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Role of epigenetic mechanisms in cisplatin-induced toxicity

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ABSTRACT

Cisplatin (CDDP) is a highly effective antineoplastic agent, widely used in the treatment of various malignant tumors. However, its major problems are side effects associated to toxicity. Considerable inter-individual differences have been reported for CDDP-induced toxicity due to genetic and epigenetic factors. Genetic causes are well described; however, epigenetic modifications are not fully addressed. In the last few years, many evidences were found linking microRNA to the development of CDDP-mediated toxicity, particularly nephrotoxicity. In this review, we described how genetic and epigenetic modifications can be important determinants for the development of toxicity in patients treated with CDDP, and how these alterations may be interesting biomarkers for monitoring toxicity induced by CDDP. Considering the validation in different studies, we suggest that miR-34a, -146b, -378a, -192, and -193 represent an attractive study group to evaluate potential biomarkers to detect CDDP-related nephrotoxicity.

1. Introduction

Cisplatin (cis-diamminedichloroplatinum (II); CDDP) is a highly effective antineoplastic agent, widely used in the treatment of various malignant tumors, including ovary, endometrium, pulmonary, bladder, head and neck, testicular, breast and colorectal cancer (Dasari and Tchounwou, 2014; Prestayko et al., 1979). This chemotherapeutic drug is known as Peyrone's salt, he first synthesized it in 1844, however, its antioncogenic activity was accidentally discovered by Rosenberg et al. (Rosenberg et al., 1965, 1969) in the 1960's, they described the potent antiproliferative effect of CDDP in *Escherichia coli* cultures and then in a xenograft model. Clinical trials with CDDP started in 1971, and was approved as the first platinum compound for use in testicular and ovarian cancer by the US Food and Drug Administration (FDA) in 1978 (Dilruba and Kalayda, 2016; Kelland, 2007). The usefulness of this drug in the treatment of cancer is recognized, being associated with complete or partial remission, or stabilization of the disease. However, its major problem are side effects associated to toxicity, such as nephrotoxicity, neurotoxicity, and ototoxicity, among others (Mollman, 1990; Peres and da Cunha, 2013; Zhu et al., 2015). Regarding CDDP-induced toxicity, considerable inter-individual differences have been reported. Some patients have certain toxicities, but others tolerate the treatment very well. Several factors must be considered for different degrees of toxicities and outcomes for the same drug, including age, sex, healthy factors, environmental factors, exposure to tobacco smoke, alcohol, co-medication and genetic factors. Therefore, we can group the causes of CDDP-induced toxicity in genetic and epigenetic factors.

Genetic causes are well described and include genetic variants that affect encoding genes of transporters involved in efflux and influx of CDDP and metabolizing enzymes responsible for the absorption, distribution, metabolization and excretion of the drug. Nevertheless, epigenetic modifications involved in the regulation of these genes and how these would be associated to CDDP-induced toxicity are not fully addressed. Interestingly, in the last few years many evidence were found linking microRNA (an epigenetic mechanism of genetic regulation) with the development of CDDP-mediated toxicity, particularly with nephrotoxicity in patients treated with this chemotherapeutic drug.

In this review we describe how genetic and epigenetic modifications

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can be important determinants for development of toxicity in patients treated with CDDP, and how these alterations may be interesting biomarkers to monitor toxicity by CDDP.

2. Mechanism of action

CDDP is a platinum coordination compound, characterized by a square planar configuration with a central atom of platinum linked to two chloride and two NH_3 groups in cis conformation. Passive diffusion has been described as the main route for CDDP to enter the cell, since its uptake is concentration-dependent and non-saturable. However, the participation of active transport mediated by membrane proteins, such as copper transporter 1 (CTR1) and 2 (CTR2), P-type copper-transporting ATPases ATP7A and ATP7B, organic cation transporter 2 (OCT2), and multidrug and toxin extrusion transporter 1 (MATE1), was also reported as being important (Ciarimboli, 2014; Dilruba and Kalayda, 2016; Gately and Howell, 1993).

