Mechanisms of Uptake and Interaction of Platinum Based Drugs in Eukaryotic Cells

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Abstract The platinum group elements are significant compounds used in numerous fields of human life. Besides of often discussed toxic effect the platinum compounds show the therapeutic effects. Nowadays, platinum-based cytostatic are still the most frequently used drugs in oncology. Due to their proved medicinal purposes the behavior in the organism should to be intensively studied as well as their interactions with DNA and other important biological molecules. This review summarizes the recent results in the platinum drug field and discusses the behavior of platinum compounds in cells. The interaction of platinum and DNA with respect to the change of the DNA structure are also clarified.

1 Introduction

Platinum group elements (PGEs) can be naturally found only at very low concentration (Sikorova et al. 2011). They are emitted to the environment predominantly in the metallic form, and therefore have been considered to be inert and their bioavailability to be low. PGEs contamination occurs in airborne particulate matter (Zereini et al. 2005), roadside dust (Gomez et al. 2002), soil (Zereini et al. 2007), vegetation (Hooda et al. 2008) and water, which finally results in bioaccumulation of these elements in the living organisms (Ravindra et al. 2004). Emissions of platinum metals and grow of their concentrations in the environment lead to the questions about their potential to have a negative effect on the human health

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(Sikorova et al. 2011). Platinum compounds exhibiting toxic, carcinogenic or mutagenic effects (Wang and Li 2012).

Platinum due to its physicochemical properties is used in many sectors. Its ability to catalyze various chemical reactions is used in automotive industry, organic and inorganic chemistry and designing of sensors and biosensors (Siriviriyanun et al. 2013; Yang et al. 2013; Eremia et al. 2013). Exhaust gases from combustion engines are purified by platinum-based catalytic converters (Piskulov and Chiu 2013) and can be improved by synergic effect of platinum and Bronsted acid (Fu et al. 2013). The platinum plays an important role in hydrogenation, oxidation, dehydrogenation, hydrogenolysis (Furstner 2009) and is used in synthesis of acetic acid (carbonylation), n-butanal (hydroformylation) (Crundwell et al. 2011), polymers (Ikeda et al. 2000) etc.

Platinum compounds are still the most effective cytostatic drugs, although Ru (II), Os(II), Ir(II) etc. have a quite similar properties (Dhahagani et al. 2014). New generations of platinum (complexes and nanoparticles) chemotherapeutics offer the prospect of combating platinum resistance and expanding the range of treatable cancers. The best known platinum cytostatic drugs are shown in Fig. 1.

Nanotransporters (micelles, dendrimers, liposomes, nanoparticles) (Oberoi et al. 2013; Gheybi et al. 2014) and platinum-peptide complexes are used to overcome this side effects (Graf et al. 2012). Recently it was revealed that metal nanoparticles can have similar anti-tumor effect as platinum complexes and its anti-tumor properties mostly depend on a size and material (Manikandan et al. 2013). However, as it is shown in Fig. 2, platinum related research is still far more related to medicine (Ali et al. 2013; Muscella et al. 2013; Ruggiero et al. 2013).

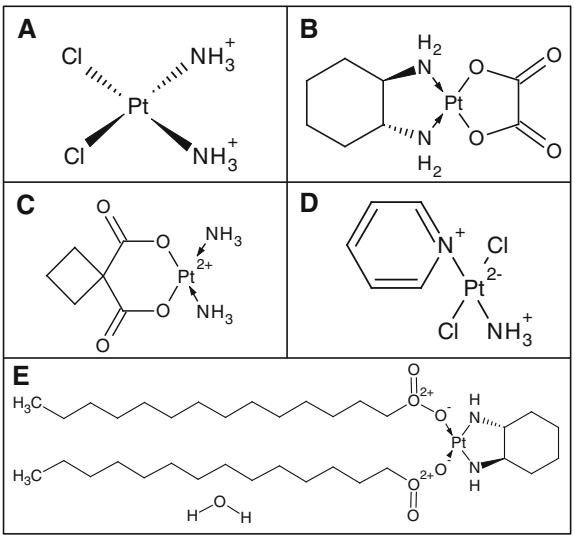

Fig. 1 The table of different Pt-drugs mentioned in the text and their chemical structures: *A* Cisplatin, *B* Carboplatin, *C* Oxaliplatin, *D* Miriplatin, *E* Ampyplatin

