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Computational metallomics of the anticancer drug cisplatin

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ABSTRACT

Cisplatin, cis-diamminedichlorido-platinum(II), is an important therapeutic tool in the struggle against different tumors, yet it is plagued with the emergence of resistance mechanisms after repeated administrations. This hampers greatly its efficacy. Overcoming resistance problems requires first and foremost an integrated and systematic understanding of the structural determinants and molecular recognition processes involving the drug and its cellular targets. Here we review a strategy that we have followed for the last few years, based on the combination of modern tools from computational chemistry with experimental biophysical methods. Using hybrid Quantum Mechanics/Molecular Mechanics (QM/MM) simulations, validated by spectroscopic experiments (including NMR, and CD), we have worked out for the first time at atomic level the structural determinants in solution of platinated cellular substrates. These include the copper homeostasis proteins Ctr1, Atx1, and ATP7A. All of these proteins have been suggested to influence the pre-target resistance mechanisms. Furthermore, coupling hybrid QM/MM simulations with classical Molecular Dynamics (MD) and free energy calculations, based on force field parameters refined by the so-called "Force Matching" procedure, we have characterized the structural modifications and the free energy landscape associated with the recognition between platinated DNA and the protein HMGB1, belonging to the chromosomal high-mobility group proteins HMGB that inhibit the repair of platinated DNA. This may alleviate issues relative to on-target resistance process. The elucidation of the mechanisms by which tumors are sensitive or refractory to cisplatin may lead to the discovery of prognostic biomarkers. The approach reviewed here could be straightforwardly extended to other metal-based drugs.

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1. Introduction

Physico-chemical properties of molecular and supra-molecular systems, including static and dynamic aspects, are more and more probed by integrated experimental approaches, where the combination of vibrational, electronic, and resonance spectroscopies allows studies under physiological conditions and in a non-invasive way. However, the interpretation and rationalization of structural, energetic, and dynamic features of molecular and supra-molecular systems of current scientific and technologic interest can be difficult due to their inherent complexity. In such a complex scenario, theoretical studies can be extremely helpful in (i) supporting and complementing the experimental results to determine structural and dynamical features of target molecule(s), (ii) dissecting and quantifying the role of different contributors, (iii) calculating molecular and spectroscopic properties for novel/modified systems. For this reason, computational spectroscopy is rapidly evolving from a highly specialized research field into a versatile

and fundamental tool for investigating large molecular systems in complex environment. In this focused review is highlighted the application of computational spectroscopy to the case of antitumoral drug cisplatin.

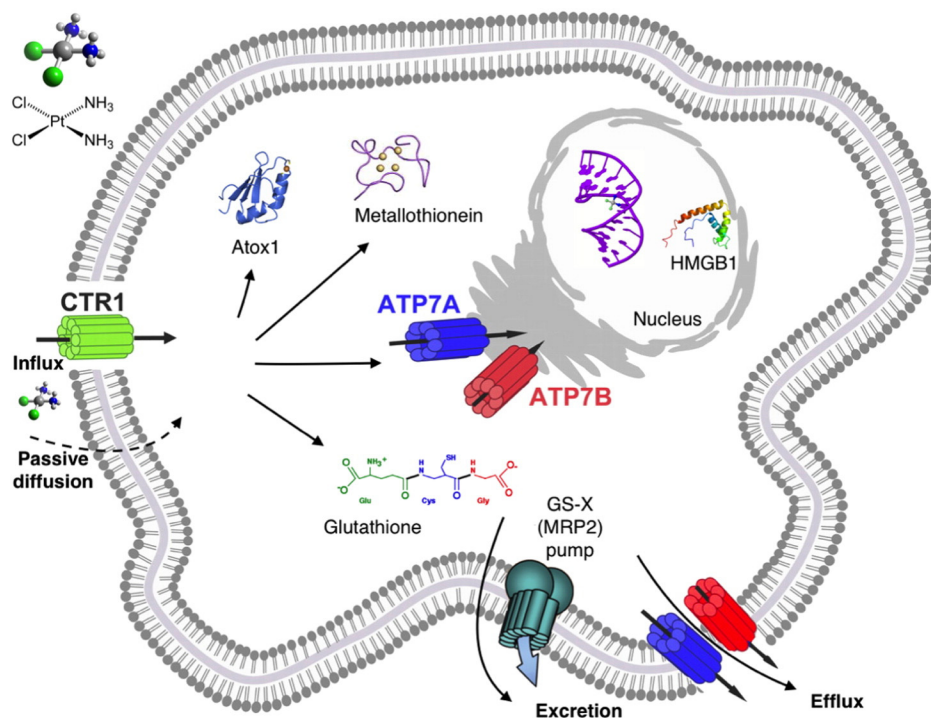
Cisplatin, cis-diamminedichlorido-platinum(II), is one of the most widely used anticancer drugs, especially effective in treating testicular cancer (96% of success cure rate) [1–6]. Its beneficial effect is mainly caused by the formation of covalent adducts with DNA [2,6], forming preferentially (>80%) 1,2-intrastrand cross-links with guanines [2,6,7] that bend DNA. The DNA lesions, in turn, lead to tumor cell apoptosis [7,8].