The chloride ions are stable in bloodstream (high chloride concentrations, 100 nM). Inside the cells, the low chloride concentration (4–20 mM) facilitates CDDP hydrolysis, producing positively charged species that react with cytoplasmic nucleophilic molecules such as glutathione, methionine, metallothionein and other cysteine-rich proteins (Boulikas and Vougiouka, 2003). The reactive form of CDDP interacts with DNA to form DNA adducts through covalent bonds, preferably at the N7-sites of adenine and guanine in DNA. This reaction allows the interactions DNA-protein and DNA-DNA to form interchain and intrachain crosslinks (Siddik, 2003). However, intrachain adducts are reported as the most common and responsible for the cytotoxic action of CDDP (Pinto and Lippard, 1985). These DNA adducts interfere with cellular processes, such as the replication and transcription of DNA, they can arrest the cell cycle in the G2 phase and interfere with several pathways that control differentiations and stress response, subsequently, culminating in the activation of apoptosis (Siddik, 2003). Furthermore, CDDP induces the production of reactive oxygen species (ROS) with lipid peroxidation and disrupt calcium homeostasis, increasing the efflux of calcium from the mitochondria. This disruption of calcium homeostasis causes cellular respiration to be interrupted, decreasing the production of adenosine triphosphate (ATP) and other cofactors by enzyme inhibition (Fig. 1) (Dasari and Tchounwou, 2014).

3. Cisplatin toxicities

Nephrotoxicity is the most frequent toxicity associated to CDDP treatment. CDDP nephrotoxicity is dose-dependent, estimations point that patients who receive an initial dose of 50–100 mg/m^2 of CDDP can develop acute renal failure in approximately 30% of the cases, reaching values as high as 60% (Kidera et al., 2014; Latcha et al., 2016; Peres and da Cunha, 2013; Prasaja et al., 2015; Ries and Klastersky, 1986; Sastry and Kellie, 2005). Furthermore, most patients who develop some degree of renal dysfunction never fully recover (Dentino et al., 1978).

CDDP excretion is mostly renal, biliary and intestinal excretions are minimal. A recent study showed that approximately 50% of the drug is excreted in the urine within the first 48 h, most of the excretion occurs in the first 12 h (Visacri et al., 2017). The drug accumulates in the kidneys, even at non-toxic blood levels. Toxic effects are initially seen on the proximal tubules, where CDDP concentrations are higher due to drug accumulation. These high concentrations in the proximal tubule cells are primarily associated to the presence of membrane transporters CTR1 and OCT2, located in the basolateral membrane of proximal tubule cells (Ciarimboli, 2014; Filipski et al., 2009). However, CDDP can cause damage to the kidneys at the glomerular and interstitial levels too (Peres and da Cunha, 2013).

The pathophysiological bases of CDDP-induced nephrotoxicity are being widely studied the last decades and are still not fully understood. A study presented an interesting approach based on the inhibition of the Na^+/K^+-ATPase pump in renal cells as a key element of the pathophysiological process of CDDP-induced nephrotoxicity (Eljack et al., 2014). The Na^+/K^+-ATPase is essential to maintain the cellular concentration gradient of sodium, being the only enzyme in the plasma membrane that performs this function (Huliciak et al., 2012). Reports show that CDDP specifically inhibits the Na^+/K^+-ATPase enzyme, while other platinum drugs like carboplatin and oxaliplatin did not affect the enzyme activity (Daley-Yates and McBrien, 1982; Kubala et al., 2014). Sodium concentration is crucial for the transport of nutrients such as glucose, Ca^{2+}, H^+, and is important in the osmotic potential for water reabsorptions, thus, the inhibition of Na^+/K^+-ATPase enzyme in the tubular cells reduces the reuptake of these nutrients, resulting in the failure of the whole system (Kubala et al., 2014).

