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# Modifications of DNA by platinum complexes
# Relation to resistance of tumors to platinum antitumor drugs

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**Abstract**

The importance of platinum drugs in cancer chemotherapy is underscored by the clinical success of cisplatin [*cis*-diamminedichloroplatinum(II)] and its analogues and by clinical trials of other, less toxic platinum complexes that are active against resistant tumors. The antitumor effect of platinum complexes is believed to result from their ability to form various types of adducts with DNA. Nevertheless, drug resistance can occur by several ways: increased drug efflux, drug inactivation, alterations in drug target, processing of drug-induced damage, and evasion of apoptosis. This review focuses on mechanisms of resistance and sensitivity of tumors to conventional cisplatin associated with DNA modifications. We also discuss molecular mechanisms underlying resistance and sensitivity of tumors to the new platinum compounds synthesized with the goal to overcome resistance of tumors to established platinum drugs. Importantly, a number of new platinum compounds were designed to test the hypothesis that there is a correlation between the extent of resistance of tumors to these agents and their ability to induce a certain kind of damage or conformational change in DNA. Hence, information on DNA-binding modes, as well as recognition and repair of DNA damage is discussed, since this information may be exploited for improved structure–activity relationships.


*Keywords:* Cisplatin; Transplatin; New platinum drugs; Trinuclear platinum drugs; DNA; Repair; p53; NF-κB; Telomerase

## 1. Introduction

Platinum antitumor compounds, such as cisplatin [*cis*-diamminedichloroplatinum(II)] and its analogues, are widely used in the treatment of testicular and ovarian cancers and a variety of other human solid tumors, but many are intrinsically resistant and, even among initially sensitive tumors, acquired resistance commonly develops during treatment. Acquired resistance is a particular problem, as tumors may become resistant not only to the drugs used to treat them, but also to other drugs with different mechanisms of action. Elucidation of the molecular mechanisms that mediate cisplatin resistance holds promise for the design of pharmacological strategies for preventing, overcoming, or reversing this form of drug resistance.

The target for platinum antitumor compounds is DNA, to which they bind efficiently forming a variety of adducts which block replication and transcription and induce cell death (Johnson et al., 1989). The nature of DNA adducts affects a number of transduction pathways and triggers apoptosis or necrosis in tumor cells (Fuertes et al., 2003). Along with factors that do not operate directly at the level of DNA adducts, this plays an important role in the biological activity of platinum complexes including their cytotoxicity and processes underlying resistance of tumor cells.

Platinum drug resistance can occur by several mechanisms, including increased drug efflux, drug inactivation, alterations in drug target, processing of drug-induced damage, and evasion of apoptosis (Brabec and Kasparkova, 2002; Morin, 2003; Siddik, 2003). All these aspects of resistance span a broad area of molecular pharmacology and have been reviewed extensively. This review focuses on one of these aspects. We provide first some new insights into mechanisms of resistance and sensitivity of tumors to conventional cisplatin associated with DNA modifications, which have not been reviewed or have been reviewed only

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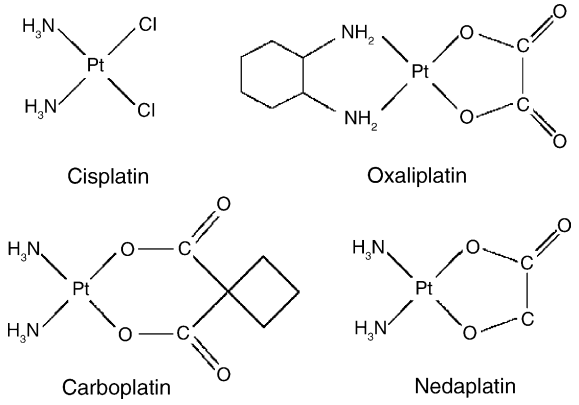


Fig. 1. Platinum complexes used clinically.

