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Mini review

Cancer cell death induced by ruthenium complexes

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Summary. Cancer is a complex and often fatal disease characterized by uncontrolled cell division. The most commonly used chemotherapeutics target rapidly dividing cancer cells but, at the same time, damage healthy dividing cells. New metal-based complexes, such as ruthenium complexes, that possess cytotoxic properties, have been developed to overcome these challenges. Ruthenium complexes achieve their antitumor effect mainly by inducing apoptosis. In recent years, induction of other types of cell death, such as ferroptosis and autophagy, was also reported. The dual role of autophagy in cancer cells is a major challenge for the application of metallocomplexes in cancer treatment, either as inducers or inhibitors of autophagy. Also, the effect of ruthenium complexes on other cellular processes such as cell cycle, cell migration, and adhesion are promising approaches in cancer treatment. Our results indicated a significant influence of Ru(II) complexes on these processes in melanoma, cervical and pancreatic cancer. The aim of this review is to summarize the latest data on the effect of ruthenium complexes on different types of cell death.

Keywords: apoptosis, autophagy, ferroptosis, ruthenium complexes.

METALLOCOMPLEXES AND CANCER

Cancer has been among the leading causes of death in the world. According to data from the International Agency for Research on Cancer GLOBOCAN, in 2020, 19.3 million new cancer cases and almost 10 million deaths were recorded worldwide (Ferlay et al. 2021). Chemotherapy, radiotherapy, surgical interventions, and immunotherapy are the most often used to treat malignant tumors (Akkin et al. 2021).

Cisplatin is the first metal-based chemotherapeutic drug used in clinical practice, whose cytotoxic properties were documented more than 50 years ago. About 50% of patients worldwide are treated with platinum-based chemotherapeutics, including cisplatin, carboplatin, and oxaliplatin (Armstrong-Gordon et al. 2018). These are widely used in the treatment of numerous human cancers, including testicular, ovarian, cervical, esophageal, bladder, lung, head and neck, breast, brain cancer, melanoma, lymphoma, and other cancer types (Dasari and Tchounwou 2014; Aldosary 2019; Ghosh 2019). These Pt-based complexes achieve anticancer activity by binding to purine bases on the DNA molecule causing DNA damage that arrests the cell cycle at S, G_1, or G_2-M phases, thus inducing apoptosis (Jordan and Carmo-Fonseca 2000; Dasari and Tchounwou 2014; Johnstone et al. 2016; Aldosary 2019).

A large number of platinum-based complexes, as well as other transition metals, were synthesized during the previous decades and tested on numerous tumor cell lines. Several

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classes of such non-conventional platinum drugs may be identified: Pt(IV) derivates (Vouillamoz-Lorenz et al. 2003; Johnston et al. 2016), trans platinum(II) analogs (Coluccia and Natile 2007; Filipović et al. 2013), polynuclear Pt complexes (Mangrum and Farrell 2010; Farrell 2015; Bondžić et al. 2022), Pt(II) compounds with sulfur and phosphorus donors (Mügge et al. 2011), heterometallic complexes containing palladium and platinum centers (Jovanović et al. 2016). Although efficient against numerous types of cancer, platinum-based chemotherapeutics cause severe side effects, such as toxicity to healthy cells, resistance, limited solubility, and inactivity against many common cancers. This is why many other potential metal transition complexes have been developed and studied.