Other mechanisms of CDDP nephrotoxicity were described and

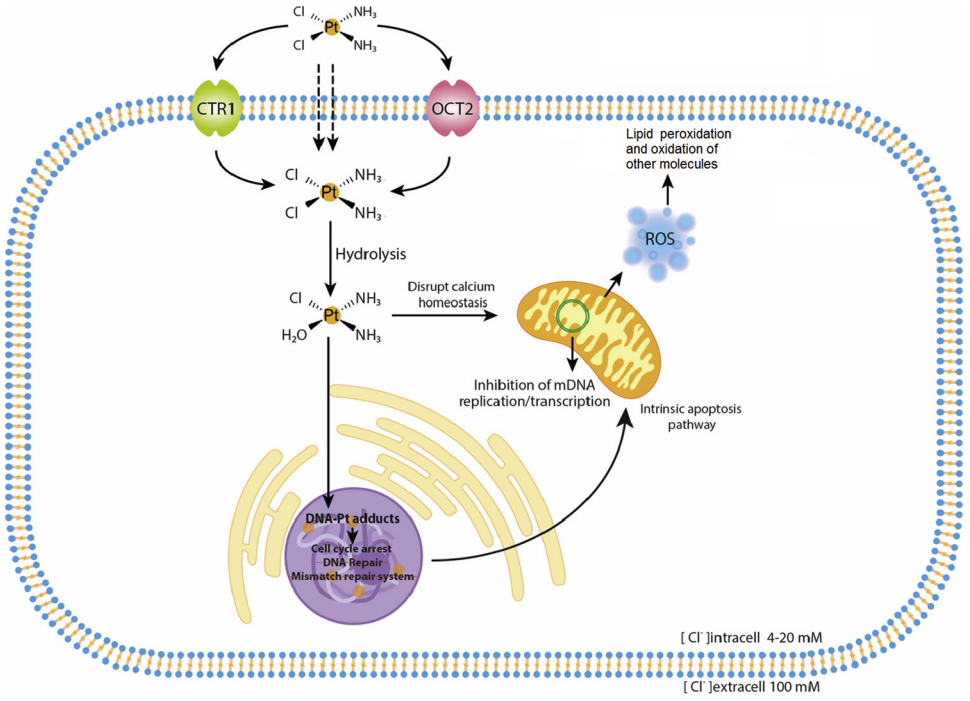

Fig. 1. CDDP mechanism of action. CDDP may enter tumor cells *via* copper transporter, organic cation transporters, and organic cation/carnitine transporters or by passive diffusion. DNA-Pt adducts block DNA replication, transcription, other nuclear functions and activates signal transduction pathways, which result in apoptosis and necrosis in tumor cells. In dividing tumor cells, the formation of DNA adducts is supposed to cause growth inhibition and cell death, thus, eliminating the tumor cells. CDDP also disrupts calcium homeostasis by linking with mitochondrial DNA, and dysregulates ROS production, causing lipid peroxidation and oxidation of other molecules, such as proteins and carbohydrates, enhancing cellular damage. Caption: OCT2: organic cation transporter-2; CTR1: copper transporter 1; ROS: Reactive oxygen species.

include proteins of different cellular pathways, such as TNF and Fas (extrinsic apoptosis pathway); the tumor suppressor gene p53 (intrinsic apoptosis pathway) through p53 upregulated modulator of apoptosis-α (PUMA-α) and p53-induced protein with a death domain (PIDD); CDK2 and p21 (cell cycle regulation); mitogen-activated protein kinases (MAPKs) involved in the regulation of different processes including proliferation, differentiation and apoptosis (Karasawa and Steyger, 2015; Miller et al., 2010; Pabla and Dong, 2008).

Oxidative stress and ROS production were also associated with CDDP-induced nephrotoxicity in many studies (Marullo et al., 2013; Santos et al., 2007). Oxidative stress biomarkers in human samples were already associated with alterations in renal parameters (Tuan et al., 2016). A recent study showed that hydrogen peroxide (H_2O_2) production is associated with nephrotoxicity induced by CDDP and higher grades of serum creatinine increases, as well as creatinine clearance reductions in head and neck cancer patients (Quintanilha et al., 2017b).

Regarding clinical characteristics that demonstrate renal failure, the patients present high concentrations of blood urea nitrogen and serum creatinine, the urine may contain glucose and small amounts of proteins as indicative of proximal tubular dysfunction, hypomagnesemia, hypocalcemia, hypophosphatemia, hypokalemia, hyponatremia and hyperuricemia, metabolic acidosis, among others (Arunkumar et al., 2012; Miller et al., 2010; Tsang et al., 2009).

Ototoxicity is a frequent side effect, being present between 11% and 97% of patients treated with CDDP. Usually, it starts as a symmetrical and irreversible sensorineural hearing loss which initially involves high frequencies followed by low frequencies, being related to the dose of CDDP used and having a cumulative nature (Harrison et al., 2015; Mukherjea and Rybak, 2011; Schell et al., 1989). Histopathological studies from human temporal bone specimens with minimal post-mortem autolysis obtained from autopsy, indicate that the damage included loss of inner and outer hair cells in the basal turn of the cochlea, degeneration of the stria vascularis and a significant decrease in spiral ganglion cells, predominantly in the upper turns (Goncalves et al., 2013; Hinojosa et al., 1995).

