Platinum Resistance: The Role of Molecular, Genetic and Epigenetic Factors

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Active platinum compounds have important applications in treatment of number of malignant tumors and are used in the treatment of lung, ovarian, head and neck, testicular, cervical, colorectal and relapsed lymphoma. The success of platinum drugs in treatment of various types of cancers has been challenged by problems of intrinsic and acquired resistance. Biochemical and genetical studies have confirmed that platinum resistance is multifactorial and includes changes in drug transport leading to decreased drug accumulation, increased drug inactivation or detoxification, changes in DNA repair and damage bypass and alterations in the apoptotic cell death pathways. Molecular studies have revealed that genetic factors and epigenetic mechanisms are linked to platinum resistance. Proteomimetics might prove to be clinically useful as new anticancer agents capable of overcoming apoptosis resistance. The study summarizes the current and future trends of novel molecular discoveries which will find new ways to combat platinum resistance and permit the designing of patient-specific pharmacological interventions to circumvent platinum resistance and increase the drug efficacy.

Key words: Anticancer agents, epigenetic factors, platinum resistance, proteomimetics

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INTRODUCTION

Chemotherapy is an important approach for treatment of various types of cancers, yet this type of treatment is facing the problem of drug resistance. Drug resistance was discovered in early days of cancer chemotherapeutic treatment by nitrogen mustard and recent investigations have shown that the problems of resistance encounter other active chemotherapeutic compounds (Goodman et al., 1946; Raguz and Vague, 2008). Several mechanisms are involved in development of drug resistance toward various antitumor agents, e.g., alteration in drug transport and metabolism, mutation and amplification of drug targets and others (Table 1). In addition, arising multidrug resistance creates thorny clinical problems which are difficult to overcome (Bidgoli et al., 2006; Garattini, 2007; Zahreddine and Borden, 2013). Another important point in this area of research is the genetic basis of resistance. The genetic mutational root of resistance was reported in cancer cells (Iwasa et al., 2006). Whereas other studies have shown that anticancer drug resistance and cross resistance are also under epigenetic control (Robert et al., 2006; Ibrahim, 2010a). There are three main molecular epigenetic routes, DNA methylation, histone modifications and RNAi, which might lead to drug resistance in various types of cancers. In this connection, there are increasing support of possible involvement of epigenetic mechanisms in emerging of drug resistance in cancers cells and that the induction of epigenetic changes results in acquired resistance to cytotoxic drugs (Baker and El-Osta, 2003; Egger et al., 2004; Glasspool et al., 2006). For that, the aim of the present study is to review the recent advances of biochemical, genetic and epigenetic basis of platinum drugs resistance and their implication on cancer treatment.

PLATINUM DRUGS AND CANCER THERAPY

Active platinum compounds have important applications in treatment of number of malignant tumors. For almost three decades, they have been used in the treatment of lung, ovarian, head and neck, testicular, cervical, colorectal and relapsed lymphoma (Galluzzi et al., 2012). The best known compound in this group is cisplatin [cis-diammine-dichloroplatinum(II)] with MW of 300.1 and chemical formula (cis-[PtCl2(NH3)2]), also known as cis-DDP (Rabik and Dolan, 2007). The bioactivity of cisplatin was first discovered more than four decades ago, it showed inhibitory effect against Eschericia coli (Rosenberg et al., 1969); since then it has been shown as an anti-tumor drug and was approved by FDA in 1978 (Galluzzi et al., 2012). The drug is currently widely used in treatment of advanced or metastatic tumor of small cell lung carcinoma and non-small cell lung carcinoma, head and neck cancers, testis and ovarian tumors (Chu, 1994; Yoshida et al., 1994; Jamal et al., 2006). In contrast to cisplatin, the transplatin which possess the amine ligands in the trans-position is not effective as an antitumor agent (Kelland et al., 1994; Rabik and Dolan, 2007). Because of the toxicities associated with cisplatin therapy, namely, the nephrotoxicity, neurotoxicity and ototoxicity (Cvilkovic et al., 1977; Kelland, 2007), two more platinum drugs with lower toxicity profiles were introduced to clinical practice. These are carboxoplatin [cis-diammine (cyclobutane-1,1-dicarboxylate-O-O') platinum(II)] and oxaliplatin [(1R, 2R)-cyclohexane-1,2-diamine]ethanedicarboxylate-O-O'] platinum(II) which have fewer adverse effects but similar antitumor activity (Kidani et al., 1978; Harrap, 1985; Galluzzi et al., 2012). In addition, these studies have shown that the substitution of the chloride in cisplatin with bulky groups as in carboxoplatin and oxaliplatin leads to a slower dissociation of the compounds into electrophilic species that interact with nucleophilic centers in DNA (mainly guanine N7). Carboxoplatin is used for the treatment of ovarian cancer, while oxaliplatin is approved for treatment of colorectal cancer in association with 5-fluorouracil and folinic acid (the so-called FOLFOX protocol) (Harrap, 1985; Goldberg et al., 2004). However both drugs show cross resistance to cisplatin (Stordal et al., 2007; Galluzzi et al., 2012). The success of platinum drugs in cancer therapy has encouraged the investigators in this field to develop two more platinum drugs namely, picoplatin [amminedichloro (2-methylpyridine) Platinum] and