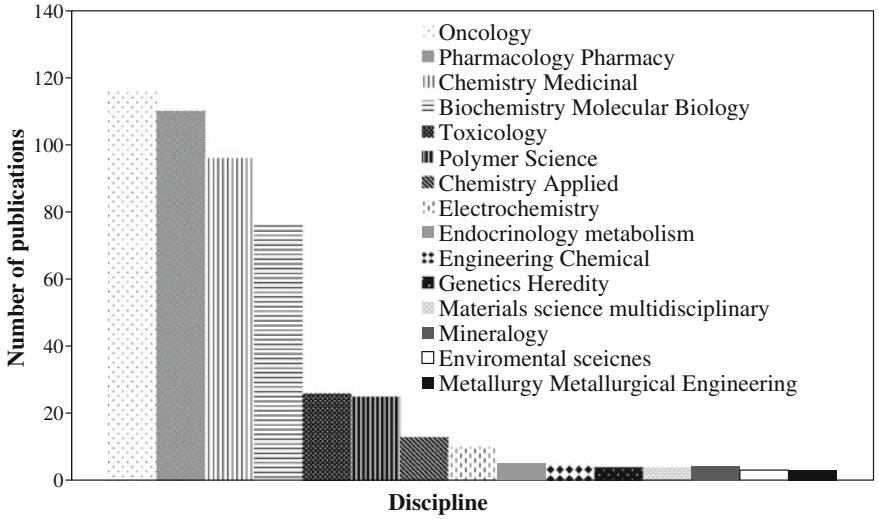

Fig. 2 The analyzed results from Web of Science database with the keyword "platinum"

2 The Effects of Platinum Compounds on Eukaryotic Cells and Their Interaction with DNA

Metals are ubiquitous and essential for cellular processes in all living organisms and theirs availability determined the life on the Earth (Gitlin and Lill 2006; Florea and Büsselberg 2011). The cell biology of metals is residing at the interface of chemistry, biology, pharmacology and medicine (Gitlin and Lill 2012; Sawyer 2006). Their special properties including redox activity, variable coordination modes and reactivity towards organic substrates are the reasons, why all transition metals are potentially toxic for cells and their intracellular concentration is tightly regulated by uptake, storage and secretion. Although the importance of metals in biology have been recognized, knowledge about metals trafficking and metabolism is still limited (Gitlin and Lill 2006).

2.1 Cellular Uptake Mechanisms of the Platinum Complexes

The effects of platinum complexes on a cell are studied mainly because platinum compounds play over 40 years a central role in cancer chemotherapy (Galanski et al. 2005). Although cisplatin is an important cytotoxic agent in the treatment of epithelial malignancies, it has several disadvantages. It damages, indiscriminately, cancerous and normal tissues. The main adverse effects of cisplatin includes renal toxicity, gastrointestinal toxicity, peripheral neuropathy, myelotoxicity, asthenia,

