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Review

Interactions between proteins and Ru compounds of medicinal interest: A structural perspective

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ABSTRACT

Ruthenium compounds have unique physicochemical properties that can be efficiently exploited in medicinal chemistry. These molecules can act using both DNA or enzymes as target. The molecular bases that govern DNA versus protein binding selectivity are not known, but a number of investigations has allowed one to obtain significant information on these recognition processes. Here we review some relevant crystallographic studies focused on the characterization of the interaction between proteins and selected ruthenium compounds of medicinal interest. Details of the interactions between Ru compounds and protein residues are described and the reactivity of the compounds towards different targets is compared with that observed analyzing analogous Pt-based drugs-protein adducts. Data provide important information that can be useful to a deeper understanding of the mechanism of actions of the analyzed compounds.

Contents

1. Introduction

Metals compounds are effective for the treatment of a variety of human diseases [1–3]. The Pt(II) compound *cis*-[Pt(NH_3)$_2$$Cl_2$], also known as cisplatin (Fig. 1), is currently the most widely used chemotherapeutic agent [4]. This molecule is active on many solid tumors, including testicular and ovarian carcinomas, lymphoma, melanoma and neuroblastoma [5]. The cytotoxicity of this drug and of its second generation derivatives carboplatin and oxaliplatin (Fig. 1) seems to be due to the formation of DNA lesions at the double-helix level that interfere with transcription, resulting in cellular apoptosis. A crucial role in this process is played by reactive Pt species that form upon hydrolysis [6].

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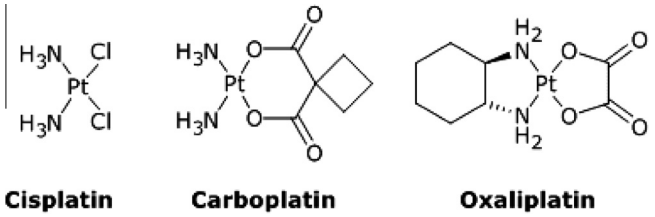

Fig. 1. Structure of cisplatin, carboplatin and oxaliplatin.

Despite their successful applications in clinics, cisplatin, carboplatin, oxaliplatin and the other Pt(II) compounds developed in the last few years are of limited efficacy, since they show severe toxicity and are associated with intrinsic or acquired resistance. This is probably due to the small size and square planar geometry of the Pt species that yield poor discrimination in DNA binding sites, with the forming adducts that are platinated preferentially at the most solvent-accessible guanine bases [7,8]. The success of Pt-based drugs on one side and their limitations on the other side prompted the design, synthesis and characterization of novel chemotherapeutic agents based on the use of alternative metal compounds, such as those containing gold, osmium, iridium and ruthenium [9–12]. Among the large number of non-Pt cytotoxic compounds tested as chemotherapeutic agents, those based on ruthenium are promising (for recent reviews see [13–15]), since they

(1) Show a ligand exchange process similar to that of Pt(II) complexes. In this respect, it is useful to recall that ligand exchange kinetics are favorable when compared to rates of cell division [16].
(2) Have the metal centre that can experience different oxidation states under physiological conditions (Ru can easily access the oxidation state +2, +3 and even +4) [17–19]. Thanks to this feature Ru(III) compounds can transform into active Ru(II) species in reducing environment of tumor cells.
(3) Present a higher degree of site selectivity and size discrimination when compared to Pt(II) compounds, thanks to the octahedral geometry of metal coordination sphere [20,21].
(4) Due to the similarity Ru/Fe, they can be transported by iron carrier proteins, like transferrin [17,22], and can accumulate into tumors.

These favorable properties result in low general toxicity and higher selectivity than those exerted by Pt-based drugs against specific cancer cells [23] and could allow one to inject into blood larger doses when compared to Pt-based drugs [24].