Ruthenium complexes have been shown as the most promising alternative to platinum-based metallodrugs. Compared to platinum complexes, Ru-complexes show less toxicity, better selectivity, a different mechanism of action, and activity on types of cancer and metastases where platinum complexes were inactive. (Abid et al. 2016; Thota 2016; Southam et al. 2017). Ruthenium is a transition metal that can exist in three oxidation states under physiological conditions (Ru(II), Ru(III), and Ru(IV)), which differ in their biological activities. Ru(IV) compounds are unstable, while Ru(III) complexes have good stability and can undergo activation via reduction, leading to the conversion of the more inert form of Ru(III) into the more biologically active Ru(II) form (Oberoi et al. 2013). Namely, in the conditions of lower molecular oxygen concentration, faster metabolism, and poorer blood supply that characterize tumor tissue, inert Ru(III) is transformed into active Ru(II). At physiological oxygen levels, Ru(II) is easily oxidized to non-toxic Ru(III) (Allardyce and Dyson 2001). Higher selectivity of ruthenium complexes compared to platinum complexes comes from the ability of ruthenium to replace iron in proteins rich in this metal ion, particularly transferrin (Kratz and Messori 1993). Cancer cells divide faster and have a higher need for iron, which causes an expression of more transferrin receptors on their surface, and, consequently, an increased intake of ruthenium when applied to tumor tissue (Champion et al. 2007; Naves et al. 2019). The complete process of increased Ru-complex uptake by tumor cells is a basis for a greater selectivity of Ru complexes against healthy cells. Ruthenium complexes are characterized by a different mechanism of action compared to platinum complexes which dominantly bind to DNA molecules. Namely, Ru-complexes can also interact with proteins, thus affecting various signaling pathways in cancer cells (Vergara et al. 2013). Many ruthenium complexes have been synthesized in the last few years, and their anticancer properties are being investigated. NAMI-A, KP1019, NKP1399, and TLD 1443, have been studied in clinical trials, but as of yet none of them are in clinical use as anticancer drugs (Redemaker-Lakhai et al. 2004; Hartinger et al. 2008; Trondl et al. 2014; Monro et al. 2019).

METALLOCOMPLEXES AND PHOTODYNAMIC THERAPY

As new types of cytostatics are developed, scientists focus on their more efficient and precise delivery by creating appropriate carriers. In this way, the investigation focuses on the controlled delivery of cytostatics to the tissues where the pharmacological action of cytostatics is desired, reducing the damage to the surrounding healthy tissue to a minimum. The concept, however, is not limited exclusively to the controlled delivery but also to the controlled release rate of cytostatics from the carrier, which affects the concentration of a drug and the effectiveness of the therapy itself. Given this, various multifunctional drug delivery systems have been developed (Patra et al. 2018; Majumder and Minko 2021), resulting in a new field in cancer therapy that arose along with the development of nanomaterials. In the last few years, the focus has been on the design of new nanoparticles intending to improve the solubility of a drug, preservation of therapeutics in circulation to extend their half-life, passage through biological barriers, and enabling sustained drug release (Altammar 2023). Nanoparticles can be used independently as active therapeutics or cytostatic carriers for delivery to diseased tissues. When they are used as carriers, it is important that they have a property that can be changed by stimulating and releasing the drug in that way (Ding et al. 2016). Stimuli for the activation of drug release can be internal and external. Tumor tissue usually has acidic pH and an elevated concentration of reactive oxygen species (ROS) compared to the healthy one (Zhu and Torchilin 2013). According to that, carriers are synthesized so that they undergo a change during exposure to such internal stimuli and release the drug through the transition from healthy to diseased tissue. Although convenient for on-site drug activation, internal stimuli cannot be adjusted. Therefore, scientists focus more on external stimuli like temperature, ultrasound, magnetic field, and light to trigger drug release from the nanocarrier or to locally activate a drug (Farjadian et al. 2022).

Photodynamic therapy (PDT) is a new approach in clinical praxis, which demonstrated success in the therapy of certain diseases, including cancer. PDT uses light as an external stimulus and light-sensitive compounds – photosensitizers (PSs). First, a PS is inserted and accumulated in the patient's tumor tissue due to the enhanced permeability and retention effect. The process is followed by illumination with light of the appropriate wavelength, which is determined by the absorption spectrum of the PS. After excitation, there is

no direct reaction between the PS and biomolecules. In fact, illumination transfers energy from light to molecular oxygen, creating ROS such as singlet oxygen ($1O_2$), superoxide radical anion (O2•-), hydroxyl radical (HO•), and hydrogen peroxide (H_2O_2). Increased concentration of ROS can lead to damage of biomolecules and induction of programmed cell death (PCD) (Correia et al. 2021). Another process, which is also common in PDT and uses transition metallocomplexes, is the initiation of photo-substitution reactions that foster transition metal's interaction with a target molecule in cancer (White et al. 2017). Various organic and inorganic compounds have been investigated as PSs for PDT. So far, only five PSs have been approved for clinical use: Photofrin, ALA, ALA esters, Foscan, and Verteporfin (Hamblin 2020).

