Redox-Active Anticancer Complexes

Redox-Active Metal Complexes for Anticancer Therapy

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Abstract: The redox properties of both metals and ligands in transition metal complexes offer unusual routes for new mechanisms of anticancer therapy. Metal complexes can introduce artificial reductive and oxidative stress into cancer cells, including behavior as photoactivatable agents and catalysts. Relatively inert metal complexes (“prodrugs”) can be activated by redox processes within cancer cells. Examples of pharmaceuticals activated by bioreduction include three PtIV and two RuIII compounds that have already entered clinical trials. More recently, novel CoIII, FeIII, PtIV, Ru(III/II), OsII, and IrIII complexes have been reported to exhibit redox-mediated anticancer activity. Redox activation strategies can introduce new methods to increase cancer cell selectivity and combat drug resistance. Using combination therapy together with redox modulators to increase potency is also possible. This essay focuses on metal complexes that are activated in the reducing environment of cancer cells.

Introduction

Hypoxia is a serious problem in cancer therapy. Tumors contain a more reducing environment compared with healthy tissues due to accelerated metabolic activity, high rates of cell growth, and proliferation.[1] Chemotherapy and radiotherapy are unsuccessful for tumor cells that up-regulate drug resistance genes in hypoxic environments.[2] However, studies show that hypoxia can be exploited for therapeutic selectivity, as it differentiates cancer cells from normal cells.[3] The redox properties of both metals and ligands in transition metal complexes offer unusual routes for redox activation. The reducing tumor microenvironment provides an opportunity for inert oxidized metal prodrugs to be selectively activated by cancer cells in hypoxic environments. Thus, there is much potential for the development of bioreducible metal prodrugs.

Metal complexes contain a variety of structural and electronic features that can be exploited in drug design.[5,4] The metal itself and its oxidation state can be varied, as well as coordination geometries and coordination numbers. These properties allow the fine-tuning of chemical reactivity, including the rates of ligand exchange, the strengths of metal–ligand bonds, metal- and ligand-based redox potentials, ligand conformations, and outer-sphere interactions.[3] As well as the metal, the ligands can also play important roles in biological activity. They can be involved in target recognition and, when released, interfere in biochemical pathways.[5]

In this essay, we discuss metal complexes activated by the redox balance in cancer cells. The redox activation mechanism provides a highly effective cancer therapy strategy, especially because it offers selectivity over normal cells. Metal complexes can interfere in cellular redox chemistry in several ways: directly through metal or ligand redox centers or indirectly by binding to biomolecules involved in cellular redox pathways. Upon cellular reduction, platinum(IV) prodrugs can not only release an active PtII complex but also additional bioactive substances that function in a manner orthogonal to PtII, providing a “dual-threat” mode of action. We have studied a wide range of redox-active organometallic RuII/OsII/RhIII/IrIII complexes as anticancer agents.[5,6] The anticancer activity of OsIII-arene complexes, for example, can achieve nanomolar potency toward cancer cells in combination with the redox modulator L-buthionine sulfoximine, an inhibitor of the synthesis of glutathione, which is an antioxidant in cells.[5] Here we discuss applications of metal-based drugs for anticancer therapy involving redox-activated prodrug strategies and redox modulation.

Redox Systems in Cells

The redox balance is tightly regulated in living organisms. The disturbance of this balance can cause, or arise from, many dis-
Reactive nitrogen species (RNS) include nitric oxide (NO), peroxynitrite (ONOO−), and dinitrogen trioxide (N2O3). RNS are often linked to ROS, for example, in the formation of peroxynitrite causing nitrosative stress. Oxidative and nitrosative stress have been etiologically implicated in a wide variety of disease processes and states: aging, hypertension, atherosclerosis, ischemia/reperfusion (I/R) injury, renal diseases, diabetic neuropathies, Alzheimer’s disease and cancers.[10]

An antioxidant is most simply defined as a molecule capable of slowing down or preventing redox changes in cancer cells. Cancer cells have developed several endogenous antioxidant systems to deal with over-produced cellular ROS. The redox equilibrium is tuned by cellular antioxidants, which can be divided into enzymatic and non-enzymatic groups.