The exact mechanism of CDDP-induced ototoxicity is unclear; A study proposed that plasma membrane transporters that play a role in CDDP influx could lead to CDDP-induced ototoxicity. The transporters include CTR1, CTR2, OCT2, the transient receptor potential channel family members, calcium channels, multidrug resistance-associated proteins, mechanotransduction channels, chloride channels, among others (Waissbluth and Daniel, 2013). Recently, studies proposed that the increased production of ROS is important in the pathophysiology of hearing loss (Dehne et al., 2001; Goncalves et al., 2013).

CDDP hematotoxicity is characterized by anemia, leucopenia, neutropenia, lymphopenia, and thrombocytopenia. Anemia and lymphopenia are more frequent (Visacri et al., 2017), however, neutropenia seems to cause more serious consequences, such as febrile neutropenia (Quintanilha and Visacri, 2017). CDDP-induced anemia occurs by bone marrow aplasia, hemolysis, and erythropoietin deficiency secondary to nephrotoxicity (Dlott et al., 2004; Gao et al., 2006, 2013; Son et al., 2011; Vandendries and Drews, 2006). Leucopenia and thrombocytopenia are associated with aplasia. Some studies showed that oxidative stress is associated with myelosuppression, the administration of antioxidants prevented this toxicity (Fuchs-Tarlovsky et al., 2011; Karale and Kamath, 2017; Markovic et al., 2011; Olas et al., 2004; Sinha et al., 2015).

Hepatotoxicity may be observed following the administration of large CDDP doses (Cvitkovic, 1998; Iraz et al., 2006) or small repeated doses, probably due to accumulation in the liver (Fenoglio et al., 2005; Pratibha et al., 2006). Studies suggest that the oxidative stress generated by CDDP plays an important role in hepatic injuries (Iraz et al., 2006; Mansour et al., 2006; Pratibha et al., 2006). CDDP increases aspartate aminotransferase and alanine aminotransferase of liver enzymes, alters the energy metabolism in the liver (reduces the concentration of ATP, glutathione and NADPH), causes lipid peroxidation, oxidative damage to cardiolipin and proteins with sulfhydryl groups, and hepatic cell death by apoptosis *via* mitochondria (Martins et al., 2008).

Nausea and vomiting are very common in CDDP toxicity because this antineoplastic presents a higher emetogenic potential when compared to other cancer drugs (Rolla et al., 2006). A study showed that 64.4% and 47.5% of head and neck cancer patients treated with one cycle of high-dose CDDP experienced nausea and vomiting, respectively, even with the regular use of antiemetics (Visacri et al., 2017). These side effects are very debilitating and significantly affect the quality of life of oncologic patients (Mitchell, 2006). Evidence suggests that oxidative stress may be one of the mechanisms by which CDDP causes emesis (Alam et al., 2017; Gupta and Sharma, 1996; Matsuki et al., 1993; Ullah et al., 2017). The hypothesis is that ROS generation may trigger the serotonin release from enterochromaffin cells of the small intestine, which stimulates the afferent vagus nerve and causes the vomiting reflex (Alam et al., 2017; Torii et al., 1994).

4. Genetics in cisplatin toxicities

Considerable inter-individual differences exist in CDDP-induced toxicity. As already mentioned, several factors may influence different degrees of toxicities and outcomes for the same drug, including age, sex, healthy factors, environmental factors, exposure to tobacco smoke, alcohol, co-medication and genetic factors. Regarding genetic factors, they usually lead to permanent changes in proteins involved in drug transportation and disposition (Ma and Lu, 2011). Many studies were performed to verify the influence of genetics and genetic variants in CDDP-induced toxicities. These genetic variants eventually alter the synthesis and function of important proteins in the pharmacodynamics and pharmacokinetics of CDDP, such as transport proteins, proteins responsible for DNA repair, and proteins involved in metabolization and detoxification.