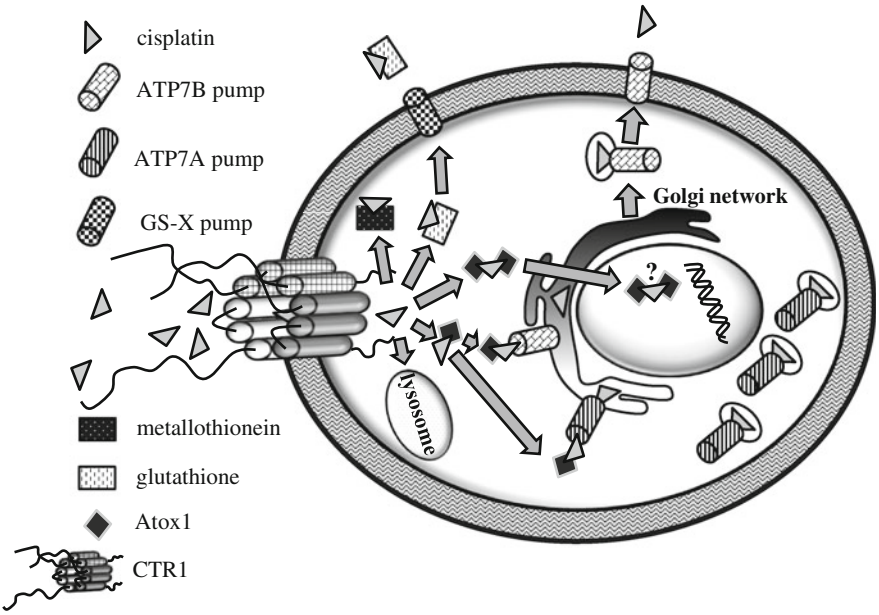

Fig. 3 Scheme of cisplatin trafficking. Cisplatin taken up by CTR1 is transported to lysosome and bound to glutathione (Shoeib and Sharp 2013), metallothionein (Zitka et al. 2013; Zhang et al. 2011; Knipp et al. 2007) or Atox1 (Palm-Espling et al. 2014; Palm et al. 2011). The platinum-GSH complex is exported by GS-X pump (Ishikawa and Aliosman 1993). Atox1 transfer platinum via ATP7A/B to Golgi network (GN) and induces structural changes that lead to the vesicular sequestration of the drug and trafficking of the ATP7A/B containing vesicles from the GN to peripheral sites for a drug efflux (Samimi et al. 2004). The mechanism of cisplatin entry to the cell nucleus has not been yet elucidated, but we assume, that the translocation of Atox1 dimer is possible

ototoxicity and also resistance to cisplatin have negative influence on the treatment results.

The cytotoxic effect of the platinum complexes is directly related to the quantity of drug that enters the cell (Fig. 3). Cisplatin, carboplatin and oxaliplatin are highly polar molecules, which do not diffuse across lipid membranes (Hall et al. 2008). Although cisplatin shares a little similarity with Cu ions in terms of physical properties, the cellular uptake of these substances is tightly connected. The Copper transporter 1 (CTR1), the main Cu influx transporter, has been found to mediate the cisplatin and its analogues transport into the cell via creation of membrane pore-like —homotrimer (Howell et al. 2010; Aller and Unger 2006). Cisplatin and copper are able to down-regulate CTR1 (its own influx transporter) expression (Holzer and Howell 2006). Several mechanisms of cisplatin influx were suggested. The diffusion of platinum through the pore after complete loss of ligands down the concentration gradient was proposed by Arnesano et al. (2007). Cisplatin can also bind to sulfur of CTR1 methionine extracellular N-terminus and after release of ammine

ligands migrates through the pore by trans chelation reaction that pass the Cu or Pt based drug from one ring of methionine to the next one and eventually to the ring of cysteine (Wang et al. 2011; Larson et al. 2010). Although, the loss of ligands after coordination to methionine was also confirmed by Arnesano et al. (Arnesano and Natile 2008), it is believed that cisplatin has to keep the two ammine ligands to be active (Todd and Lippard 2009). It supports the thesis of multiple pathways of cisplatin influx into a cell. It must be also pointed out that only 1 % or less of the intravenously administrated cisplatin binds to DNA (Reedijk 1999). CTR2 was proved to be involved in cisplatin influx, too. Although CTR1 and CTR2 are structurally similar, CTR1 knockdown reduces Pt drug uptake, knockdown of CTR2 enhances cisplatin uptake (Abada and Howell 2010; Blair et al. 2009).

Trafficking of the endocytic vesicles, which absorb part of extracellular solution with all surrounding chemicals, is another potential pathway of Pt-based drugs into a cell. In addition, these vesicles can protect cisplatin and its analogues from cytosolic platinophiles like metallothioneins (MTs) and glutathione (GSH). Petis et al. described the mechanism of copper-stimulated clathrin-mediated endocytosis CTR1 (Petris et al. 2003).

