Drug Resistance Updates 20 (2015) 1–11

Contents lists available at ScienceDirect

Drug Resistance Updates

journal homepage: www.elsevier.com/locate/drup

Review

New mechanisms for old drugs: Insights into DNA-unrelated effects of platinum compounds and drug resistance determinants

Laura Gatti [1], Giuliana Cassinelli [1], Nadia Zaffaroni, Cinzia Lanzi, Paola Perego *

Molecular Pharmacology Unit, Department of Experimental Oncology and Molecular Medicine, Fondazione IRCCS Istituto Nazionale dei Tumori, Via Amadeo 42/via Venezian 1, 20133 Milan, Italy

ARTICLE INFO

Article history:
Received 31 October 2014
Received in revised form 27 April 2015
Accepted 29 April 2015

Keywords:
Platinum compounds
Cell death
Drug resistance
Mitochondria
Lysosomes

ABSTRACT

Platinum drugs have been widely used for the treatment of several solid tumors. Although DNA has been recognized as the primary cellular target for these agents, there are unresolved issues concerning their effects and the molecular mechanisms underlying the antitumor efficacy. These cytotoxic agents interact with sub-cellular compartments other than the nucleus. Here, we review how such emerging phenomena contribute to the pharmacologic activity as well as to drug resistance phenotypes. DNA-unrelated effects of platinum drugs involve alterations at the plasma membrane and in endo-lysosomal compartments. A direct interaction with the mitochondria also appears to be implicated in drug-induced cell death. Moreover, the pioneering work of a few groups has shown that platinum drugs can act on the tumor microenvironment as well, and potentiate antitumor activity of the immune system. These poorly understood aspects of platinum drug activity sites may be harnessed to enhance their antitumor efficacy. A complete understanding of DNA-unrelated effects of platinum compounds might reveal new aspects of drug resistance allowing the implementation of the antitumor therapeutic efficacy of platinum compound-based regimens and minimization of their toxic side effects.

Contents

* Corresponding author.
E-mail address: paola.perego@istitutotumori.mi.it (P. Perego).
[1] Equal contribution.

http://dx.doi.org/10.1016/j.drup.2015.04.001
1368-7646/

1. Introduction

Following the first report of biological activity of cisplatin, initially shown to display an antibacterial activity (Rosenberg et al., 1965), a large body of evidence supported the potent antitumor activity of platinum (Pt) compounds (Kelland, 2007). The clinically available Pt drugs including cisplatin, carboplatin and oxaliplatin, are the cornerstones of treatment of solid tumors such as ovarian, colorectal, testicular cancer, and non-small cell lung cancer (NSCLC) (Muggia, 2009). Although Pt compounds play an important role in the treatment of certain cancer types, drug resistance phenomena remain a major obstacle in the efficacy of Pt-based therapeutic regimens (Cossa et al., 2009). Cellular resistance has been recognized as a complex phenomenon in which tumor cells exhibit multiple alterations aimed at decreasing the drug capability to kill tumor cells (Assaraf, 2006). Such alterations can be already present prior to treatment (intrinsic resistance) or can be acquired during the course of treatment (acquired resistance). Resistance to Pt compounds has been associated with genetic and epigenetic alterations and with stable and reversible phenotypes (Glasspool et al., 2006; Perego et al., 1998; Sharma et al., 2010).

The antitumor activity of Pt compounds has been mainly ascribed to the interference with DNA structure and function via formation of intra-strand, inter-strand and DNA–protein cross-links (Kelland, 2007). In fact, the chemical features of such drugs which behave as electrophilic species, allow the occurrence of covalent linkages involving the drug and the nucleophilic residues of nucleobases such as guanine and adenine. Since nucleophilic residues are present in multiple cellular macromolecules, Pt drugs have the potential to interact with a variety of cellular components. Indeed, DNA-unrelated effects of these agents as well as indirect effects [e.g., reactive oxygen species (ROS) induction] may be exploited to modulate drug efficacy, and may therefore become of therapeutic interest. Of note, cisplatin-induced apoptotic signaling has been shown to occur independently of DNA damage using cytoplasts (Mandic et al., 2003). In addition, cisplatin can form Pt-protein as well as Pt-RNA adducts (Burger et al., 2010; Osborn et al., 2014). Specifically, cisplatin accumulates in and stresses different organelles, in which death signaling is activated, including mitochondria, lysosomes, endoplasmic reticulum (ER), nucleus, cell membrane, cytoskeleton as well as cytosol (Galluzzi et al., 2014a). Therefore, cisplatin resistance can emerge from alterations directly related to the molecular damage provoked by the drug to such cellular components, as well as to enzymatic systems that regulate their preservation/turnover (on-target resistance).