Genetic variants in influx transporters, such as OCT2, CTR1, or in efflux transporters such as MATE1, ATP7A, ATP7B ATP-Binding Cassette Protein family or ABC transporters, may be determinant for overall CDDP-induced toxicity. OCT2 is the main OCT in the kidney; therefore, a genetic variant involving this transporter may be associated with CDDP-induced nephrotoxicity. Studies observed that patients having A270S (rs316019) variant for OCT2 showed protection from nephrotoxicity, while patients with the reference genotype did not (Filipski et al., 2009; Iwata et al., 2012). The A270S variant is caused by G > T substitution at the 808 position of the *SLC22A2* gene (Song et al., 2008). Another recent study performed by Qian et al. (Qian et al., 2016) with platinum-based chemotherapy (CDDP and carboplatin in association with other antineoplastics), showed that patients with non-small cell lung cancer (NSCLC) carrying the G allele and OCT2 rs316019 have better tolerance to hematological toxicity and hepatotoxicity.

Regarding the transporter MATE1, it is encoded by the *SLC47A1* gene and expressed in the liver and the brush border membrane of renal proximal tubule cells (Otsuka et al., 2005). A study in mice demonstrated that MATE1 (-/-) mice receiving CDDP presented increased nephrotoxicity compared to wildtype controls (Nakamura et al., 2010), however, another study revealed that the rs2289669 G > A MATE1 was not associated with CDDP-induced toxicities(Iwata et al., 2012). In contrast, Qian et al. (Qian et al., 2016) showed in NSCLC patients that A allele carriers of rs2289669 have poor tolerance to hematological toxicity caused by platinum-based chemotherapy.

ABC transporters are also involved in CDDP efflux. The subfamily B member 1 (ABCB1), subfamily C member 2 (ABCC2) and 3 (ABCC3) are examples of three important subfamilies of ABC transporters. ABCB1 C1236T-TT genotype caused a higher risk to present multiple toxicities in NSCLC patients (Perez-Ramirez et al., 2016). However, the study performed by Qian et al. (Qian et al., 2016) found no association of

platinum-induced toxicities and variants in ABCC2 (rs717620, rs2273697, and rs3740066) and ABCB1 (rs1045642). Regarding ABCC3, children patients who carried the G allele of rs1051640 presented increased risk of developing ototoxicity after CDDP treatment (Pussegoda et al., 2013).

The initial influx of CDDP is mediated by CTR1, which is encoded by the gene *SLC31A1* (Larson et al., 2010). A study performed in NSCLC patients showed that patients carrying the C allele of one genetic variant of CTR1 (rs10981694 A > C) were more sensitive to ototoxicity following CDDP treatment (Xu et al., 2012). CTR1 regulates the uptake of copper into the cell, however, its removal is mediated by ATP7A and ATP7B. ATP7A is expressed in the intestinal epithelium and other tissues, except for the liver; and ATP7B is primarily expressed in the liver, the kidneys and the brain (Murata et al., 1997; Tanzi et al., 1993).

Genetic variants in other genes, which encode proteins other than that act as transporters, were also investigated in association with CDDP-induced toxicity. The elFαArg803LyzC > T variant was associated with CDDP-induced toxicity in NSCLC patients, T-carrier subjects presented better tolerance to nephrotoxicity, but poorer tolerance to ototoxicity (Xu et al., 2013). elF3a is a member of the nucleotide excision repair (NER) pathway and plays a critical role in regulating the DNA repair pathway activity. Variants of other genes involved in the NER pathway, such as xeroderma pigmentosum group C (XPC), group D (XPD), and DNA excision repair protein (ERCC) were investigated regarding their association to toxicity caused by platinum treatment. Patients with osteosarcoma presented a weak evidence of association between the CC genotype of rs2228001 (XPC) and ototoxicity (Caronia et al., 2009). Moderate/severe ototoxicity was not as common in head and neck cancer patients with XPC c.2815AC or CC genotypes and XPD c.934AA genotype. In contrast, the XPD c.934 G G genotype was more common in patients with moderate/severe nausea. In the same group of patients, moderate/severe nephrotoxicity was more common in XPD c2251AC or CC genotypes and in the ACT haplotype (variant alleles of XPD c.934 G > A, XPD c.2241A > C and ERCC1 c.354C > T) (Lopes-Aguiar et al., 2017). Moreover, the heterozygous for ERCC1 19007 T/C and 8092 C/A genotypes reported a higher risk of CDDP-induced nephrotoxicity in a study performed with ovarian cancer patients (Khrunin et al., 2010). The ERCC1 C118T-T allele and ERCC2 rs50872 − CC genotype reported a higher risk of general toxicity, the ERCC2 Asp312As genotype reported a higher risk of presenting multiple toxicities, and the rs50872 − CC genotype was also associated with grade 3–4 for hematological toxicity or platinum-based chemotherapy (CDDP and carboplatin) in NSCLC patients (Perez-Ramirez et al., 2016).