Titanium dioxide (TiO_2) nanoparticles are promising PSs and photoactive drug carriers (Flak et al. 2015; Rehman 2016; Matijević et al. 2021). Thanks to properties such as chemical stability, accessibility, large surface area, and the possibility of modifying the surface, which enables the binding of different drugs, TiO_2 is the second most used material in our daily lives (Brun et al. 2014). TiO_2 nanoparticles are biocompatible at low concentrations and inactive in the dark, while their photoactivity and photo-cytotoxicity are expressed when exposed to UV light. Their photo-cytotoxicity has been demonstrated *in vitro* on a large number of cell lines, such as cervical cancer cell line HeLa, glioblastoma cells T98G, melanoma A375, SK-MEL 30 and breast cell line MCF-7 (Mohammadalipour et al. 2017; Geng et al. 2020; Fuster et al. 2021; Matijević et al. 2021).

In addition to the fact that many Ru complexes have shown potent cytotoxic effects, research in recent years has been focused on using Ru complexes in PDT (Liu et al. 2015). Ru complexes have been shown to lead to the formation of 1O2. Light-interaction effectively "turning on" the Ru drug's activity was reported on Ru(II) polypyridyl complexes (Heinemann et al. 2017; Banerjee 2021) as well as Ru(II) with porphyrin (Moura et al. 2022) and arene ligand (Basu et al. 2019). For example, [Ru(bpy)2(dppz-7-OMe)]2+ has shown a high phototoxic index comparable to or even better than several PSs used in clinics under similar experimental conditions (Heinemann et al. 2017). It localizes in the nucleus and induces DNA damage in cancer cells upon light illumination. Also, porphyrin derivatives bearing attached ruthenium have shown high generation of singlet oxygen and good cellular uptake, making them efficient candidates as PS in PDT against resistant B16F10 melanoma cells (Moura et al. 2022). Moreover, porphyrin arene ruthenium(II) derivatives have shown excellent phototoxicity toward human melanoma cells when illuminated with laser light at 652 nm, and it was found that they accumulate in the cytoplasm of melanoma cells (Schmitt et al. 2008). Among all of them, Ru(II) polypyridil complex TLD-1443 has recently entered phase II of clinical trials for photodynamic therapy modality against human non-muscle invasive bladder cancer (Monro et al. 2019).

Numerous studies are focused on the physicochemical properties of the bond between ruthenium complexes and nanostructured TiO_2. The obtained results demonstrated the potential of such nanocomposite systems (NCS) as efficient catalysts (Kumar et al. 2015) or units for solar energy conversion (Nazeeruddin et al. 2003). However, the NCS, which is synthesized by binding a potential cytostatic – complex cis-dichlorobis(2,2'-bipyridyl- 4,4'dicarboxylic acid) ruthenium(II) for the support – colloidal TiO_2 nanoparticles have demonstrated very good potential for controlled cytostatic delivery, with the possibility of its activation with light and controllable release, depending on the wavelength of the light used for illumination. Low cytotoxicity levels in the absence of light stimulus, and measurable photocytotoxic effect on human melanoma A375 cells, enable effective PDT of melanoma using this NCS (Nešić et al. 2017).

RUTHENIUM COMPLEXES AND CELL DEATH

The most common type of cell death induced by metal-based anticancer agents is apoptosis. Autophagy can also be triggered, but its role in cancer treatment is still controversial. Recently, ferroptosis has also been reported as a type of cell death caused by metallocomplexes, and in the next chapters, we will give an overview of various types of cancer cell death induced by metallocomplexes.