Enzymatic antioxidants include superoxide dismutases (SODs), catalase, peroxidases, and glutathione S-transferase (GST), several of which require trace metal cofactors.[11] For example, there are two types of SOD enzymes present in mammalian cells, Cu-Zn SOD (cytoplasmic/nuclear) and Mn SOD (mitochondrial). Hydrogen peroxide generated after SOD activity is further converted to water by catalase and peroxidases. Catalase is relatively limited in cellular distribution (e.g. peroxisomes and a few other locations). Glutathione peroxidase and peroxidases, as classes, are of comparable, if not potentially greater, importance than catalase. Catalase catalyzes the decomposition of H2O2 to O2 and H2O. It is an important enzyme in protecting the cell from oxidative damage by ROS. But, under prolonged oxidative stress with oxidation of NADPH, catalase activity drops.[12,13]

Cellular redox systems also utilize non-enzymatic antioxidants such as the tripeptide glutathione (GSH, γ-L-Glu–L-Cys–Gly), vitamin C (ascorbic acid), and thioredoxin (Trx). Non-enzymatic antioxidants react directly with the oxidants. Such antioxidants are said to be “scavengers”; their roles are unavoidably suicidal. Ascorbic acid can directly scavenge hydroxyl radicals by forming the semidehydroascorbate free radical that is subsequently reduced by GSH.[14] GSH, present at concentrations of 0.5–10 mM, is the predominant non-protein thiol in cancer cells.

The glutathione system of reduced GSH, oxidized GSSG, and glutathione peroxidase (GPx) is important for maintaining the cellular redox balance.[15] It is a major thiol–disulfide redox buffer in the cell and acts as the central mechanism for reducing H2O2.[16] This complements catalase as a reducing system for H2O2 but exceeds catalase in its capacity to eliminate additional types of toxic peroxides. The key enzyme in the glutathione system responsible for the reduction of H2O2 is GPx.[17] The reducing capacity of GPx enzymes is based on high levels of GSH. GPx reduces hydrogen peroxide to water by oxidizing glutathione to its disulfide (GSSG) (Table 1). The GSSG is reduced back to GSH by the reaction of GSH reductase (GR) with NADPH.[18] This capacity to recycle GSH gives the glutathione system a key role in the antioxidant defense mechanism of a cell and prevents depletion of cellular thiols.[19] Curiously there are situations in which GSH appears to act as a pro-oxidant. For example, GSH can react non-enzymatically with superoxide (O2−), nitric oxide (NO), hydroxyl radical (·OH), and peroxynitrite (ONOO−). GSH can also induce oxidation of metal thiocarbonates (M-SR) to metal sulfenates [M-S(O)-R].[19,20]

Trx is an oxidoreductase enzyme containing a dithiol–disulfide active site (–Cys–Gly–Pro–Cys–).[21] Oxidized Trx contains a disulfide bridge (–S–S–) between two cysteines, whereas reduced Trx is a dithiol with two cysteines.[19] The thioredoxins are maintained in the reduced state by the flavoenzyme thioredoxin reductase, in a NADPH-dependent reaction. Trx is important in signal transduction, inflammatory responses, and other biological functions such as apoptosis, cell growth, and proliferation.[19–23]

Here we describe the potential role of redox modulation in the mechanism of action of metal anticancer prodrugs, particularly in cobalt, platinum, ruthenium, osmium, and iridium complexes. To what extent is modulation of cellular redox processes involved in their activity? High-oxidation-state metal complexes can undergo intracellular reduction and release anticancer drugs in the reductive environment in cancer cells, for example, CoIII is reduced to CoII, and PtIV is reduced to PtII. Organometallic
complexes can act as biocatalysts for modulating the redox state of cancer cells.