In addition to genes involving DNA repair pathways, those involving platinum detoxification of platinum-based drugs, such as glutathione S-transferases (GSTs) (*e.g.* GSTP1, GSTM1, and GSTT1), are also subjects of studies on genetic variants. Human GSTs constitute a multigene family and the genes are polymorphic, either due to single nucleotide polymorphisms (SNPs) or due to deletions (Motohashi and Inui, 2013). The homozygous condition suppresses enzymatic activity and may reduce CDDP detoxification. A study performed with NSCLC patients found that those who possessed the 105Val allele or the GSTP1*B haplotype presented less neutropenic toxicity after platinum-based chemotherapy treatment (Booton et al., 2006). Other study on testicular cancer patients verified that homozygosity for GSTP1 105Val was protective against CDDP-related ototoxicity (Oldenburg et al., 2007). SNP analyses in a rare case of CDDP toxicity (alopecia, fever, and severe pancytopenia) on a laryngeal cancer patient showed that the patient presented GSTT1 deletion and wild GSTP1 105IleIle, in addition to variant MSH3 1045ThrThr and wild BAX-248GG genotypes (Lopes-Aguiar et al., 2015).

A study performed with head and neck cancer patients reported that moderate/severe vomiting was associated to GSTP1 c.313AG or GG genotype alone and combined to XPD c.934 GA or AA, XPF c.2505TC or CC, and CASP9 CASP9 c.-1339AG or GG genotypes. This was the first evidence of a combination of abnormalities in isolated apoptosis pathway and combined with DNA repair pathway in CDDP-induced emesis (Carron et al., 2017).

Studies proposed a role for CYP2E1 in CDDP-induced nephrotoxicity and hepatotoxicity as a site for the generation of ROS and a significant source of catalytic iron (Liu et al., 2002; Liu and Baliga, 2003; Masubuchi et al., 2006). A recent review on the relationship between the CYP450 and CDDP toxicity encouraged studies assessing genetic variants to evaluate the influence of these variants in CDDP-induced toxicity, mainly in CYP2E1 and for nephrotoxicity and hepatotoxicity (Quintanilha et al., 2017a). However, this association with genetic variants in CYP2E1 has not been established yet. Khrunin et al. (Khrunin et al., 2010) did not found it after investigating three variants (rs2031920, rs6413432, and rs2070676) in CDDP-based chemotherapy in ovarian cancer patients.

Studies performed on patients to investigate the influence of genetic variants in CDDP-induced toxicities present some difficulties that limit the interpretation and create discrepancies among the results, such as other antineoplastic co-administrated with CDDP and the limited number of patients. However, we can observe that the genetics alone is not sufficient to explain the inter-individual differences in CDDP-induced toxicity. This is one of the reasons why epigenetic studies became so important, to better understand the different grades of toxicity shown by different patients, thus, being increasingly closer to the reality of personalized medicine.

5. Epigenetics in cisplatin toxicities

The term epigenetics refers to heritable changes of gene expression without underlying changes in the encoding DNA sequence (Holliday, 2006). These changes can be modified by the environment and explain some interindividual differences that traditional genetics do not (Wu and Morris, 2001). Epigenetic regulation is fundamental for many physiological processes, including gene expression, suppression of transposable elements, cellular differentiation, embryogenesis, X-chromosome inactivation and genomic imprinting. Epigenetic modifications regulate both physiological processes and pathological processes (Portela and Esteller, 2010). In addition to the environment, patients' characteristics (like sex and ethnicity), lifestyle, diseases, and medications can contribute to epigenetic modifications and to individual phenotypes (Fisel et al., 2016). Epigenetic modifications regulating gene expression usually include DNA methylation, non-coding RNAs (ncRNAs), and histone modification (Goldberg et al., 2007). We will only discuss DNA methylation and ncRNAs in this review.

