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Review

Harnessing ruthenium(II) as photodynamic agents: Encouraging advances in cancer therapy

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ABSTRACT

Despite their past triumphs, platinum-based therapeutics remain limited by chemo-resistance and severe side effects. As an alternative therapeutic modality which bypasses these issues, photodynamic therapy (PDT) holds great promise. The first FDA approved PDT agent, Photofrin, stimulated an outpouring of porphyrin-motif studies, while metallodrugs have long been underappreciated in this area. Due to their unique and versatile properties, ruthenium complexes are receiving increasing attention in the field of PDT. Herein, we introduce the recent advances in Ru(II)-based PDT agents ranging from single molecules to delicate nanomaterials, how these agents are unique suited to PDT and the merits provided by their various forms.

Contents

Abbreviations: BODIPY, 4-bora-3a,4a-diaza-s-indacene; bpy, 2,2′-bipyridine; dFppy, 4,6-difluorophenylpyridine; dmb, 4,4′-dimethyl-2,2′-bipyridine; dmeb, 4,4′-dimethylester-2,2′-bipyridine; dmphen, 2,9-dimethyl-1,10-phenanthroline; dpb, 2,3-bis(2-pyridyl)benzoquinoxaline; dpp, 2,3-bis(2-pyridyl)pyrazine; dppn, benzo[i]dipyrido-[3,2-a:2′,3′-c]phenazine; dppz, dipyrido[3,2-a:2′3′-c]phenazine; dtbb, 4,4′-di-*t*-butyl-2,2′-bipyridine; dtp, dipyrido[3,2-a:2′,3′-c][1,2,5]thiadiazolo[3,3,4]phenazine; H_2TPP, tetraphenylporphyrin; ippy, 2-(1-pyrenyl)-1H-imidazo[4,5-*f*][1,10]phenanthroline; mpdppz, 3-methylpyrazino[2,3-h]dipyrido[3,2-a:2′,3′-c]phenazine; pbbs, (1,10-phenanthroline-4,7-diyl)bis(benzenesulfonate); pdppz, pyrazino[2,3-h]dipyrido[3,2-a:2′,3′-c]phenazine; phen, 1,10-Phenanthroline; PIP, 2-phenyl-1H-imidazo[4,5-f][1,10]phenanthroline; py-R, 4-substituted pyridine; TAP, 1,4,5,8-tetraazaphenanthrene; TPP, triphenylphosphine; tpy, 2,2′:6′,2″-terpyridine.

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1. Introduction

Cancer has long been one of the world's deadliest diseases. Currently, the main cancer treatments used clinically include invasive surgery, radiotherapy and chemotherapy. However, invasive surgery may facilitate cancer metastasis, radiotherapy is likely to induce radiation poisoning and runs the risk of forming secondary neoplasm and chemotherapy can cause severe systemic toxicity originating from a lack of selectivity and often gives rise to chemo-resistance in tumors. These sobering facts have prompted continuous efforts towards actualizing novel treatment platforms with minimally invasive operations, high selectivity and low adverse side effects to obviate the above drawbacks.

Photodynamic therapy (PDT), an emerging clinical modality dealing with light-matter interactions [1], has evolved as a promising therapeutic regimen for the management of localized cancers [2], such as cancers of the skin, oesophagus, lung, and bladder, etc [3–6], and non-malignant diseases, such as fungal strains, atherosclerosis, bacterial infection, and viral infection, etc [7–13]. In principle, PDT involves the interactions of three individually non-toxic components, i.e., a photosensitizer (PS), light (of an appropriate wavelength) and oxygen (O_2). Specifically, the PS is activated to the triplet excited state which subsequently returns to the ground state and releases energy to excite oxygen into reactive oxygen species (ROS) which rapidly cause cell death by apoptosis or necrosis. The anti-tumor effect of PDT is realized primarily by three mechanisms [2]: direct damage to cancer cells, lesions on tumor-associated vasculature which leads to tumor infraction, and a subsequent inflammatory response which gives rise to systemic immunity. Since the half-life and diffusion radius of ROS are very limited, PDT exerts immediate efficacy only in the vicinity of the PS. Using a fiber-optic device the non-toxic PS can be converted into a potent anti-tumor drug with spatiotemporal selectivity, profoundly lowering the adverse side effects associated with cancer therapy. Moreover, PDT's efficacy in the treatment of tumours is not inhibited by radio- or chemo-resistance [2]. Despite possessing these advantages over conventional cancer therapies, PDT has remained underappreciated since it was first developed as a treatment over 100 years ago. It was not until the 1990s when the first clinically available PS was approved by the FDA that interest in PDT has been rekindled, sparking tremendous research efforts in the area of cancer therapeutics [14,15]. It remains a great challenge to design a PS that exhibits [16]: (i) a proper retention time; (ii) robust anti-bleaching properties; (iii) a low dark toxicity; (iv) a high extinction coefficient, especially in the therapeutic window between 700–900 nm [17]; (v) favorable bioavailability. In addition to the challenges of biocompatibility and PS performance, clinical PDT must overcome the problems that arise when attempting the simultaneous assembly of its three fundamental components in a tumor. Light intensity fades dramatically when penetrating thick tissues to deeply embedded tumors [18]; a shortage of oxygen arises due to the unsound neovasculature within the tumor (and is exacerbated by PDT itself) [14]; poor bioavailability and tumor-specific selectivity requires a higher PS dosage to maintain efficacy which elevates the systemic toxicity [19]. To fulfill the PS capability in PDT application, studies aiming at resolving the problems above have already been launched.