RUTHENIUM COMPLEXES AND APOPTOSIS

The process of apoptosis can be induced through the death receptor and/or the mitochondrial pathway, with the Bcl-2 protein and the family of caspases playing a key role in both signaling pathways.

Literature data indicate that many ruthenium complexes, including NAMI and KP 1019, exert their antitumor properties by inducing apoptosis. Kisova et al. (2011) have shown that the monofunctional Ru(II)-arene complex [(η6-arene)Ru(II)(en)Cl]+, where en = 1,2-diaminoethane and the arene is para-terphenyl, induces apoptosis by inhibiting DNA synthesis, overexpression and activation of p53, expression of proapoptotic proteins p21(WAF1) and Bax. Several ruthenium(II) arene complexes with the 4-(biphenyl-4-carbonyl)-3-methyl-1-phenyl-5-pyrazolonate ligand, and related 1,3,5-triaza-7-phosphaadamantane (PTA) derivatives were analyzed on HeLa, MCF-7, HepG2, and HCT-116 cells. The increase in the levels of the 89 kDa PARP fragment and the down-regulation of Bcl-2 expression was detected in all cell lines (Pettinari et al. 2014). Another induction of apoptosis through activation of the mitochondrial pathway and

changes in Bax/Bcl-2 ratio in favor of apoptosis was reported by Sun et al. (2016) for ruthenium (II) polypyridyl complex on A549 cells. Activation of caspase 3 and PARP-1clevage in A549 lung carcinoma cells has been reported by Soares Costa et al. (2010) for Ruthenium (II) complex cis-[RuII(ŋ2-O2CC7H7O2)(dppm)2]PF6-hmxbato complex.

Until now, most of the research on the proapoptotic effect of ruthenium complexes has been concentrated on examining the activation of the mitochondrial pathway. However, so far very little is known about the role of cell membrane proteins in the mechanisms of action of the Ru complexes. Previous research has shown differences in the expression of cell membrane receptors in cancer and normal cells. These findings enable the development of a new strategy for designing drugs that target cancer based on this difference. Death receptors are cell surface receptors of the tumor necrosis factor (TNF) receptor superfamily, the activation of which can induce the extrinsic apoptotic pathway. A new class of Ru complexes containing phenylterpyridine derivatives was synthesized by Jiang et al. (2023). Their increasing planarity significantly improved lipophilicity and cellular uptake. The [RuII(4-NO2-phtpy)(phen)Cl]ClO4 complex accumulates on the cell membrane and interacts with death receptors to activate the extrinsic apoptosis signaling pathway by significantly increasing caspase 8 activity in A375 melanoma cells (Jiang et al. 2023). Increased caspase 8 activity was also observed in MCF-7 cells after treatment with dinuclear trithiolato-bridged arene ruthenium complex diruthenium-1 (DiRu-1) (Koceva-Chyła et al. 2016). De Carvalho et al. (2018) synthesized a ruthenium complex with xanthoxylin that exhibits potent cytotoxicity in different cancer cells. Its cytotoxic effect is associated with the induction of caspase- and ERK1/2-mediated apoptosis in HepG2 cells by a p53-independent pathway.