5.1. DNA methylation

DNA methylation is an epigenetic mechanism used by the cell to regulate gene expression, particularly to "turn it off" (Phillips, 2008). The mechanism consists of the addition of a methyl group in the cytosine that precedes a guanine, usually in regulatory regions of the genes, called cytosine-phosphate-guanine (CpG) dinucleotide. Methylation occurs through the action of the DNA methyltransferase (DNMT) family of enzymes, which adds a methyl (− CH3) at the 5′ position of cytosines; the methyl group is transferred from S-adenosylmethionine. The presence of these methyl groups on the cytosines on CpG can inhibit the binding of transcription factors to these regions, the non-binding of these to their specific sites results in the absence of gene transcription (Portela and Esteller, 2010; Szyf, 2007). Therefore, when the promoter region of a gene becomes hypermethylated, the consequence is the inhibition of gene expression. Since DNA methylation is crucial in gene expression, alterations in methylation levels may explain variations in the response to environmental stimuli and treatment.

CDDP is the most important chemotherapeutic inducer of DNA hypermethylation, probably due to conformational changes induced by CDDP adducts, which turns the DNA into a better substrate for DNA cytosine 5-methyltransferase (Nyce, 1989). Although many studies

evaluated DNA methylation levels and response to CDDP treatment, research on biomarkers and indicators that can simultaneously monitor both treatment response and CDDP-induced toxicities are scarce. Wang et al. (Wang et al., 2015), found an association between DNA methylation levels in two genes often methylated in lung cancer patients (APC and RASSF1A) and total plasma DNA concentration with tumor response and toxicities in patients with advanced lung cancer treated with CDDP-based therapy. They found higher grades of toxicity (mainly hepatotoxicity, nephrotoxicity and gastrointestinal symptoms) in patients who presented higher methylation levels 24 h following chemotherapy ($meth_{24h} > meth_{0h}$) and total plasma DNA ratio after 24 h and before chemotherapy higher than 2 ($DNA_{24h}/DNA_{0h} > 2$).

Brown et al. (Brown et al., 2017), performed an epigenome wide association study and analyzed ototoxicity susceptibility in CDDP-treated pediatric patients with embryonal tumors. They identified and replicated novel CpG methylation loci (cg14010619) that may regulate PAK4 activity. This methylation was inversely associated with ototoxicity grades, they also found evidence of a possible downstream PAK4 gene expression. The PAK4 gene encodes a serine/threonine p-21-activated kinase (PAK), which is expressed by the inner and outer cochlear hair cells (Shen et al., 2015). This gene is important to regulate stereociliary bundle migration, orientation and positioning during the organ of Corti development (Lee et al., 2012; Sipe and Lu, 2011). Sensory hair cells are the primary suspected target of CDDP-induced ototoxicity. Therefore, the genome-wide study presented the hypothesis that PAK4 expression provides protection against CDDP-induced damage.

Epigenetic regulation of transporter gene expression by DNA methylation has been studied for members of SLC transporter family, such as OCT1, encoded by *SLC22A1* gene, which was hypermethylated after long-term of CDDP treatment and caused CDDP resistance in human esophageal cancer cells (Lin et al., 2013). These studies were not performed with the objective of assessing the influence of DNA methylation in CDDP-induced toxicities, however, we can extrapolate the results and hypothesize the consequences of these methylation in toxicities. Given the hypermethylation results in the inhibition of gene expression, a hypermethylated transporter can directly influence CDDP intake and efflux within the cells, and consequently, in the toxicities of the cells expressing these transporters. However, further studies must be performed to investigate these hypothetical associations.

5.2. Non-Coding RNAs

NcRNAs comprise a class of RNA molecules that do not encode proteins, but exert a regulation of protein expression (Mattick and Makunin, 2006). NcRNAs can be subdivided in small interfering RNAs (siRNAs), microRNAs (miRNAs), PIWI-interacting RNAs (piRNAs), small nucleolar RNAs (snoRNAs), large intergenic non-coding RNAs (lincRNAs), transcribed ultraconserved regions (T-UCRs), and long noncoding RNAs (lncRNAs). These ncRNAs regulate gene expression under physiological and pathological conditions, acting at various steps along the protein biosynthetic process. The most studied class of ncRNAs are miRNAs (Esteller, 2011; Li et al., 2017).