CoIII Complexes

Cobalt complexes, in general, have two accessible oxidation states: Cobalt(III) is kinetically inert due to its low-spin 3d6 configuration, and CoII is labile (high-spin 3d7). Thus, CoIII complexes can act as carriers for selective delivery of anticancer agents to the hypoxic regions of a tumor.[24–26] It has been demonstrated that coordination of anticancer agents to CoIII can inhibit their cytotoxic properties. When CoIII is reduced to CoII in a hypoxic environment, the active molecule is released and restored to its active form to kill cells. Active CoIII complexes studied thus far include those with quinoline,[27] amine,[28] nitrogen mustard,[29,30] marimastat,[31] and curcumin ligands.[32]

Nitrogen mustards are highly toxic due to their DNA alkylation and cross-linking activity. In vivo these agents are not selective for tumor tissue; however, they can be deactivated by coordination to CoIII and released on reduction to CoII in hypoxic tumor tissue, thereby reducing systemic toxicity.[33] The CoIII mustard complex [Co(Meacac)2(DCE)]+ [Figure 1a, Meacac = 3-methyl acrylamide, DCE = N,N-bis(2-chloroethyl)ethylenediamine] is 20 times more active against hypoxic cancer cells rather than normoxic cells.[34] For a series of Co Meacac complexes, the redox potential has been shown to be of importance for hypoxic selectivity. Recently, Hambley et al. reported a CoIII complex that releases a curcumin ligand upon reduction in a hypoxic environment (Figure 1b).[35] This curcumin-containing CoIII complex exhibits selective cytotoxicity to cancer cells over non-tumorigenic cells.

FeIII Complexes

Iron(III) complexes with salen/salphen ligands and their derivatives have been extensively explored for anticancer activity.[35–37] Iron–salen/salphen complexes[36] having phenolato donors induce tumor-selective apoptosis and cytotoxicity toward cisplatin-resistant cancer cells due to FeIII/Feh Chen and salen/salphen-substituted ligands. Mandal and co-workers have described a water-soluble FeIII-salen that cleaves DNA/RNA in vitro under a reducing environment and induces apoptosis in human cells via a mitochondrial pathway (Figure 2a).[35,36] Lange et al. and Lee et al. have explored the potential of FeIII-salophene complexes for ovarian cancer therapy and leukemia, respectively.[37]

PtIV Complexes

Platinum anticancer drugs (e.g. cisplatin, cis-[PtCl2(NH3)2]) are the most important antitumor agents currently available in the clinic, and they have proved to be highly effective towards a variety of solid tumors.[40] However, severe side-effects as intrinsic or acquired drug resistance limit the applications of PtII complexes.[42] To address these drawbacks, a number of novel strategies are being explored, including PtIV prodrugs.[43] The administration of non-toxic PtIV prodrugs that can be activated selectively by reduction at tumor sites might reduce unwanted reactions with biomolecules and thus minimize the undesired side-effects. Potential agents for PtIV reduction in cancer cells include glutathione (PtIV + 2GSH → PtII + GSSG + 2H+),[44] ascorbate (vitamin C), NAD(P)H, and cysteine-containing proteins.[45] GSH is abundant inside cells (0.5–10 mM) as a reductant of PtIV complexes, but it can also coordinate to and deactivate the active PtII species.

So far, four octahedral PtIV prodrugs have entered clinical trials, namely, tetraplatin, iproplatin, satraplatin, and LA-12 (Figure 3a–d).[46] However, LA-12 failed in phase I trials, and tetraplatin could not be investigated further after phase I due to high neurotoxicity. Iproplatin had limited success in phase II trials. The first orally available Pt drug candidate, satraplatin, was abandoned recently in phase III trials.[46] The lower efficacy of these PtIV prodrugs with respect to that of cisplatin, together with variability in drug uptake and side-effects, has meant that these PtIV prodrugs have not yet been approved for clinical use. Thus, there is a need to explore other novel PtIV prodrugs with high anticancer efficacy, high cell uptake efficiency, and sensitivity to reduction.
These prodrugs kill hormone-dependent, cisplatin-cross-link-triggered apoptosis for cancer “immuno-chemotherapy”. Therefore, tryptophan conjugates for combined immunomodulation and DNA cross-link-triggered apoptosis for cancer “immuno-chemotherapy”.