briefly. We also discuss molecular mechanisms underlying resistance and sensitivity of tumors to the new platinum compounds which differ in antitumor activity and were synthesized with the goal of overcoming tumor resistance to conventional platinum drugs in clinical use {cisplatin, *cis*-diaminecyclobutanedicarboxylatoplatinum(II) (carboplatin), [(1*R*,2*R*-diaminocyclohexane)oxalatoplatinum(II)] (oxaliplatin) and *cis*-diamine-glycolatoplatinum(II) (nedaplatin) (Fig. 1)}. These new platinum complexes also exhibit improved pharmacological properties and a narrower range of resistance in comparison to older platinum drugs. Importantly, a number of these new platinum compounds were designed to test the hypothesis that there is a correlation between clinical efficacy of platinum compounds (and/or extent of tumor resistance) and their ability to induce a certain sort of damage or conformational change in DNA (Vrana et al., 1986). Hence, information on DNA-binding modes, recognition and repair of DNA damage is also discussed, since such information may be exploited to develop new classes of platinum compounds with improved structure–activity relationships and pharmacological properties.

## 2. Cisplatin

Despite the clinical success of cisplatin, whose antitumor activity was discovered more than 30 years ago, details of the molecular mechanisms that underlie its antitumor effects and resistance of a broad range of human tumors remain elusive. Thus, there continues to be great interest in DNA modifications by this drug, repair of platinum-DNA adducts and recognition by proteins. These features of the mechanism of action of cisplatin have been reviewed extensively (Brabec, 2002; Brabec and Kasparkova, 2002; Cohen and Lippard, 2001; Fuertes et al., 2003; Jamieson and Lippard, 1999; Jordan and Carmo-Fonseca, 2000; Kartalou and Essigmann, 2001b). In this article we focus on several recent reports that describe new findings associated with DNA damage by cisplatin and new aspects underlying its mechanism of antitumor effects and tumor resistance.

### 2.1. Interactions of cisplatin with DNA in chromatin

Most cisplatin-induced DNA modifications have been investigated using purified DNA. These studies are of fundamental importance, but should be further complemented by cellular and organism-level studies that explore the complex ramifications of the drug–DNA interaction within the tumor cells of cancer patient. The incorporation of DNA into chromatin alters the dynamic and structural properties of the DNA and, therefore, the reactivity of the DNA toward a variety of chemical agents (Millard, 1996). Studies on the reactivity of cisplatin with nucleosomes have been limited to overall platination of genomic DNA-containing chromatin and core particles. In general, these studies conclude that cisplatin primarily targets DNA, with a similar rate of binding for free and nucleosomal core DNA (Lippard and Hoeschele, 1979). An examination of the distribution of DNA lesions within chromatin suggests that, at low DNA:cisplatin ratios, linker DNA is preferentially targeted for modification over core DNA (Bubley et al., 1994; Foka and Paoletti, 1986; Galea and Murray, 2002; Hayes and Scovell, 1991). However, both site-specific enhancement and depression of cisplatin interstrand cross-linking in the nucleosomal samples relative to free DNA was observed independently of the level of the modification (Millard and Wilkes, 2000). These observations were in contrast with clinically ineffective transplatin (the *trans* isomer of cisplatin), which primarily forms specific cross-links (CLs) between histone proteins (Lippard and Hoeschele, 1979; Thompson and Arquilla, 1982).

### 2.2. Nucleotide excision repair of cisplatin-DNA adducts in chromatin

Nucleotide excision repair (NER) is a major cellular defense mechanism against the toxic effects of cisplatin (see below), and a major factors contributing to tumor resistance to this drug. Therefore, how nucleosome structure modulates NER of cisplatin-DNA adducts is of great interest. Comparison of the extent of repair by mammalian cell extracts of free and nucleosomal DNA containing the same platinum-DNA adduct reveals that the nucleosome significantly inhibits NER (Wang et al., 2003). Interestingly, post-translational modification of histones can modulate NER from damaged chromatin. Phosphorylation and acetylation of histones causes nucleosomal structural changes, increasing accessibility of other proteins. These events facilitate the binding of the remodeling complex and repair proteins to the nucleosome, thereby stimulating DNA repair (Cheung et al., 2000; Kwon et al., 2000; Wang et al., 2003) and helping cells to survive cisplatin-induced stress. In other words, selective post-translational modification of histones on platinated nucleosomes may provide a general cell strategy for recruiting NER factors more efficiently and overcoming the nucleosome barrier to excision repair, which may facilitate processes that lead to cell resistance to cisplatin (Wang et al., 2003; Wang and Lippard, 2004).