Most currently available PSs for clinical use are based on tetrapyrrole structures [2], which are often plagued by issues with solubility, stability, pharmacokinetics, and penetration depth, etc [16]. In contrast, metal-based drugs, especially some Ru(II) complexes, which remain underutilized in PDT, have revealed an astonishing range of biological applications, with great potential in the field of cancer therapeutics [20–27].

The biological activity of some Ru(II) complexes has long been established [28–30]. Unlike planar cisplatin, Ru(II) complexes are d^6 hexa-coordinated octahedral architectures with a 3D arrangement of ligands, which dramatically enriches their potential for modification. The judicious selection of ligands can shape Ru(II) complexes with various activities including solubility, cellular uptake level, targeting ability, photo-stability, photophysical properties, and ROS yield, etc [31–36]. The pioneering biological trials of Ru (II) complexes initiated by Dwyer et al. in 1952 [37–39] have fostered an increasing number of studies on Ru(II)-based anticancer drugs. NAMI-A, as the first approved Ru(II) complex in clinical trials, was found to be effective in inhibiting tumor metastasis. However, the clinical trials on NAMI-A were terminated due to its low therapeutic efficacy and the progression of disease in clinical studies [22]. KP1019 and its better soluble salt KP1339 are undergoing clinical trials [40–42]. Interestingly, Ru(II) complexes have been found to be easily excreted by living organisms which is beneficial for *in vivo* testing [43–45]. In terms of biological applications, Ru(II) complexes have been concentrated in the fields of interactions with DNA, lately cellular imaging and therapeutics [46–48]. However, their extraordinary photosensitizing properties combined with their aforementioned appealing characteristics has brought them great attention in the arena of PDT. In addition, many coordinatively saturated and substitutionally inert Ru(II) complexes have shown superior photostability compared to organic compounds. Indeed, an inert Ru(II) polypyridyl complex, TLD1433, developed by McFarland et al. has reached phase IB clinical trials for PDT treatment of bladder carcinoma. Therefore, studies on Ru(II)-based PSs can potentially make a great contribution to the development of PDT. In this review, we primarily focus on the progress made since 2010, and emphasize the issues resolved by the emerging field of Ru(II)-based PSs in PDT. We hope that this overview, from molecules to nanomaterials, will provide the readers a comprehensive perspective of the roles played by Ru(II) in PDT to date, and inspire researchers in their future Ru(II)-based PS development.

2. Classification of PDT

PDT is classified into two types (type I and type II) according to the deactivation pathway of the triplet excited PS. The excited PS can directly interact with oxygen by energy transfer producing singlet oxygen ($^1O_2$, type II). Alternatively, the excited PS releases its energy through an electron transfer process with the participation of a substrate, such as the cell membrane or a molecule, forming radicals which ultimately react with oxygen to generate ROS (type I) [14,49,50]. Also, some frontier studies reckoned that analogous type I processes might involve a reaction with water yielding toxic radicals, such as hydroxyl radicals and superoxide anions, which substantially reduces the oxygen dependence of PDT [51–53]. Type II is mechanistically much simpler than type I, and is considered to be the predominant mechanism for most PSs.

3. Ru(II) in simple molecular complexes

3.1. Tuning PS performance

Simple complexes are the most extensively studied form of PS. By manipulating their properties of the complex such as the hydrophilicity, charge distribution or steric hindrance, the cellular uptake efficiency, intracellular localization, or even toxicity mechanism of Ru(II) complexes can be altered [31–34,54–57], all of which affect the PDT efficacy. Glazer et al. [33] compared two structurally similar homoleptic Ru(II) polypyridyl complexes, $[Ru(dip)_3]^{2+}$ and $[Ru(pbbs)_3]^{4-}$ (**1**–**2**, Ref. [26], Fig. 1), with different charges and corresponding hydrophilicities. They found that these two complexes exhibited divergent physical properties and