2.2 The Significance of Copper

The cytoplasmic step on the pathway of copper ions involves small pathway specific metal binding proteins (metallochaperones) including antioxidant 1 (Atox1), copper chaperone for superoxide dismutase 1 (CCS) and cytochrome c oxidase (COX17). To our best knowledge, the possible platination of CCS and COX17 have not been proved (Suzuki et al. 2003; Burdon 1995). Totally different example is Atox1. The soluble cytosolic Cu chaperone Atox1 (previously known as HAH1) delivers Cu to a copper-transporting ATPases (ATP7A and ATP7B) in secretory vesicles by direct protein-protein interaction to facilitate copper excretion (Strausak et al. 2003; Walker et al. 2002; Banci et al. 2005). Copper binds to metal-binding sites (MXCXXC motif), which are highly conversed in Atox1 and also are presented in ATP7A/B N-terminus (Muller and Klomp 2009). Safaei et al. found out that the role of Atox1 in mechanism of Cu homeostasis is distinct from that involved cisplatin (Safaei et al. 2009). Although Atox1 facilitates Cu movement from CTR1 to ATP7A/B exporters leading to Cu efflux, it is involved in ATP7A mediated cisplatin accumulation in vesicular compartments. It was proved that cisplatin is able to bind to Atox1 CXXC motif and retains the two ammine ligands or induces Atox1 dimer formation (Arnesano et al. 2011). Atox1 was also identified as the copper-dependent transcription factor (Itoh et al. 2008). Copper can induce Atox1 nucleus translocation, binding to a novel cis element of the cyclin D1 promoter and transactivation, thereby promoting cell proliferation. Furthermore, copper overload was observed in various tumors (Crowe et al. 2013; Wang et al. 2010). It suggests that Atox1 play far more complex role in the regulation of the cell physiology. Question, which should

be answered, is how Atox1 can exhibit two functions as a transcription factor and chaperone.

Export of Cu in mammalian cells involves two P-type ATPases (ATP7A and ATP7B). When extracellular copper concentrations are low, ATP7A and ATP7B are localized in the trans-Golgi network. Exposure to increased copper levels results in reversible re-localization of ATP7A to the plasma membrane and of ATP7B to intracellular vesicular compartments (Kalayda et al. 2008). ATP7A is involved in the transport of Cu from cytoplasm to trans-Golgi network, where Cu is bound to Cu-requiring enzymes, or export it from cell via the vesicular secretory pathway. On the other hand, Samimi et al. revealed, that ATP7A mediates cisplatin sequestration into compartments from which it is unable to reach the DNA and exert cytotoxicity (Samimi et al. 2004). The same mechanism of sequestration was also confirmed for oxaliplatin and carboplatin (Katano et al. 2002). The overexpression of ATP7B was proved to increase the resistance to cisplatin in prostate cancer (Komatsu et al. 2000). Katano et al. suggests that ATP7B enhances cisplatin efflux by sequestering it into the vesicular export pathway, which is known to efficiently export Cu (Katano et al. 2004).

2.3 Cytoplasmic Interactions

In plasma, where high chloride concentration occurs, cisplatin mostly remains in a native inactive form. Inside the cell chloride ions dissociate from the platinum due to the low chloride concentration, and are replaced by water molecules. Consequently positively charged platinum complex binds to the cell nucleophiles in DNA, RNA and proteins (Cohen and Lippard 2001). Inactivation by creation of stable Pt-thiol adduct is believed to be important Pt-based drug sink (Reedijk 1999). Pt was showed to bind to methionine, cysteine and histidine residues and have high affinity to most abundant cytosolic thiols, glutathione, and 50-times higher for metallothionein (Hagrman et al. 2003). The glutathione S-conjugates efflux can be mediated by some members of ATP-binding cassette (ABC) transporter superfamily (MRPs, multidrug resistance proteins), which regulate the sensitivity to chemotherapy including cisplatin and are in this case called the GS-X pump (Yamasaki et al. 2011; Zaman et al. 1995; Ishikawa and Aliosman 1993).