RUTHENIUM COMPLEXES AND AUTOPHAGY

Autophagy is a highly conserved catabolic process that involves the formation of autophagosomes, double-membrane vesicles for recycling damaged cytoplasmic components. The formation and turnover of autophagosomes are controlled by evolutionarily conserved autophagy-associated genes (ATGs). This process is usually divided into four key steps: initiation, nucleation, maturation, and degradation (Gałczyńska et al. 2020). Autophagosome initiation and formation is a complicated process regulated by three major protein complexes. The ULK1 (unc-51-like kinase 1) complex plays a key role in the initiation process. This complex consists of ULK1 itself, ATG (autophagy-related protein) 13 (ATG13), FIP200 (focal adhesion kinase family interacting protein of 200 kDa), and ATG101. Furthermore, autophagy is promoted by AMP-activated protein kinase (AMPK), a key energy sensor that regulates cellular metabolism to maintain energy homeostasis. Conversely, autophagy is inhibited by the mammalian target of rapamycin (mTOR), a central cell-growth regulator that integrates growth factors and nutrient signals. Under glucose starvation, AMPK promotes autophagy by directly activating Ulk1 through phosphorylation of Ser 317 and Ser 777. Under nutrient sufficiency, high mTOR activity prevents Ulk1 activation by phosphorylating Ulk1 Ser 757 and disrupting the interaction between Ulk1 and AMPK. This coordinated phosphorylation is important for Ulk1 in autophagy induction. Upon autophagy induction, the ULK1 complex translocates to autophagy initiation sites (Zachari and Ganley 2017). In the nucleation step, the ULK1 complex phosphorylates and activates the Beclin-1-VPS34 complex. Both initiation and nucleation proteins promote the membrane formation of autophagic vesicles. This membrane stems either from mitochondria, plasma membrane, or endoplasmic reticulum. For the formation of autophagosomes during the maturation step, the conjugation of the ATG5 protein to ATG12, and the conjugation of LC3 (ATG8) to the lipid phosphatidylethanolamine (PE) are necessary. This lipid-conjugated form of LC3 typically serves as an autophagosome marker. Finally, the autophagosome fuses with the lysosome, the contents are degraded, and the macromolecular precursors are recycled or used to drive metabolic pathways. The adapter protein sequestosome 1 (p62), which targets specific substrates to autophagosomes and LC3II, is degraded with other cargo proteins and can be used to measure autophagic flux (Onorati et al. 2018).

Autophagy maintains cellular homeostasis and breaks down damaged proteins and organelles. In addition, many studies suggest that autophagy is associated with an important role in several diseases, including cancer. It is still unclear whether autophagy has a protective or inhibitory role in cancer. It achieves its inhibitory function by eliminating damaged cells and organelles during tumor initiation and malignant transformation. On the other hand, autophagy has a protective role because it ensures tumor cells' metabolic and energy needs during cancer development (Yun et al. 2020). Despite the confusing dual role of autophagy in cancer, much work is being done to develop therapeutics based on manipulating the autophagy process. Most of the work is focused on autophagy inhibition (Levy et al. 2017), since it is widely accepted that inhibition of autophagy is a reasonable approach in cancer therapy. Autophagy inhibitors can be used alone or as potential adjuvant therapy with other established therapeutic agents. However, a problem in applying autophagy inhibitors in cancer therapy is that autophagy is context-dependent, including possible adverse effects on tumor cells.

For now, only a few studies indicate autophagy induc-

tion as a mechanism of cell growth inhibition caused by metallocomplexes (Sun et al. 2021). Oxaliplatin induces autophagy of hepatocellular carcinoma cells and MGC-803 gastric cancer cells. This mechanism is approved by suppressing autophagy with pharmacological inhibitors (3-methyladenine or chloroquine) and RNA interference of different autophagic genes (Gałczyńska et al. 2020). An oxaliplatin derivative E-Platinum induces autophagy in BGC-823 gastric gland cancer cells by suppressing the mTOR signaling pathway. Autophagy was activated after treatment of breast cancer cells with Ru(III) complexes. Ru(II) complexes can induce autophagy in lung cancer cells and eliminate apoptosis-resistant cells (Sun et al. 2021). Ru(II) imidazole, [Ru(Im)4(dppz)]2+ (dppz=pyrido[3,2-a:2',3'-c]phenazine), induced the formation of autophagosomes and acidic vesicular organelles accompanied by upregulation of LC3-II in A549 and NCI-H460 cancer cells. It also caused mitochondrial dysfunction and ROS generation in A549 cells, partially inducing caspase-3-dependent apoptosis and autophagy mediated by the extracellular signal-regulated kinase (ERK) signaling pathway. The antitumor activity of [Ru(Im)4(dppz)]2+ complex was demonstrated *in vivo* in mice bearing A549 xenografts. Tumor weight and volume were significantly reduced after the treatment with the above-indicated Ru complex, and expressions of LC3-II, cleaved caspase-3, CD-31, and Ki-67 were increased. The simultaneous activity of the Ru complex on apoptosis and autophagy was also observed in glioblastoma cells (Sun et al. 2021). Anticancer activity of Λ-WH0402 Ru complex is mediated through promoting the Beclin-1-dependent autophagy pathway in human liver HCCLM6 cells (Yuan et al. 2015).