Lippard et al. have investigated a variety of PtIV prodrug approaches,[47] for example PtIV-(D)-1-methyltryptophan conjugates (Figure 3e, f), for combined immunomodulation and DNA cross-link-triggered apoptosis for cancer “immuno-chemotherapy”.[48] These prodrugs kill hormone-dependent, cisplatin-resistant, human ovarian cancer cells effectively, inhibiting indoleamine-2,3-dioxygenase (IDO) by transcriptional deregulation of the autocrine-signaling loop IDO-AHR-IL6. IDO is an immunosuppressive enzyme found in human tumors, and it is involved in immune evasion and tumor tolerance. These compounds are the first Pt drug candidates with immune checkpoint blockade properties that induce kynurenine production and promote T-cell proliferation. They have low toxicity in mice and are stable in blood.

Photoactivatable PtIV-azide prodrugs, such as trans,trans,trans-[Pt(N3)2(OH)(OCOCH2CH2-Py)] and [Pt(N3)2(OH)2(Py)2] (Figure 4a, b),[49,50] upon irradiation with light, can be selectively activated to be-come potently cytotoxic toward a number of cancer cell lines. Perhaps surprisingly, in view of the role of amine NH groups in stabilizing DNA adducts of PtIII ammine anticancer complexes, replacing one or two NH3 ligands with pyridine (Py) in [Pt(N3)2(OH)(NH3)2] leads to higher photocytotoxicity and visible-light activation. Trans-[Pt(N3)2(OH)2(NH3)(Py)] forms trans-G adducts both with model G derivatives and with plasmid DNA. Moreover, DNA–protein cross-links also form readily, and DNA repair synthesis on plasmid DNA platinitated by photoactivated [Pt(N3)2(OH)2(NH3)(Py)] is markedly lower than that for trans-platin.

The complex trans,trans-[Pt(N3)2(OH)2(py)2]2, conjugated to a cyclic peptide containing the RGD sequence (–Arg–Gly–Asp–) (Figure 4c), is selectively recognized by αVβ3 and αVβ5 integrins.[51] Upon visible-light irradiation, phototoxocity is induced preferentially in SK-MEL-28 melanoma cancer cells over-expressing αVβ3 integrin compared to that in control DU-145 human prostate carcinoma cells. Photoactivation of the platinum–guanidinoneomycin conjugate (Figure 4d) in the presence of 5′-guanosine monophosphate (5′-GMP) leads to the formation of trans-[Pt(N3)2(py)2(5′-GMP)]+, as does the photoactivation of the parent platinum(IV) complex. Binding of the PtIV photo-product (PtN3(py)2)3+ to guanine nucleobases in a short, single-stranded oligonucleotide is also observed.[52] This provides a novel approach to visible-light-driven dual control of cancer selectivity and drug release. Moreover, the released active trans-Pt complexes have a different anticancer spectrum from that of cisplatin. Recently, the nitroxide spin-labelled photoactivatable PtIV prodrug trans,trans,trans-[Pt(N3)2(OH)(OCOCH2CH2-CONH-TEMPO)(Py)2](Pt-TEMPO, TEMPO = 2,2,6,6-tetramethylpiperidine 1-oxyl) (Figure 4e) has been reported, which is activated by photoreduction.[53] Irradiation with blue visible light gives rise to PtIV and azidyl as well as nitroxyl radicals. Pt-TEMPO exhibited low toxicity in the dark, and on photoactivation, it was as active as the clinical photosensitizer chlorpromazine and more active than cisplatin toward human ovarian cancer cells under the same conditions. The anticancer activity of Pt-TEMPO may be the result of attack on DNA as well as the activity of the reactive azidyl and TEMPO radicals. The complex might be suitable for the treatment of surface cancers such as bladder and oesophageal cancers.

