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HIGHLIGHT

Ir(III) and Ru(II) Complexes in Photoredox Catalysis and Photodynamic Therapy: A New Paradigm Towards Anti-cancer Applications

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Abstract: Individually, photoredox catalysis (PC) and photodynamic therapy (PDT) are well-established concepts that have experienced a remarkable resurgence over past years, leading to significant progress in organic synthesis for PC and clinical approval of anticancer drugs for PDT, respectively. But, very recently, new photoredox catalyst systems based on Ir(III) and Ru(II) complexes have garnered significant interest in cancer cells that can simultaneously be used as PDT agents apart from their demonstrated PC activity. This highlight discusses the unique PC behavior of emerging Ir(III) and Ru(II) based systems while also examining their potential PDT activity in cancer treatment.

Light-driven catalysis is an impactful transformative strategy that draws divergent applications in environmental remediation, plastics recycling, and energy.[1] Inspired by human biology, wherein biochemical processes are mediated via enzymes and biocatalysts, scientists are re-visiting this field to tackle one of humanity’s serious challenges: cancer.[2] In recent years, photodynamic therapy (PDT) and photoredox catalysis (PC) have demonstrated promising results in anticancer treatment in-vitro and in-vivo environments (Scheme 1). PDT, a non-invasive technique that uses an organic photosensitizer that transfers energy from irradiation of light to molecular oxygen in the tissues to generate the highly toxic reactive oxygen species (ROS), which kills cancer cells either by the type I/II mechanism of action.[3] Whereas in photoredox catalysis, direct electron transfer involves between the substrate and light irradiated excited state catalysts (Ru(II), Ir(III) complexes, for instance), which is later utilized in reaction with other biomolecules subsequently.[4] Presently, Ru(II) and Ir(III) based metal complexes offer a clear advantage over organic photosensitizers by being photo-stable, having a long excited-state lifetime that positively impacts the singlet oxygen generation, and killing the tumor cells even under hypoxic conditions. Major Ru(II) polypyridine complexes are activated via UV-A or blue irradiation to derive PDT effects, but the critical limitation, in this case, is the penetration depth in the tissues. This limits the possibility of tackling deep-seated or large tumors. Gasser and co-workers recently circumvented this bottleneck for the first time by using an in-silico guided search for ideal PDT PSs with a spectral redshift in the biological spectral window.[5] In this study, they were able to design a clinically relevant, selective phototoxic Ru(II) polypyridyl complex, which upon irradiation with 595 nm, led to perturbation of glycolysis and mitochondrial respiration in 2D monolayer cells as well as 3D multicellular tumor spheroids. In another work, Chao, Gasser, and co-workers used a similar approach to obtain Ru(II) (E,E)-4,4′-bisstyryl-2,2′-bipyridine complexes capable of showing the highest 1- and 2-Photon absorption so far. While these were non-toxic under dark, phototoxicity in 2D monolayer cells and 3D multicellular tumor spheroids was observed. Further, this complex was able to eradicate multi-resistant tumors inside the mouse model. Similarly, in Ir(III) based complexes, the structural accessibility aids in enhancing its emission in a broader range of wavelength mainly due to its access to more excited-state electronic configurations, making it a suitable PDT candidate.[4] In a recently published article, Ir(III) complex bearing distyryl boron dipyrromethene (BODIPY-Ir) strongly absorbed at 550-750 nm amplified the light-to-ROS/heat conversions and promoted singlet oxygen generation and photothermal effect with almost negligible phototoxicity in 2D monolayer cells and 3D multicellular tumor spheroids. In 2019, Sadler, Chao, Gasser and co-authors reported novel, highly oxidative and robust Ir(III) based catalyst [Ir(ttpy)(pq)Cl]PF6 against 4T1 breast cancer cells.[6]

The growing interest in developing new photoredox catalyst systems, especially in Ir(III) and Ru(II) based systems, has yielded complexes that can be simultaneously used as PDT agents apart from their PC activity in cancer cells. Here in the present manuscript highlighted the recently reported literatures based on the emerging use of metal (Ir(III) and Ru(II)) complexes as photoredox catalysis and new approaches in PDT.

Visible Light (400-700 nm)

Scheme 1. Schematic representation of transition metal complexes in photodynamic therapy (PDT) and photoredox catalysis (PC).

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Density plots of 5′-d2, photosensitization occurred under light irradiation, and decreased ATP concentration when in hypoxia conditions, suggesting a different photocatalysis mechanism. Zhou and co-authors reported one of the first Ru(II) complex applications in photoredox catalysis and PDT in human ovarian cancer cells SKOV-3 under hypoxia with a 470 nm LED light source (Fig. 1c). They integrated chloromethyl groups into [Ru(II)(bpy)]2+ (bpy = 2,2’-bipyridine), which served a dual purpose of being a light harvester and carbon radical generator. Lipophilic Ru(II) cationic complexes accumulated in mitochondria while chloromethyl incorporation aided in mitochondria targeting ability. In this work, photosensitization occurred via a type I mechanism wherein carbon radicals led to DNA damage in an Anorgan atmosphere and cancer cells apoptosis. Density plots of SKOV-3 treated with 3 µM in the dark showed 96.01 % cells alive while with 30 min of irradiation under hypoxia, the apoptotic population increased to 21.15 %. NADH depletion was not observed under dark; however, cellular NADH decreased gradually with a concentration dependence with irradiation.

