specific binding to DNA and proteins and enzymes, which allows drugs to treat diseases beyond the capabilities of existing DNA-targeting treatments.

Structure-Activity Relationship (SAR)

The studies on structure-activity relationships need to be conducted because they help to improve the effectiveness of anticancer treatments. The cytotoxicity and selectivity and resistance properties of the metal center and its oxidation state and ligand type and complete charge alterations undergo complete transformation

[3]Barry, N. P. E., & Sadler, P. J. (2013). Exploration of the medical periodic table: Towards new targets. Chemical Communications, 49(45), 5106–5131. https://doi.org/10.1039/c3cc41143e

[4]Alessio, E. (2017). Thirty years of the drug candidate NAMI-A and the myths in the field of ruthenium anticancer compounds. European Journal of Inorganic Chemistry, 2017(12), 1549–1560. https://doi.org/10.1002/ejic.201601055

[5] Hartinger, C. G., & Dyson, P. J. (2009). Bioorganometallic chemistry—from teaching paradigms to medicinal applications. Chemical Society Reviews, 38(2), 391–401. https://doi.org/10.1039/b707077m

[6] Gasser, G., Ott, I., & Metzler-Nolte, N. (2011). Organometallic anticancer compounds. Journal of Medicinal Chemistry, 54(1), 3–25. https://doi.org/10.1021/jm100020w

through these changes. Structure-activity relationship investigations show that even small structural changes lead to major biological effects which help in developing safer and more effective next-generation metallodrugs.

Metal Ion	Common Oxidation State	Typical Coordination Geometry	Primary Anticancer Mechanism
Platinum	+2	Square planar	DNA cross-linking
Ruthenium	+2 / +3	Octahedral	DNA/protein binding, redox activation
Gold	+1 / +3	Linear / Square planar	Enzyme inhibition, mitochondrial damage
Copper	+1 / +2	Distorted octahedral	ROS generation
Iron	+2 / +3	Octahedral	Redox-mediated cytotoxicity

Table 1: Classification of Anticancer Metal Complexes by Metal Ion, Source: Author Generated

Ligand Type	Functional Role	Therapeutic Advantage
Chelating ligands	Increase stability	Reduced premature deactivation
Bioactive ligands	Add pharmacological activity	Synergistic anticancer effects
Targeting ligands	Enhance selectivity	Reduced systemic toxicity
Stimuli-responsive ligands	Controlled activation	Tumor-specific drug release

Table 2: Role of Ligand Design in Anticancer Metal Complexes, Source: Author Generated

Mechanisms of Action in Cancer Treatment

The different biochemical pathways which metal complexes interact with lead to their effectiveness against cancer through mechanisms that differ from standard organic chemotherapeutics. The unique characteristic of metal-based drugs enables them to destroy cancer cells through multiple mechanisms. The treatment shows improved effectiveness because it requires less time to achieve results while decreasing the risk of cancer cells developing resistance.

DNA Interaction and Damage

The main way that anticancer metal complexes work to fight cancer lies in their ability to bind directly with DNA. Metal complexes establish two types of bonds with nucleobases which lead to intra- and interstrand cross-links and helix distortion while they stop DNA replication and transcription processes[7]. The cell uses checkpoint pathways to respond to DNA damage which ultimately leads to programmed cell death. Cancer cells face increased difficulty in repairing three-dimensional DNA damages that metal complexes create because these complexes show different binding patterns than most organic drugs which use single-site binding.

Oxidative Stress and Reactive Oxygen Species Generation

The second critical mechanism functions to create oxidative stress. Redox-active metal complexes initiate electron transfer reactions which generate reactive oxygen species (ROS) that include superoxide radicals and hydrogen peroxide and hydroxyl radicals[8]. The higher ROS levels disrupt the cellular redox balance which leads to oxidative damage of DNA and proteins and lipids. Cancer cells exhibit increased sensitivity to reactive oxygen species (ROS) because they experience higher baseline oxidative stress than normal cells which results in selective cell death.

Inhibition of Enzymes and Targeting of Proteins

Metal complexes function as inhibitors of essential enzymes which cancer cells require for their survival and growth. The tested complexes demonstrate high binding affinity towards amino acid residues that contain sulphur or nitrogen because this binding leads to the inhibition of proteases and kinases and redox-regulating proteins[9]. The process of enzyme inhibition creates two effects because it disrupts essential metabolic pathways while increasing cancer cell vulnerability to apoptosis. Metal complexes extend their capability to target proteins because they possess DNA-binding functions.

Mitochondrial Localisation

Mitochondria function as essential components of cellular energy production while they also control the programmed cell death process. Mitochondria selectively absorb particular metal complexes because these

[7] Galanski, M., Jakupec, M. A., & Keppler, B. K. (2005). Update of the preclinical situation of anticancer platinum complexes. Current Medicinal Chemistry, 12(18), 2075–2094. https://doi.org/10.2174/0929867054637626

[8]Wang, X., & Guo, Z. (2013). Towards the rational design of platinum(II) and gold(III) complexes as anticancer agents. Chemical Society Reviews, 42(1), 202–224. https://doi.org/10.1039/c2cs35258a

[9]Casini, A., &Reedijk, J. (2012). Interactions of anticancer platinum drugs with proteins: An overlooked topic? Chemical Science, 3(11), 3135–3144. https://doi.org/10.1039/c2sc20798h

complexes display both lipophilic properties and positive electrical charge. The substances cause changes to mitochondrial membrane potential which prevents electron transport chain operation and enables pro-apoptotic molecule release. Cancer cells experience energy loss through mitochondrial dysfunction which increases their internal apoptotic signaling process[10].