Ruthenium complexes accumulate significantly more in organelles, such as mitochondria, endoplasmic reticulum and lysosomes, than in the nucleus (Puckett and Barton 2007; Groessl et al. 2011). Since the endoplasmic reticulum plays a significant role in tumor cell apoptosis and autophagy (Sano et al. 2012; Fernandez et al. 2015; Živković-Zarić et al. 2019), one emerging tendency is the identification of drug candidates that target this organelle. Ruthenium compounds, synthesized by various investigators, target ER complexes and can induce endoplasmic reticulum stress (ERS) (Gill et al. 2013; Sano and Reed 2013). ERS can activate cell autophagy through UPR (unfolded protein response) signaling or the release of Ca^{2+} from the endoplasmic reticulum into the cytoplasm.

In addition, ruthenium complexes can target another important participant in autophagy, lysosomes, inducing autolysosome production and hydrolase release (Tan et al. 2010; Castonguai et al. 2012; Chen et al. 2016). Ruthenium complexes containing 5-Fu derivatives as ligands can localize in lysosomes and increase the intracellular reactive oxygen species (ROS) level, thereby causing the death of HeLa cells through a dual mode of apoptosis and autophagy (Pan et al. 2022).

Considering the dual role of autophagy in cancer cells, additional research is necessary regarding the application of metallocomplexes and other agents in cancer treatment, either as inducers or inhibitors of autophagy.

RUTHENIUM COMPLEXES AND FERROPTOSIS

Morphological and biochemical characteristics of ferroptosis differ from other types of PCD (e.g., apoptosis, necroptosis, pyroptosis, and autophagy). Ferroptosis is a type of cell death that depends on iron and ROS. Iron accumulation and lipid peroxidation primarily initiate oxidative membrane damage during ferroptosis. The underlying molecular mechanism of ferroptosis involves the regulation of oxidation and the balance between cell damage and antioxidant defense. Excess H_2O_2, usually present in tumor cells, can lead to ferroptosis due to the creation of hydroxyl radicals through a reaction with iron and ferrous ions. Mitochondria are essential sites of ROS generation and fatty acid metabolism, and provide specific lipid precursors for ferroptosis. Morphologically, mitochondria in cancer cells undergoing ferroptosis show evident changes compared to those in healthy cells. Mitochondrial volume in a cell decreases while cristae reduce or disappear, and shape changes from a long rod to a pointed shape with a ruptured outer membrane. The regulation of ferroptosis depends on the competition between the ferroptosis antioxidant defense system and the ferroptosis execution system. The antioxidant defense system of ferroptosis is mainly divided into GPX4-dependent and GPX4-independent systems (Wang et al. 2022). A long-chain acyl-CoA synthetase (ACSL) has a significant role in ferroptosis. The ACSL family consists of proteins mainly expressed on the endoplasmic reticulum and the mitochondrial outer membrane, responsible for forming acyl-CoA from fatty acids. These proteins have five isoforms - ACSL1, ACSL3, ACSL4, ACSL5, and ACSL6 (Soupene et al. 2008). Only the ACSL4 form of the protein has a significant role in ferroptosis. This form mainly acts on long-chain polyunsaturated fatty acids, such as arachidonic acid (AA) or adrenergic acid (Ada). It converts them to arachidonic CoA and adrenal CoA, respectively, which are more likely to be oxidized and form lipid peroxides (Wang et al. 2022). The accumulation of AA in cells is much lower than other fatty acids in physiological conditions. Increased expression of ACSL4 is considered a biomarker and contributes to ferroptosis, and it can esterify free polyunsaturated fatty acids into membrane phospholipids by lysophosphatidylcholine