2.4 Reactive Oxygen Species and Apoptosis

Heavy metals are known to cause oxidative damaging of bio-molecules by initiating free radical mediated chain reaction resulting in lipid peroxidation, protein oxidation and oxidation of nucleic acids like DNA and RNA (Flora et al. 2013). Platinum drugs have been used in the chemotherapy of cancer for a long time, but the mechanism of its action is still not clear (Zitka et al. 2007). The most important

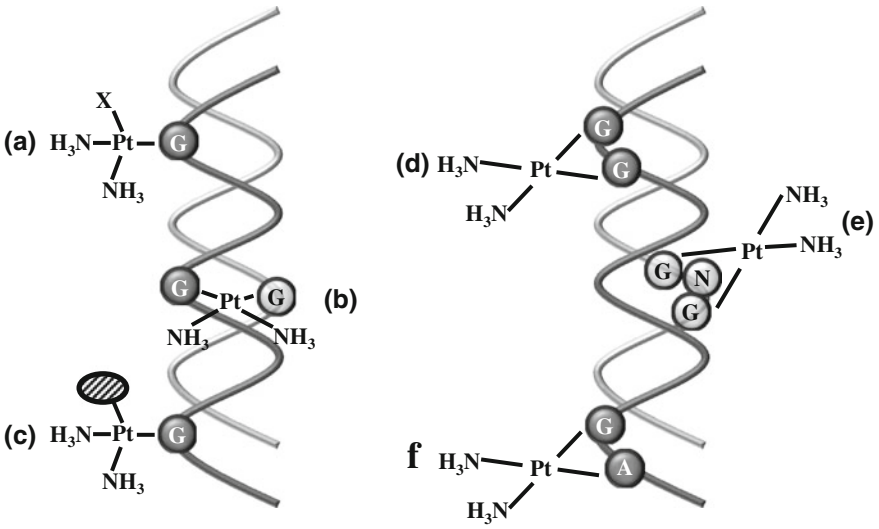

Fig. 4 Cisplatin DNA adducts: *a* Cisplatin bound monofunctionally to guanine (X—original chloride, or a hydroxyl group); *b* interstrand cross-link; *c* cisplatin guanine—protein cross-link; *d* GpG-intrastrand cross-link; *e* GpNpGintrastrand cross-link (N represents a base); *f* ApG-intrastrand cross-link. Adopted and modified according to Crul et al. (2002)

mechanism could be non-covalent DNA intercalation, formation of covalent DNA adducts, DNA-DNA cross-linking, DNA strand-breaks caused by inhibition of topoisomerase II, or the effect of the radicals (Stiborova et al. 2010) (Fig. 4). Platinum chemotherapy is beneficial for human epithelial cancers because the platinum agents induce DNA damage signaling, leading to initiation of cell cycle arrest and apoptosis, and ultimately to a tumor cell death (Guerrero-Preston and Ratovitski 2014). It was observed that oxaliplatin, its enantiomeric analogue, or cisplatin can migrate from one strand to another in double-helical DNA (Malina et al. 2013). Cisplatin, carboplatin and oxaliplatin are neutral platinum (II) complexes with two amine ligands and two additional ligands that can be aquated for further binding with DNA (Kao et al. 2013). Pt(IV) compounds are usually administered as prodrugs, which are reduced in the hypoxic environment of cancer cells to active Pt(II) species. Platinum(II) moiety forming in the process of binding Pt(IV) to genomic DNA causes cell death (Song et al. 2013).