Under similar conditions, the clinical pro-drug 5-ALA, a precursor of the photosensitizer protoporphyrin, was inactive under hypoxia under light irradiation. Under Normoxia complex showed reduced Photocytotoxicity in the presence of singlet oxygen scavengers (Na2S2O4, d-maninito) for A549 cells. The reactive oxygen species (ROS) inhibitors had no adverse effect on photocytotoxicity under hypoxia conditions, suggesting a different photocatalysis mechanism. NADH concentration was unaffected under normoxia when the complex was used in A549 cells in dark conditions. However, it showed a dramatic decrease in NADH concentration under light irradiation, and decreased ATP concentration was observed. Later, Huang and co-authors demonstrated a group of Ir(III) photocatalyst for PDT and photoredox catalysis for cancer therapy in in-vitro and in-vivo models (Fig. 1b). The biocompatible, water-soluble [[Ir(CO)3(bpy)(CH2(N(CH3)2)])PF6]3 (CO6 = coumarin 6; bpyCH2N(CH3)2 = 4,4′-bis(N,N,N-trimethylmethanaminium)-2,2'-bipyridine)) and exhibited dormancy to normal cell lines under dark while selective photocytotoxicity towards cisplatin and sorafenib-resistant cell lines. The above catalyst remained biocompatible with non-tumorigenic LO2, 293T, and NP69 cell lines in the dark, while against CNE-2Z, HepG2-SR, HepG2, A549, and AP549R cancer cells, it didn’t exhibit any toxicity up to 200 µM in the dark. However, it was highly photo-cytotoxic at the half-maximal inhibitory concentration (IC50) as low as 5 µM with a photo-cytotoxic index of 40-172. The main mechanism of action was a combination of a single electron transfer (SET) pathway and photosensitization. It is well known that concentration alteration in NADPH/NADH leads to intracellular redox homeostasis and changes in electron transport in mitochondria leading to cell death. In this work, EPR studies indicated the formation of NADPH+ by the catalyst in PBS/methanol mixture when photo-irradiated with 465 nm for 10 min in the presence of NADPH. Due to this irradiation, H2O2 was also detected by H2O2 test paper indicative of superoxide anion conversion to peroxide. Significant alteration in mitochondrial membrane potential was also observed with the catalyst after photo-irradiation with model cancer cell line CNE-2Z that verifies the mechanism of action proposed. In-vivo zebrafish and mouse cancer models demonstrated excellent biocompatibility and anticancer efficiency of the Ir(III) catalyst.

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In a just-published article by the same research group, red-light triggered anticancer response was achieved in A549, A549/DDP (cisplatin-resistant A549), and SKOV-3 cell lines with a nitroanthraquinone group attached Ru(II) bis (2,2′-biquinoline) complex (Fig. 1d). Upon irradiation, the Ru (III) and anthraquinone anion centers are generated, which can oxidize NADH/NADPH and generate O2− radicals that elicit PDT and photoredox catalysis. In addition to this, the complex also exhibits an activated chemotherapeutic (PACT) when internalized inside tumor cells wherein by using irradiation spatiotemporally, a non-toxic pro-drug can be transformed into an anticancer agent within. While PDT and photoredox are oxygen dependent, PACT is oxygen-independent. Further, even if the study had been carried out at 600 nm, the phototherapeutic action can be observed from 600-900 nm. Upon irradiation for 30 min, the IC50 was 1 µM against A549 and SKOV-3, while the photo-cytotoxicity against A549/DDP was close to 0.96 µM. Under hypoxic conditions for A549 cells, the IC50 was 6.5 µM which has been ascribed as the PACT contribution.

Tweaking the structure in emerging PC complexes for anticancer application, additional PDT effect has been observed for organometallic Ir(III) and Ru (II) systems. This allows to circumvent key drawbacks associated with PDT anticancer complex and can open new fronts in anticancer treatment wherein a specific wavelength of light elicits triggered response to cancerous cells while being non-cytotoxic to other cell lines. Further, the possible in-vivo response of these complexes is also promising. Complexes that can exhibit photocytotoxicity in visible and near-visible wavelengths and with a shorter duration can be a new way forward in this research. Further, it will also be critical to study the fate of these complexes’ post-cancer response to envision translational clinical trials in the future.
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Keywords: Ir(III) and Ru(II) complexes • Photodynamic therapy • Photoredox catalysis • Anticancer treatment


This highlight covers the recent works on light triggered Ir (III) and Ru (II) based organometallic complexes that elicit selective in vitro and in vivo responses to cancerous cells while being non-toxic to normal cells via photodynamic therapy (PDT) and photoredox catalysis (PC). It indicates promising avenues in translational research for cancer treatment via examining stable transition metal complexes that envision clinical trials in the future.

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