**Ru(III/II) Complexes**

Three RuIII coordination compounds have entered clinical trials: [InH][trans-RuCl4(DMSO)Im] (NAMI-A, Im = imidazole), [InH][trans-RuCl4In2] (KP1019, In = indazole), and NKP-1339 (the sodium salt of KP1019) (Figure 5a–c).[54] The first Ru-based anticancer drug candidate in clinical trials was NAMI-A, followed by KP1019 in 2003. Both successfully completed phase I, but NAMI-A has recently been withdrawn from the clinic after phase II because of unconvincing efficacy; the likelihood of further clinical studies of NAMI-A is uncertain.[55,56] These RuIII complexes may be activated in vivo by reduction to RuII. The RuIII/RuII redox potentials of KP1019 and NAMI-A in 0.20 M phosphate buffer at pH 7.0 are 0.03 and 0.25 V vs. NHE, respectively,[57] almost unaffected by the buffer system used, and physiologically accessible by intra- and extracellular reducing agents (e.g., glutathione, \( E^{0} = -0.25 \) V or ascorbic acid, \( E^{0} = +0.06 \) V vs. NHE).
at pH 7.0), as well as some proteins. Thus the complexes can readily undergo reduction in biological systems.

Organoruthenium(II) complexes, such as \([\text{Ru(η}^6\text{-bip})(en)\text{Cl}]^+\) (RM175)\(^\text{[59]}\) and RAPTA-C,\(^\text{[60]}\) have promising anticancer activity (Figure 5d, e). Interestingly, although RM175 reacts with the thiol in GSH to form \([\text{Ru(η}^6\text{-bip})(en)\text{SG}]^+\), this is not the end product. Oxygen addition to the bound thiolate sulfur easily affords the sulfenate complex \([\text{Ru(η}^6\text{-bip})(en)(\text{S(O)G})]^+\). Further oxidation can take place to give the sulfinate adduct \([\text{Ru(η}^6\text{-bip})(en)(\text{S(O)2G})]^+\).\(^\text{[61]}\) Unlike the behavior of PtII drugs, such binding to GSH, when followed by oxidation, promotes binding to guanine in DNA. Displacement of the sulfenate ligand by guanine N7 provides a redox-mediated pathway to DNA binding for these arene–RuII–diamine complexes.\(^\text{[62]}\)

[IrIII Complexes](#)

Iridium complexes have attracted much recent attention in a wide range of areas, especially catalysis. Organoiridium(III) complexes have interesting biological (e.g. as luminescent probes),\(^\text{[65]}\) and anticancer applications.\(^\text{[66]}\)

Unlike RuII and OsII, it is not possible to stabilize IrIII with an arene ligand, and instead cyclopentadienyl and preferably pentamethylcycopentadienyl ligands are used. A range of organometallic IrIII cyclopentadienyl complexes of the type \([\text{(η}^5\text{-Cpx})\text{Ir(L L)Z}]^0/\text{+}\) {where Cpx = Cp*, Cpxph (phenyltetramethylcyclopentadienyl) or Cpxxbiph (biphenyltetramethylcyclopentadienyl), L L = bidentate ligand with nitrogen and/or carbon donor atoms, Z = Cl or py} have been synthesized and characterized as potential anticancer agents (Figure 6).\(^\text{[67–69]}\) There are effective strategies for switching on and/or controlling the anticancer activity, involving modifications to the three ligands. In the phen/Cl series (Figure 6a), addition of phenyl substituents to the Cp* ring markedly increases the potency. In the bpy series, replacement of a chelated N by isoelectronic C causes a dramatic increase in activity (Figure 6b), and further addition of a biphenyl substituent and replacement of Cl by pyridine achieves nanomolar activity (IC50 = 100 nM; Figure 6c).\(^\text{[70]}\)

Facile conversion of coenzyme NADH to NAD\(^+\) can be achieved through hydride transfer using IrIII Cp* complexes.\(^\text{[71]}\) Hydride transfer from NADH results in the formation of Ir–H species (\(^1\text{H NMR Ir–H peak at ca. 15 ppm})\). The hydride can further be transferred to oxygen to generate \(\text{H}_2\text{O}_2\).\(^\text{[72]}\) Thus it is possible to perturb the intracellular ratio of NADH/NAD\(^+\) as well...
as carry out reductions which might normally be achieved by enzymes, such as the conversion of pyruvate to lactate (lactate dehydrogenase). These organoiridium complexes can have potent antiproliferative activity towards a wide range of cancer cells and will provide a means of probing NADH-mediated cell signaling pathways and coupling hydrogenations to biological processes.