Initiation of Apoptotic Pathways

The combined effects of DNA damage and oxidative stress and enzyme inhibition along with mitochondrial dysfunction lead to the activation of apoptotic pathways. Metal complexes can induce both intrinsic (mitochondria-mediated) and extrinsic (death receptor-mediated) apoptosis which results in controlled cancer cell death instead of necrosis. The regulated cell death process decreases inflammation while protecting surrounding tissues which results in safer treatment outcomes.

Mechanism	Primary Target	Cellular Outcome	Therapeutic Significance
DNA interaction	Nuclear DNA	Replication arrest	Effective against fast-dividing cells
Oxidative stress	Redox balance	Biomolecular damage	Selective cancer toxicity
Enzyme inhibition	Key metabolic enzymes	Pathway disruption	Overcomes drug resistance
Mitochondrial targeting	Mitochondria	Energy depletion	Triggers intrinsic apoptosis
Apoptosis induction	Cell death pathways	Programmed cell death	Reduced inflammation

Table 3: Mechanisms of Action of Anticancer Metal Complexes, Source: Author Generated

Metal Complexes in Pharmaceutical Delivery Systems

Metal complexes show poor cancer treatment results because their toxic effects damage entire systems and their low water solubility leads to rapid body elimination and their intended purpose fails to deliver results. The development of complex drug delivery systems (DDS) establishes new methods to enhance the pharmacokinetic and pharmacodynamic performance of metal-based medications[11]. Custom carriers that use metal complexes as their main component establish two major advantages which include enhanced tumor targeting ability and improved drug protection during circulation and better controlled release at disease sites.

Nanocarrier-Enhanced Delivery

The delivery of metal complexes through nanocarriers serves as one of the most efficient delivery platforms that scientists have developed. Polymeric nanoparticles liposomes dendrimers and metal-organic frameworks (MOFs) create protective systems through their ability to encapsulate or conjugate metal complexes which prevents the complexes from deactivating while reducing their toxic effects on non-targeted areas. The nanocarriers use the increased permeability and retention (EPR) effect to achieve selective tumor tissue accumulation which occurs because of damaged blood vessels and lower lymphatic drainage. Encapsulation transforms hydrophobic metal complexes because it improves their solubility and stability[12].

Precision Pharmacotherapy

The delivery methods which scientists developed for targeted delivery purposes enhance the accuracy of metal-based treatment methods. The process of surface functionalisation enables carriers to acquire specific identification abilities which permit them to detect cancer cell receptors that show higher than normal expression levels through the use of antibodies and peptides and folic acid and sugar moieties. The active targeting method increases cell uptake through receptor-mediated endocytosis while it decreases the amount of medication which enters normal body tissues[13]. The system enables researchers to create metal complexes which use ligand-directed technology to achieve selective binding with proteins that exist in tumors thus providing a unified solution which includes both targeting abilities and therapeutic capabilities.

[10]Kostova, I. (2006). Platinum complexes as anticancer agents. Recent Patents on Anti-Cancer Drug Discovery, 1(1), 1–22. https://doi.org/10.2174/157489206775246413

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[13] Dilruba, S., & Kalayda, G. V. (2016). Platinum-based drugs: Past, present and future. Cancer Chemotherapy and Pharmacology, 77(6), 1103–1124. https://doi.org/10.1007/s00280-016-2976-z

Regulated and Prolonged Release

The controlled release function here of pharmaceutical systems which are normally to use metal complexes as their delivery method always provides major advantages to their operation. The release of medications from the system can be precisely controlled through the design of carrier materials and the selection of specific metal and ligand combinations[14]. The system enables extended medication delivery which maintains therapeutic drug concentrations throughout an extended period thus reducing the need for multiple doses and decreasing the risk of side effects that occur during medication peaks. This situation proves beneficial for metal complexes which show strong therapeutic effectiveness yet have restricted medical treatment capacity.

Responsiveness of the Tumour Microenvironment

Modern delivery methods make use of the unique characteristics found in the tumour microenvironment which consists of acidic pH levels and increased glutathione levels and conditions of hypoxia and the presence of excessively active enzymes. The carriers which respond to stimuli will release metal complexes only when certain conditions are present which allows the activation of drugs to occur in specific locations. The redox-responsive systems of cancer cells use their reducing environments to make prodrugs into toxic agents through ligands exchange and metal reduction. Acidic tumour environments pH-sensitive carriers to facilitate their release inside cells[15].

The use of metal complexes into modern drug delivery systems signifies a revolutionary approach in cancer treatment. Delivery methods which enable selective targeting and reduce toxic effects on the body together with site-based drug activation result in better clinical outcomes for metal-based anticancer treatments.

Challenges, Clinical Limitations, and Future Prospects

The medical field currently faces multiple obstacles which prevent metal complexes from being used as anticancer drugs. The problem of systemic toxicity exists because metal-based medications tend to build up in non-target areas of the body which results in neurotoxic and nephrotoxic effects and permanent metal accumulation. The process of finding optimal chemical properties needs research which will help decrease unwanted chemical reactions between substances. The main challenge with medications occurs when they lose their strength after extended time periods. The body experiences this condition because it becomes less able to take in substances while it gains better abilities to eliminate them and because its internal systems function more effectively and because cancer cells develop stronger capacity to fix DNA damage.

Clinics face multiple obstacles which include metal-based drug formulations that require expensive syntheses and their unknown human body processes and regulatory agencies which impose strict controls. The gap between preclinical success and clinical efficacy demonstrates the necessity for better disease models and biomarker-based assessments.

The development of more selective and safer medications will proceed through research which focuses on drug design and systems which deliver drugs specifically to tumors and systems which create prodrugs through reaction to specific stimuli. The combination of metal complexes with nanotechnology and personalized medicine and combination treatments will create metallodrugs which achieve better results within the human body.

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