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saratraplatin [(OC-6-43)-bis(acetato) amminedichloro (cyclohexylamine) platinum] (Choy, 2006; Eckardt et al., 2009), which are undergoing clinical trials.

Now-a-days, cisplatin is considered the most prominent anticancer drug of platinum compounds. Its therapeutic action is unquestionable in treatment of solid tumors. It is worth noting that testicular cancer can be cured by treatment with cisplatin combined with bleomycin and etoposide (Rabik and Dolan, 2007). The authors also indicated in their work that cisplatin is also used in combination with carboplatin for treatment of ovarian, cervical, head and neck, non-small cell lung and lymphoma.

MODES OF ACTION OF PLATINUM DRUGS

The mechanisms of anticancer activity of platinum drugs are well studied. It is established that the primary target of cisplatin and other active platinum drugs is DNA, yet other biological targets are important, since the nucleophilic sulfhydryl groups present in glutathione (GSH) and proteins are also targeted for platination (Jamieson and Lippard, 1999). The involvement of the Multi-drug Resistance Proteins (MRPs) in the transport of glutathione-platinum conjugates is also well known (Doeley et al., 2006; Zhou et al., 2008). Much research has been done on the aquation and pre-association multistage process of cisplatin and some of its derivatives binding to DNA and the formation of inter-/intra-strand cross-links. As a result of these studies their main mode of action has been proposed to be via covalent binding to DNA (Suntharalingam et al., 2013). Another recent study showed the critical role of B-ring hydroxyls of flavonols in their interactions with a cisplatin-bound double stranded DNA surface. These molecular interactions between cisplatin and flavonols increased the efficacy of cisplatin when combating cancer (Zwang et al., 2013).

DNA cross links can halt proliferation as a consequence of prevention of DNA replication and the signaling events leading to cell death (Cruel et al., 1997). Carboplatin and oxaliplatin have similar modes of action and form identical lesions on DNA (Chaney et al., 2005; Rabik and Dolan, 2007). The intra-strand cross links formed by oxaliplatin treatment bends the double helix more than intra-strands formed by cisplatin and carboplatin, whereas inter-strand lesions induce even more steric changes in DNA (Misset et al., 2000, Di Francesco et al., 2002). The High Mobility Group (HMG) of proteins is known to bind the platinated DNA strongly, this binding increases the degree of distortion of platinated DNA and it has been suggested that these complexes may shield DNA from intracellular repair, leading to cytotoxicity (Park and Lippard, 2012). In addition, cisplatin can induce cells to undergo apoptosis (Jamieson and Lippard, 1999).

PROBLEM OF DRUG RESISTANCE

Cisplatin and the other two platinum drugs (carboplatin and oxaliplatin) form the most effective and widely used agents for treatment of solid tumors (lung, bladder, ovary and testicular carcinoma). However, the development of secondary resistance remains a major obstacle to clinical efficacy. It was reported that prolonged cisplatin treatment raise the frequency of emergence of resistant tumors (Kartalou and Essigmann, 2001; Allingham-Hawkins et al., 2010; Olivier et al., 2010). Mechanisms of resistance to these drugs are well studied and arise as a result increased levels of DNA repair, reduced uptake, inactivation by glutathione and other anti-oxidants (Rabik and Dolan, 2007).