**Os**II Complexes

In general, the redox activity of Os**II** complexes is associated with the formation of ROS in cells and, as in the case of Ru complexes, might lead to activation in the reductive environment of tumors.[73,74] Changing the arene from p-cymene to biphenyl and the monodentate ligand from chloride to iodide in the library of Os**II** complexes of the formula [Os(η⁶-arene)-(L)]⁺ {L = azopyridine derivatives (Azpy-R) or iminopyridine N,N-chelators, X = Cl or I, arene = p-cymene or biphenyl} results in a significant increase in anticancer activity (Figure 7).[75–79] Azopyridine Os**II** complexes with electron-donating substituents on the phenyl ring (e.g. OH or NMe₂) or electron-withdrawing groups on the pyridine ring (e.g. F, Cl, Br or I) are an order of magnitude more active than their unsubstituted analogs. This might be related to the involvement of redox processes associated with the azo group[74,75] (e.g. reductive attack by glutathione[80]). Notably, [Os(η⁶-biphenyl)(Azpy-NMe₂)]PF₆ (Figure 7a, R = NMe₂, X = I) has more than ten times higher anticancer potency than cisplatin (CDDP) against the kinds of tested cancer cell lines.

![Figure 7. Organometallic Os**II** anticancer complexes [Os(η⁶-arene)-(L)]⁺ {L = azopyridine derivatives (Azpy-R) or iminopyridine N,N-chelators, X = Cl or I; (a) arene = biphenyl, (b) arene = p-cymene}.](image)

FY26 (Figure 7b, R = NMe₂, X = I, Y = N) is highly active towards cancer cell lines[76,77] in particular, it exhibits submicromolar activity in A2780 ovarian, MCF7 breast, A549 lung, and HCT116 colon cancer cell lines. FY26 is more potent than cisplatin in the NCI-60 cell line screen (the average GI50 value is 0.28 μM for FY26 but 10.3 μM for cisplatin) as well as in the 809-member library of Os**II** complexes of the formula [Os(η⁶-arene)-(L)]⁺ {L = azopyridine derivatives (Azpy-R) or iminopyridine N,N-chelators, X = Cl or I, arene = p-cymene or biphenyl} results in a significant increase in anticancer activity (Figure 7).[75–79] Azopyridine Os**II** complexes with electron-donating substituents on the phenyl ring (e.g. OH or NMe₂) or electron-withdrawing groups on the pyridine ring (e.g. F, Cl, Br or I) are an order of magnitude more active than their unsubstituted analogs. This might be related to the involvement of redox processes associated with the azo group[74,75] (e.g. reductive attack by glutathione[80]). Notably, [Os(η⁶-biphenyl)(Azpy-NMe₂)]PF₆ (Figure 7a, R = NMe₂, X = I) has more than ten times higher anticancer potency than cisplatin (CDDP) against the kinds of tested cancer cell lines.

**Perspectives**

The development of resistance is a major clinical problem with current anticancer drugs, including platinum compounds. Multi-targeting by metallodrugs, or by metallodrugs in combination with clinical drugs, might provide a strategy to address this problem. In particular, the redox balance in cancer cells and the difference in the ability of cancer cells to cope with changes in the levels of redox-active species such as ROS, provides a means for selective attack on cancer cells. The unique ability of metal complexes to undergo redox activation processes involving both metal and ligand redox centers that can be tuned to specific potentials should provide them with the novel mechanisms of action required to overcome resistance. Further research in this field is now required to investigate these new possibilities for drug design.

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Redox reactions in the reducing environment of cancer cells can activate metal complexes so as to deliver bioactive ligands or modulate the redox state of cancer cells. Such redox activation strategies can provide novel mechanisms of action that increase drug selectivity and combat resistance.

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