Cisplatin induced reactive oxygen species (ROS) generation significantly caused loss of mitochondrial membrane potential in sensitive cells, but not in resistant cells to cisplatin. The induction of wild-type p53 can enhance cisplatin-induced apoptosis not only by inducing apoptosis regulator protein Bax but also by suppressing anti-apoptotic proteins through inhibition of Akt (protein kinase B) (Kim et al. 2013). By employing a panel of normal and cancer cell lines and the budding yeast *Saccharomyces cerevisiae* as model system, it was shown that exposure to cisplatin induces a mitochondrial-dependent ROS response that significantly enhances the

cytotoxic effect caused by nuclear DNA damage. ROS generation is independent of the amount of cisplatin-induced nuclear DNA damage and occurs in mitochondria as a consequence of protein synthesis impairment. The contribution of cisplatin-induced mitochondrial dysfunction in determining its cytotoxic effect varies among cells and depends on mitochondrial redox status, mitochondrial DNA integrity and bioenergetic function (Marullo et al. 2013). In another study the effect of cisplatin and novel platinum(II) complexes, Pt-2(isopropylamine)(4)(berenil)(2), Pt-2 (piperazine)(4)(berenil)(2), Pt-2(2-picoline)(4)(berenil)(2), Pt-2(3-picoline)(4) (berenil)(2), Pt-2(4-picoline)(4)(berenil)(2), on the redox state of human leukemic T-cells line Molt-4 was investigated. Treatment of Molt-4 with the novel complexes has shown that all compounds enhance total ROS and superoxide anion generation as well as change the activity of antioxidant enzymes such as superoxide dismutase, catalase, glutathione peroxidase and glutathione reductase. Moreover, all the above-mentioned compounds cause a decrease in the level of non-enzymatic antioxidants such as GSH as well as vitamin C, E and A (Jarocka et al. 2013). In addition, the novel platinum (II) complexes enhanced expression of Bax and cytochrome c as well as decreased the expression of Bcl-2 and p53 protein. The novel platinum(II) complexes in comparison with cisplatin disturb redox status more intensively and lead to oxidative stress in Molt-4 cells (Jarocka et al. 2013).

2.5 Binding and Interaction of Platinum Drugs to DNA

Platinum drugs can diverse interact with DNA, the intercalation in double-stranded DNA and stacking on G-quadruplex DNA was observed in the case of $[PtCl_2(NH_3)$(2-aminonaphthalene)] (Gabano et al. 2013). Miriplatin (lipophilic platinum complex) selective accumulation in tumor tissue was detected. Determined platinum concentrations were about 50-fold higher in hepatocellular carcinoma than in non-tumor liver tissues. The platinum-DNA adduct levels were about 7.6-fold higher in hepatocellular carcinoma than in non-tumor liver tissues. And significant correlations between platinum concentrations and platinum-DNA adduct levels tumors were not observed (Yasui et al. 2013). Ampyplatin trans-$[PtCl_2(NH_3)_2(py)]$; py = pyridine) has much more higher antiproliferative activity than cis-$[PtCl(NH_3)_2(py)]^+$ and is comparable to cisplatin and can be efficiently accumulated in cancer cells. Ampyplatin binds to DNA and forms monofunctional adducts (Xu et al. 2013).

Platinum anticancer agents with phthalate leaving group show great cytotoxicity, less acute toxicity, good lipophilicity as well as better aqueous solubility (Sharma et al. 2013). Combination of cisplatin with other compounds can influence the platinum-DNA adducts. Antimetabolites can increase or decrease the number of platinum-DNA adducts. Taxanes can decrease the formation of platinum-DNA adducts, while topoisomerase I inhibitors enhance the number of adducts (Crul et al. 2002). After the treatment with cisplatin, the reduction in the contour length of the DNA fragments was observed (Mukhopadhyay et al. 2005).

Upregulation of HIF-1α (hypoxia-inducible factor 1) contributes to hypoxia-induced chemotherapeutic resistance in many cancer cells (Ye et al. 2012). The resistance is caused due to interaction with thiol-containing compounds (Monneret 2011) and sEH (soluble epoxide hydrolase) inhibition alleviate cisplatin-induced nephrotoxicity. The inhibition of sEH has anti-inflammatory and antiapoptotic properties (Liu et al. 2013).