The success of *in vitro* and *in vivo* preliminary experiments carried out on several Ru complexes have led to evaluate in clinical trials two ruthenium compounds, containing heterocycles coordinated to the metal centre (Fig. 2): the anti-primary-tumor indazolium(HIn) *trans*-[tetrachloridobis(1H-indazole)ruthenate(III)] (KP1019)[9,25] and its sodium-compensated analogue NKP1339 [26,27], the anti-metastasis imidazolium(HIm) *trans*-[tetrachloride(S-dimethylsulfoxide)(1H-imidazole)ruthenate(III)] (NAMI-A) [11] [28]-developed by Keppler's group in Wien and by Mestroni, Alessio and Sava in Trieste, respectively [23].

Despite these molecules are on average about 10 times less cytotoxic than cisplatin *in vitro*, they show excellent *in vivo* anticancer activity [25]. The mechanism of action responsible for the cytotoxicity of these compounds and their cellular targets are not known.

Experimental data indicate that up to 98% of the total Ru that is administered intravenously is in the blood plasma in a protein-bound form [11,26] and that Ru-based drugs could interact with several protein targets [27,28]. Glutathione S-transferase P1-1 (GST) (which is involved in the detoxification pathway) [29], carrier proteins such as transferrin and albumin (HSA), and proteins/enzymes involved in different cellular pathways, like integrins, matrix metallo-proteinase (MMP)-2 and MMP-9, have been identified as possible final targets [30–34]. On the other hand, it cannot be excluded that DNA could be involved in some way in the mechanism of action of these drugs. Indeed, Ru anticancer agents bind to both DNA and histone components of nucleosome core particles (NCP), which are important constituents of chromatin [35–37].

In recent years, X-ray crystallography in combination with a variety of spectroscopic and spectrometric measurements has been used to unveil details on the interaction of anticancer Ru compounds with proteins and nucleic acids with the aim to obtain information on the mode of action of these potential drugs. The first crystallographic studies on complexes between protein and anticancer Ru compounds were carried out using as model proteins human carbonic anhydrase II (CAnhy) and hen egg white lysozyme

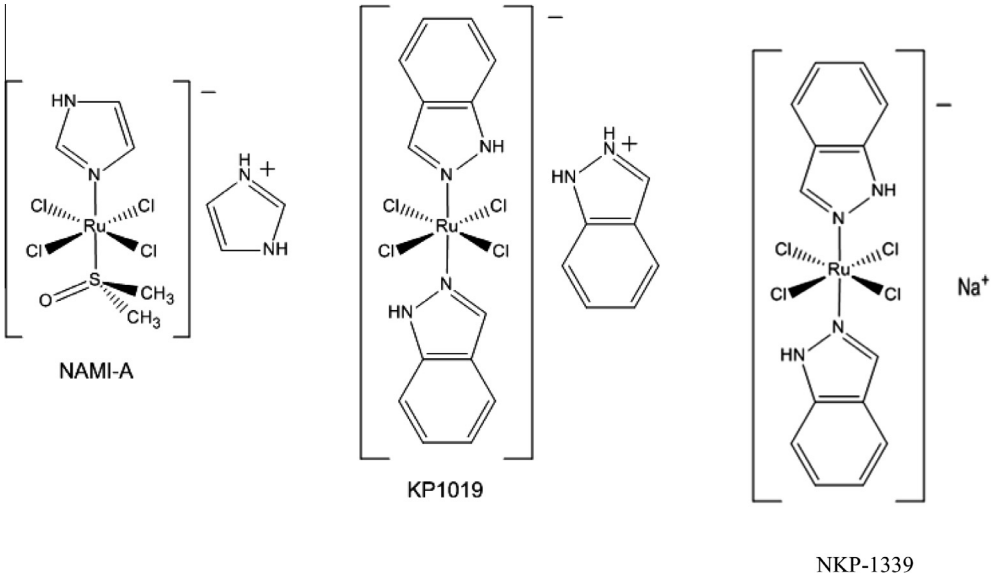

Fig. 2. Structure of NAMI-A, KP1019 and its analogue NKP-1339. These compounds entered clinical trials for cancer treatments.