An important drawback of emerging resistance to an anticancer drug is cross resistance to other antitumor drugs (Gottesman and Ling, 2006). It was reported that ovarian cancer cell lines with low to very high levels of resistance to cisplatin are 8-to 850-fold resistant to the epipodophyllotoxin derivative etoposide (Hamaguchi et al., 1993). Adriamycin-resistant sublines were found cross-resistant to MDR-related drugs, epirubicin, mitoxantrone, vincristine, etoposide and taxol but not the MDR-unrelated drug, mytomycin (Uchiyama-Kokubu and Watanabe, 2001). In a study carried out by Shen et al. (1958), cross resistance to methotrexate (MTX) and several metal salts was observed in cisplatin-resistant human hepatoma and a cervical adenocarcinoma cell lines. Accordingly, Multiple Drug Resistance (MDR) is an important cause of failures of chemotherapy; it provides a shield for tumor cells against various antitumor drugs.

GENES INVOLVED IN RESISTANCE TO PLATINUM DRUGS

The genetic factors that are involved in the mechanisms of drug resistance and cross resistance have been investigated. The genetic mutational basis of resistance was reported, in addition to the other important genetic mechanism leading to drug resistance via epigenetic routes (Iwasa et al., 2006; Roberti et al., 2006). The epigenetic routes refer to the role of three main molecular mechanisms, DNA methylation, histone modifications and RNAi on development of drug resistance in various types of cancers (Ibrahim, 2010a). Now-a-days, it is well established that epigenetic changes
are involved in the induction of resistance to cytotoxic drugs and are more frequent than gene mutation (Shoemaker, 2000; Egger et al., 2004; Glasspool et al., 2006, Chang et al., 2010). The modes of action associated with the expressions of some genes conferring resistance to platinum drugs were reported (Table 2). The products of these genes contribute to platinum drug resistance in one of following mechanisms: Copper influx/efflux transporters (Safaei et al., 2004; Safaei and Howell, 2005), multidrug resistant associated protein MRPI (Li et al., 2004), DNA-damage-responsive anticancer barrier (Siddik, 2003; Huang et al., 2005). Yeast strains were also used to investigate genes involved in cisplatin resistance. Homozygous diploid deletion pool of Saccharomyces cerevisiae was used systematically to identify three novel genes (PSY1-3, “platinum sensitivity”) that when deleted confer sensitivity to the anticancer agents cisplatin, oxaliplatin and mitomycin C (Wu et al., 2004).

ROLE OF DNA METHYLATION IN DEVELOPMENT OF CANCER AND DRUG RESISTANCE

Aberrations of genomic DNA methylation, loss of genomic methylation or hypermethylation, cause genomics malfunctions. These changes from normal state lead to development of diseases, e.g., cancers and drug resistance (Ibrahim, 2010a-c; Ibrahim, 2012). Several investigations had shown the role of DNA hypermethylation in the development of drug resistance. Nyce and her colleagues were able to show that chemotherapeutic drugs can induce DNA hypermethylation in cultured cells (Nyce et al., 1986; Nyce, 1989; Nyce et al., 1993). Whereas other investigators had reported that resistance to cisplatin was accompanied by over-expression of DNA methyltransferases (Wang et al., 2001) and the resistance could be induced by over-expression of DNA methyltransferase genes (Qiu et al., 2005). Similar results were obtained when human breast adenocarcinoma cells were treated with adriamycin (Segura-Pacheco et al., 2006). More recent study by Kastl and his colleagues were able to demonstrate that changes in the DNA methylation machinery were associated with resistance to docetaxel in breast cancer cells (Kastl et al., 2010). Chang and his colleagues provided further evidence that epigenetic promoter methylation was a frequent event during chronic cisplatin exposure and that secondary changes in gene regulation can play an important role in generating drug resistant phenotypes (Chang et al., 2010). Changes in the DNA methylation patterns are observed in RASSF1A, HIC1 and MGMT genes of male germ cell tumor whereas other genes e.g., SAT, C8orf4, LAMB3 and others were observed in cell lines (Table 3). It is worth to mention that our search showed that several genes which are linked to the platinum drug resistance (Table 2) are prone to alteration of DNA methylation patterns, e.g., CTRL (Stewart et al., 2009), bcI2 (Hanada et al., 1993), MDRI (El-Osta et al., 2002).