Despite their success, cisplatin-based therapies suffer from intrinsic and acquired resistance mechanisms appearing after repeated administrations of the drug [1,3,4]. Second- and third-generation drugs encounter basically the same problems [9].

Overcoming resistance problems requires first and foremost an integrated and systematic molecular understanding of a variety of processes (Scheme 1). These include inactivation/efflux (*pre-target resistance*), along with alterations of DNA-cisplatin adducts (uptake and *on-target resistance*), different cellular responses to cisplatin-mediated DNA damage (*post-target resistance*), altered cellular pathways not directly linked with cisplatin-elicited signals (*off-target resistance*) [4,9,19].

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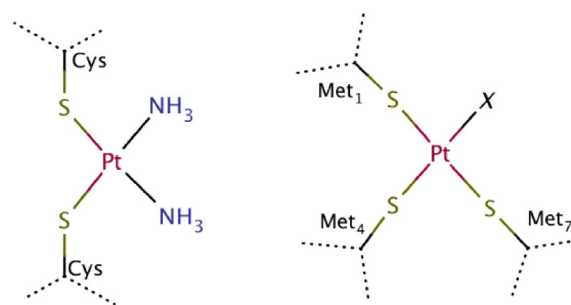
Scheme 1. Simplified scheme of cisplatin's uptake, trafficking and efflux. Cisplatin may enter cells by passive diffusion [10] or using transporters—a significant one being the copper transporter CTR1 [11]. In the cytoplasm, it preferentially reacts with sulfur-containing aminoacids, such as the tripeptide glutathione, metallothioneins [3], or metallochaperones (e.g. Atox1) [12,13]. In the nucleus, proteins such as High-Mobility Group Box proteins 1A (e.g. HMGB1) affect cisplatin's efficacy [14]. The drug can be excreted through the copper exporters ATP7A and ATP7B as well as through the glutathione S-conjugate export GS-X pump [3]. The drug can interact with several other proteins, only a small fraction having been characterized so far [15–17]. Scheme based on Fig. 1 of Wang, et al. 2011, 2, 129–137. [18].

In this respect, the first step is to characterize at structural level the platinated adducts involved in the resistance mechanisms. Detailed structural information can be acquired with time-consuming and, occasionally, challenging multi-dimensional NMR and/or X-ray crystallography studies. For the last years, we have explored a different strategy based on combining biophysical methods, such as mass spectrometry and molecular spectroscopy (including CD, EXAFS, and NMR) with modern tools of hybrid quantum mechanical/molecular mechanical (QM/MM) and enhanced sampling methods [20,21]. The stereochemistry of platinum coordination is dictated by quantum mechanical effects.² Hence, this problem is amenable for hybrid QM/MM simulation in which the platinated region (where the electronic degrees of freedom are relevant) is described by a quantum mechanical electronic structure method. Since the pioneering work of Warshel and Levitt in 1976 [20], a large and ever-growing number of biologically relevant phenomena have been successfully addressed by using mixed QM/MM methods (see for instance ref. [21] for a review). In this focused review, we summarize our recent results on cisplatin's resistance by using Density Functional Theory (DFT)-based hybrid Car–Parrinello Molecular Dynamics/Molecular Mechanics (CPMD/MM) simulations. [13,24,25] Combining CPMD/MM simulations with experimental data, we have provided for the first time the complete 3D structures of the adducts between cisplatin and some of the cellular substrates related to resistance mechanisms [26–28], such as the copper transporter Ctr1, the copper chaperon Atox1 and the copper pump ATP7A. Furthermore, using metadynamics-based free energy calculations [29–32] based on

available experimental structural information and on force field parameters refined by using the so-called “Force Matching” method [33,34], we characterized the recognition mechanisms between platinated DNA and the high-mobility group protein HMGB1. The latter inhibits the repair mechanisms of platinated DNA [35], modulating the on-target resistance.

2. Methods

We used Density Functional Theory (DFT)-based hybrid Car and Parrinello Molecular Dynamics/Molecular Mechanics (CPMD/MM) simulation [13,24,25] to characterize the platinum coordination of the studied platinated adducts. This hybrid scheme allows a description of the relevant electronic degrees of freedom along with extended environmental effects. The QM region, which includes the coordination



X= Cl⁻, OH⁻ or H₂O

Fig. 1. Possible binding modes of cisplatin to its cellular partners in solution as emerging from ESI-MS and NMR measurements.

² Reactions of hydrated forms of cisplatin with sulfur-containing amino acids cysteine and methionine, as well as, the kinetic competition of sulfur and nitrogen nucleophiles in the substitution reactions of cisplatin derivatives, have been studied using DFT-based approaches. [22] D.V. Deubel Journal of the American Chemical Society 126 (2004) 5999–6004, [23] T. Zimmermann, J. Burda Interdiscip Sci Comput Life Sci 2 (2010) 98–114–114.

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