acyltransferase 3 (LPCAT3). Hydroxyl radicals can catalyze the peroxidation of macromolecules such as polyunsaturated fatty acids (PUFA). This peroxidation can destroy the phospholipid cell membrane bilayer leading to cell death (Wang et al. 2022).

The growth of cancer cells is highly dependent on iron, which is essential for ferroptosis. Iron can directly generate excessive ROS through the Fenton reaction, thereby increasing oxidative damage. Iron can also increase the activity of enzymes responsible for lipid peroxidation and oxygen homeostasis (lipoxygenase (ALOX) or EGLN prolyl hydroxylase). Based on the latest results, it can be concluded that the dynamics between systemic and local cellular iron regulation influence ferroptosis sensitivity (Tang et al. 2021).

The main approach in treating tumors is using drugs that induce apoptosis. However, the therapeutic effect is limited due to cancer cells' inherent and acquired resistance to apoptosis. For these reasons, developing new approaches to treating cancer is necessary. Inducing ferroptosis in cancer cells is one way to overcome drug resistance.

It is known that the inhibition of xCT and GPX4 can effectively increase the sensitivity of tumors (e.g., pancreatic ductal carcinoma, NSCLC, and osteosarcoma) to gemcitabine and cisplatin. Several drugs already in clinical use are known to induce ferroptosis. Metallocomplexes for antitumor treatment have been under rapid development in recent decades. However, some tumor cells are resistant to apoptosis and not sensitive to metallodrugs that function through the apoptotic pathway. Recently, metallocomplexes have been reported to cause ferroptosis against tumor cells, which offers new opportunities for anticancer therapy (Nie et al. 2022). Metallocomplexes have unique characteristics since they contain a metal and a ligand. Metal ions have a high affinity for biothiols, leading to an imbalance in redox and lipid peroxidation, ultimately resulting in ferroptosis. Besides having well documented effects on cancer cell replication and transcription inhibition, cell cycle arrest and apoptosis induction, literature data suggest that cisplatin also induces ferroptosis, as documented in A549 and HCT116 cell lines. Due to the high affinity of platinum complexes for thiol-containing biomolecules, cisplatin reduces GSH levels and GPX activity, which plays an essential role in ferroptosis (Li et al. 2023). Another gold-based metallocomplex, auranofin (AUR), induced ferroptosis by attenuating the total thioredoxin reductase activity (TKSNRD) and increasing lipid peroxidation, while GSH content and GPX4 expression were not affected. Cisplatin could also induce ferroptosis and apoptosis through photothermal therapy (PTT) in combination with Fe(III) nanoparticles. Cisplatin consumed GSH and activated NOXs, which could produce superoxide anion radicals ($O2\bullet^-$) and H_2O_2. Fe(III)-polydopamine enabled nanocarriers to show a photothermal effect, while the released Fe3+ induced the Fenton reaction, depleted GSH, and activated p53 to cause ferroptosis and apoptosis. The iridium IrFN complex has shown high cytotoxicity in A2780 cells through HMOKS1-mediated ferroptosis (Wang et al. 2022). Overexpression of HMOKS1 increased intracellular iron content and ferritin production, ROS accumulation, and lipid peroxidation. Iridium complexes can also induce ferroptosis via photodynamic therapy (PDT) by generating $O2\bullet^-$ and •OH radicals and lipid peroxidation. Ferroptosis can also be activated via phototherapy mediated with osmium complexes. In addition to ROS generation, osmium complexes photo-catalyze intracellular NADH, activating ferroptosis by indirectly decreasing the reduction of oxidized glutathione (GSSG) to GSH (Li et al. 2023).