IMPACT OF REVERSAL OF DNA METHYLATION PROFILES ON DRUG RESISTANCE

It is possible to hypothesize that reversal of DNA aberration of cancer cells or drug resistance cells to normal states might be considered as promising approach for cancer therapy and overcoming the problem of anticancer drug resistance (Perez-Plasencia and Duenas-Gonzalez, 2006). One interesting approach to overcome platinum compounds resistance is to use DNA methylation inhibitors. A study carried out by group of researchers showed that treatment of HeLa cells with hydralazine and valproic acid lead to an increase in the cytotoxicity of gemcitabine, cisplatin and adriamycin (Chavez-Blanco et al., 2006). Other research group led by
Candelaria showed that anticancer drug resistance which was associated with changes in the DNA methylation profiles could be reversed by epigenetic drugs (Candelaria et al., 2007). Research in this field is likely to lead to the development and discovery of epigenetic drugs especially from plant origin (Kirk et al., 2008; Link et al., 2010). These drugs might have future application in cancer therapy; in addition medicinal plants might be a good source for such epigenetic drugs (Ibrahim, 2010a; Jamal et al., 2010).

NEW NOVEL APPROACHES TO OVERCOME CISPLATIN RESISTANCE

Other ways to overcome cisplatin resistance have been investigated. A recent study showed that cisplatin resistant cells accumulate Reactive Oxygen Species (ROS), this observation might prove useful in targeted therapy (Wangpachitr et al., 2012). Another approach has been directed to study the correlation between cisplatin resistance and factors involved in cell growth. It was possible to show that cisplatin resistance can be reversed by inhibition of modulators of cell growth (Wangpachitr et al., 2008). In addition, there is strong evidence which points at the association of cisplatin resistance with apoptotic resistance. Research in this area has shown that this type of resistance is under control of apoptotic regulators (Crawford et al., 2011). An important group of proteins which are involved in apoptosis process belong to Bcl-2 family of proteins and includes two types of factors, pro-and anti-apoptotic; these are acting at the mitochondrial level (Hanahan and Weinberg, 2000; Sunnaw et al., 2009). BH3 domain is an interesting feature of these proteins, it is suggested that the interactions are mediated by this domain that consists of approximately 20 amino acids (Zhai et al., 2006; Lee et al., 2007). It is possible to identify or synthesize chemicals that mimic the BH3 domain and have anti-cancer activities (Fesik, 2005; Zhai et al., 2006). In this connection, ABT-737 is an example of one of the first small-molecule that binds to Bcl-xL, Bcl-2 and Bcl-w with high affinity (Lee et al., 2007). Since apoptosis resistance is a key feature, we believe that targeting this pathway with the BH3 mimetics, e.g., ABT-737, is a viable strategy for sensitizing cisplatin resistant tumors. It is worth mentioned that despite high affinity of ABT-737 for Bcl-2, Bcl-xL and Bcl-w, many cell types proved refractory to ABT-737. It is worth mentioned that resistance in this case was attributed to the inability of ABT-737 to target Mcl-1 (Van Delft et al., 2006; Lee et al., 2007). On the other hand, a more recent study has shown the potential of this approach when used in combination with cytotoxic drugs (Joudeh and Claxton, 2012). Further, they reported that several agents target the function of anti-apoptotic Bcl-2 family members have entered clinical trials.

CONCLUSION

Cancer remains a major health problem with the incidence of solid tumors ever increasing, more so among women and the aging population. Platinum-based drugs, cisplatin, carboplatin and oxaliplatin form the most effective and widely used agents for these malignancies. Despite the powerful antitumor effects and reasonable improvement in the quality of life for many patients, the therapeutic efficacy of platinum drugs is limited because of intrinsic or acquired tumor resistance. DNA methylation is associated with resistance to active platinum compounds and some other important anticancer drugs. We believe that investigation of DNA methylation of genes, their products proved being involved in cisplatin resistance, will help in introducing molecular markers to detect acquired resistance to cisplatin and other platinum drugs in patients undergoing therapy. Furthermore, strong evidence points to the association of cisplatin resistance with apoptotic resistance resulting from the over expression of antiapoptotic Bcl-2 family of genes or under expression of the apoptotic regulators. It has also been shown that BH3 domains possess selectivity and have important applications in cancer therapy. Accordingly, it is expected that proteomimetics will have potential as anti-cancer therapeutics.

ACKNOWLEDGMENTS

The authors would like to thank the Princess Sumaya University for Technology, TTUHSC School of Pharmacy, Weill Cornell Medical College and Hamad Medical Corporation for supporting the research related to this publication.

REFERENCES