Although Pt compounds may be considered old conventional cytotoxic drugs, their precise mechanism of action and antitumor activity still remains a matter of debate. The percentage of Pt covalently bound to DNA seems to be too low to account for inhibition of tumor cell growth. However, the most cisplatin-sensitive tumor type (testicular cancer) is characterized by defects in DNA repair (Koster et al., 2013), supporting the notion that inhibition of DNA function is crucial at least under certain circumstances. From a historical perspective, it appears that the earliest studies with Pt drugs were mainly focused on unraveling the mechanisms of action in tumor cells employing in vitro and in vivo models. More recently, the tumor microenvironment has been recognized to sustain the growth and survival of cancer cells, also supporting suppression of immune responses, and Pt drugs have been shown to act on the tumor microenvironment and to potentiate the antitumor activity of the immune response (Hato et al., 2012). The biochemical and molecular analyses of the DNA-independent effects of cisplatin and other Pt compounds are expected to provide insights into novel aspects of drug resistance to be harnessed for the enhancement of the cytotoxic activity of combination chemotherapeutic treatments.

2. Distribution of platinum compounds in sub-cellular compartments: plasma membrane and beyond

Pt compounds interact with multiple nucleophilic biomolecules, apart from DNA, in different subcellular compartments (Galluzzi et al., 2014a,b; Sancho-Martinez et al., 2012). Although various pumps and transporters have been implicated in influx and cellular distribution of such Pt compounds, the mechanisms of movement of Pt drugs across the plasma membrane remain poorly defined (Howell et al., 2010). Passive diffusion as well as pinocytosis-mediated inward transport has been demonstrated to contribute to the accumulation and subsequent subcellular distribution of Pt compounds (Sancho-Martinez et al., 2012). Increased levels of glycosylation-defective transporters of the ABC superfamily have been reported in ovarian carcinoma cells with acquired resistance to cisplatin and oxaliplatin, and characterized by impaired drug accumulation (Beretta et al., 2010). It is still a matter of debate how such transporters act to increase Pt drug efflux, and one cannot exclude the possibility that they play an indirect role in drug efflux (Fletcher et al., 2010; Perego et al., 2010).

The interaction of Pt compounds with components of the plasma membrane and drug accumulation in organelles and vesicular compartments such as lysosomes, mitochondria, and ER can disrupt critical cellular functions, contributing to tumor cell death (Dimanche-Boitrel et al., 2005; Sancho-Martinez et al., 2012). Thus, these interactions are expected to be crucial in the outcome of tumor cell treatment and in determining cell death or survival. The molecular mechanisms by which Pt complexes exert their cytotoxic effect on tumor cells independently of the DNA-damaging activity have not been fully elucidated. However, it is reasonable to hypothesize that a better knowledge of these mechanisms might reveal new aspects of drug resistance allowing the implementation of the therapeutic efficacy of Pt compound-based regimens and minimization of their toxic side effects. In this context, although most studies have been carried out using cisplatin, the described interactions are expected to occur with all the clinically available Pt compounds, given their common avidity for nucleophilic residues of biomacromolecules.

2.1. Interactions of platinum compounds with the plasma membrane

Using cellular pharmacology approaches, cisplatin has been shown to react through different chemical bonds with proteins and membrane phospholipids at the plasma membrane within 15 min after the initiation of tumor cell treatment (Dimanche-Boitrel et al., 2005; Hamel et al., 1990; Jensen et al., 2010; Rebillard et al., 2007). Electron microscopy analysis demonstrated the insertion of cisplatin (used at therapeutic concentrations), into the inner monolayer of the erythrocyte membrane and the early localization of Pt spots at the plasma membrane, already 5 min after treatment of ovarian cancer cells (Beretta et al., 2002; Suwalsky et al., 2000). Such interactions at the plasma membrane result in alteration of cholesterol metabolism (Courjault-Gautier et al., 1995; Dimanche-Boitrel et al., 2005), as well as destabilization and increased fluidity of the plasmalemma (Huang et al., 2003; Liang et al., 2004). An early event occurring after cisplatin treatment is the inhibition of the Na^+/H^+ membrane exchanger-1 (NHE1) that leads to intracellular acidification and activation of acid sphingomyelinase (aSMase) (Rebillard et al., 2007; Segui and Legembre, 2010) (Fig. 1). This enzyme has been described to cleave sphingomyelin into the sphingolipid ceramide, thereby contributing to apoptosis induction via the intrinsic and extrinsic pathways, as well as via a proteolytic pathway mediated by cathepsin D (Pennarun et al., 2010; Woodcock, 2006). Although cisplatin pro-apoptotic