2.6 Effects of Platinum Drugs on DNA Repair Mechanisms

Platinum-based derivatives improve survival of non-small cell lung cancer patients. The DNA base excision repair activity of the controls was significantly higher in comparison to cancer patients, but the activity of DNA nucleotide excision repair was nearly at the same level. The changes in the amount of single strand breaks and DNA cross-links during the therapy were observed. High level of single strand breaks was detected right after the chemotherapy (Fikrova et al. 2014). Excision repair cross-complementation group 1 (ERCC1) is a DNA repair enzyme that is frequently defective in non-small cell lung cancer (NSCLC). Its low expression correlates with platinum sensitivity and also modulated PARP1/2 (Poly (ADP-ribose) polymerase) sensitivity (Postel-Vinay et al. 2013). ERCC1 important in the removal of platinum induced DNA adducts and cisplatin resistance could be the prognostic factor in bladder cancer patients receiving platinum-based neoadjuvant chemotherapy (Ozcan et al. 2013). Platinum drugs in treatment of colorectal tumors have been limited via high incidence of tumor resistance. Platinum (IV) complex induces effective elimination of colon cancer in substantially lower doses than oxaliplatin (Blanarova et al. 2013). The signal-regulated kinases (ERK1 and ERK2) contribute to the proper execution of DNA damage response in terms of checkpoint activation and the repair of DNA lesions (Lin et al. 2013). p53 as a suppressor regulates the downstream effects of E2F1 (transcription factor) in cellular stress (DNA damage stress) (Zhou et al. 2013). The p38 MAPK (mitogen-activated protein kinase) inhibition in cooperation with cisplatin kills tumor cells, and could be employable for cancer treatment (Pereira et al. 2013).

2.7 Effects of Pt Nanoparticles

The effects of platinum nanoparticles (PtNPs) on different cell types are not fully understood. It was found that PtNPs trigger toxic effects on primary keratinocytes, decreasing cell metabolism, but these changes had no effects on cell viability or migration. Moreover, smaller PtNPs exhibited more deleterious effect on DNA stability than the big ones (Konieczny et al. 2013). The cytotoxic effect towards myoblast cancer cells (C2C12) of well-crystalline colloidal Pt quantum dots (Pt-QDs) was examined (Wahab et al. 2012). The detailed analyses of MTT assay

revealed that in the presence of Pt-QDs, with increasing the incubation time, the number of cancer cells decreases. Moreover, with increasing concentration of Pt-QDs, the cancer cell death increases, confirming that the concentration of Pt-QDs has a significant role in controlling the number of cancer cells. Asharani et al. suggested p53 activation in PtNPs treated cells due to genotoxic stress, with subsequent activation of p21 leading to a proliferating cell nuclear antigen-mediated growth arrest in S phase and apoptosis (Asharani et al. 2010). Growth arrest in S phase can be caused not only by DNA damage, but also by DNA-polymerase inhibition, which exhibits high affinity to PtNPs and other metals (Pelletier et al. 1996; Popenoe and Schmaeler 1979). Cytotoxicity of PtNPs can be the result of its accumulation in lysosome and the release of Pt^{2+} (Asharani et al. 2010). The antioxidant properties of PtNPs were also investigated. Kajita et al. found that PtNPs decomposed H_2O_2 and consequently generated O_2 like catalase (Kajita et al. 2007). Further, Kim et al. (2012) confirmed that PtNPs act as antioxidants in murine osteoclasts and reduce oxidative stress induced by ovariectomy.

3 Conclusions

The platinum compounds show the wide range of the usage not only in the medicine. Although the therapeutic benefits the toxicity of platinum cannot be ignored. The cytotoxic effect of the platinum complexes is directly related to the quantity of drug that enters the cell. The positively charged platinum complex binds to the cell nucleophiles in DNA, RNA and proteins. Platinum metals interact with DNA by covalent intercalation and formation of DNA adducts. Also the formation of DNA adducts can be increased by some compounds. In this case the excision repair cross-complementation group 1 (ERCC1) is important in the removal of platinum induced DNA adducts. Platinum nanoparticles could be also employed to the tumor treatment. Finally we can conclude the cognitions of the interactions of PGEs on the cellular level could provide the better understanding to their cytotoxicity effects.

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