Ruthenium complexes, widely used in photodynamic therapy, achieve their antitumor effect mainly by inducing apoptosis. However, recent results show that ruthenium complexes can also cause ferroptosis after activation with light. Tumor tissues are often hypoxic, therefore an antitumor mechanism that relies only on the stimulation of oxidative stress might not always be efficient. For that reason, scientists have developed novel compounds that will exploit the advantages of PDT in hypoxic conditions and have synthesized Ru(II) polypyridine complexes (RuNMe, RuH, and RuCN) as novel PSs. All Ru(II) complexes have shown a high yield of singlet oxygen and $O2^{-\bullet}$ upon light irradiation. Among them, RuNMe has shown the best tumor cell inhibition effect due to high cellular uptake. The results of Qi et al. (2023) demonstrate that ferroptosis was the primary cell death mode upon PDT treatment using RuNMe as the PS, which was verified by investigating other characteristics. Namely, RuNMe efficiently reduced GSH levels and disturbed the redox balance in MCF-7 tumor cells upon light irradiation, suggesting that this Ru complex induces ferroptosis via a GPX4-dependent pathway upon PDT application.

The new photoactive sorafenib-Ru(II) complex (Ru-Sora) generates ROS upon irradiation (λ = 465 nm), which can oxidize intracellular substances such as GSH. Ru-Sora induces apoptosis and ferroptosis, as evidenced by GSH depletion, GPX4 downregulation, and lipid peroxide accumulation (Lai et al. 2022). Ruthenium complex Δ-Ru1 has shown a synergistic effect with doxorubicin in mouse breast cancer. This effect implies iron accumulation in the ferroptosis pathway and the expression of lipid peroxidation-related proteins, including upregulation of Tf, DMT1, and HO-1, and downregulation of Nrf2, SLC7A11, and GPX4 (Tang et al. 2022).

Many authors have reported lipid peroxidation accumulation by ruthenium complexes. Lipid peroxidation is one of the hallmarks of ferroptosis. [Ru(η5-C5H5)(PPh3)2CN]

complex induces significant changes in lipids of A2780 ovarian cancer cells. These changes are related to the increased extent of lipid peroxidation (Nešić et al. 2022). P-cymene–ruthenium(II) complexes induced cytotoxic activity through the generation of ROS/RNS (reactive nitrogen species), which, being highly reactive molecules, destroy cellular organelles by peroxidation of membrane lipids and lead to the death of cancer cells (Hikisz et al. 2023). Glutathione depletion, also one of the major characteristics of ferroptosis, was reported after treatment with Ru(II) complexes (Ke et al. 2021).

Some authors have also reported other types of cell death induced by ruthenium complexes, such as necroptosis (Sun et al. 2021) or pyroptosis (Liu et al. 2023). Also, other mechanisms, like cell cycle arrest (Sun et al. 2021; Žakula et al. 2021; Čolakov et al. 2022) or inhibition of cell migration (Žakula et al. 2021; Čolakov et al. 2022; Teixeira-Guedes et al. 2022) were reported for different ruthenium complexes. Finally, Ru(II) and Ru(III) complexes not only suppress primary tumors, but also effectively inhibit malignant tumor metastasis (Sun et al. 2021).

In summary, existing findings on Ru complexes indicate that they can induce various types of cell death. Apoptosis could be induced both by intrinsic and extrinsic signaling pathways. Autophagy induction by ruthenium complexes is also reported, but its role in cancer cells is still controversial. Induction of ferroptosis by ruthenium compounds has been demonstrated for PDT, based on ruthenium photosensitizers. The antitumor effect of these complexes includes not only cell death induction, but also cell cycle arrest and inhibition of cell migration. However, the precise mechanism of action of the ruthenium complex still needs to be sufficiently elucidated. Additional research is needed to fully clarify the impact of these complexes, primarily on the processes of autophagy and ferroptosis. Elucidating these processes could contribute to the development of chemotherapeutic agents with greater efficiency and better potential for clinical application.

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