MiRNAs are small molecules of simple-stranded RNA composed by approximately 22 nucleotides, they are important in the post-transcriptional regulation of gene expression (Lagos-Quintana et al., 2001; Lau et al., 2001; Lee and Ambros, 2001). This regulation occurs with the complementary binding of miRNAs to the 3′ untranslated region (3′-UTR) of the target messenger RNA (mRNA) (Baek et al., 2008; Mishra et al., 2007; Selbach et al., 2008). Since its discovery in *C. elegans* (Lee et al., 1993; Wightman et al., 1993) and recognition of its conservation in many species (Pasquinelli et al., 2000), studies involving miRNAs increased exponentially over the last few years, revealing the regulatory role of miRNAs in cellular functions. Depending on the complementarity of miRNA, it is capable of inhibiting mRNA transcription (imperfect complementarity) or even inducing the degradation of mRNA (perfect complementarity) and regulating the expression of encoded proteins (Bartel, 2004). Estimations point that approximately 60% of human mRNA can be modulated by miRNAs, suggesting that each miRNA is capable of being paired with hundreds of different mRNAs (Friedman et al., 2009).

MiRNAs can be detected in various biological fluids like plasma, urine, saliva, cerebrospinal fluid, among others (Weber et al., 2010). Although extracellular fluids present high concentrations of RNA degrading enzymes, miRNAs are highly stable since these molecules exist primarily in vesicles, such as the exosomes (Cortez and Calin, 2009; Kosaka et al., 2010), or associated with a protein complex, such as high density lipoproteins and Argonaut (Arroyo et al., 2011; Vickers et al., 2011). Many miRNAs are only found in specific fluids, other types can be found in several different fluids. Many studies started to be performed to identify miRNAs as possible disease and drug-induced toxicity biomarkers due to their high stability in extracellular fluids and specific expression in different tissues or pathological conditions.

Few studies were performed to relate CDDP-induced toxicities to the expression of miRNAs. Nephrotoxicity was the mainly CDDP-induced toxicity already related to the expression of some miRNAs, and most studies were performed *in vitro* or *in vivo* (animal models). Table 1 shows a summary of miRNAs studies on CDDP-induced nephrotoxicity. To the best of our knowledge, only one study investigated this relationship with CDDP administered in humans. In this study miR-21, -200c and -423 were found to be increased in the urine of patients with mesothelioma following CDDP infusion; however, there was no relationship between the expression of these miRNAs and renal toxicity (Pavkovic et al., 2016).

Two independent studies were performed to identify rats' urinary miRNAs that could be biomarkers of CDDP-induced nephrotoxicity (Kanki et al., 2014; Pavkovic et al., 2014). They assessed urine excreted at different times, and both concluded that peak miRNA expression occurs on the fifth day after CDDP administration, however, on the third day it may be possible to quantify a portion of them. The greatest renal damage was observed seven and eight days after the administration of the chemotherapy. After the quantification and normalization of the various miRNAs expressed, Pavkovic et al. (Pavkovic et al., 2014), found 18 miRNAs as possible biomarkers of nephrotoxicity, Kanki et al. (Kanki et al., 2014), found 25 miRNAs. Based on the miRNAs found in the study of Kanki et al. (Kanki et al., 2014), Pavkovic et al. (Pavkovic et al., 2014) also concluded that miR-15, -16, -20a, -192, -193, and -210 are the best possible urinary biomarkers of CDDP-induced nephrotoxicity. These miRNAs were statically altered in rat urine three and five days after different doses of CDDP infusion (1 mg/kg and 3 mg/kg), while the maximal tubular necrosis and the traditional biomarkers were altered eight days after the treatment (Pavkovic et al., 2014). The performance of these two studies, in parallel and independently, strengthens the potential of the suggested urinary biomarkers that are candidates for CDDP-induced nephrotoxicity.

Another study sought to relate CDDP-induced nephrotoxicity and identified significant changes in the levels of six urinary miRNAs, twelve plasmatic, and five in the kidney tissue after the administration of the antineoplastic in rats (Wolenski et al., 2017). The samples were collected and analyzed 24 and 72 h after the administration of CDDP. Wolenski et al. (Wolenski et al., 2017), concluded that miR-378 may be a good urinary biomarker of nephrotoxicity, since this miRNA presented the most elevated levels in urine and was elevated in the study performed by Kanki et al. (Kanki et al., 2014).

Studies performed on renal cells and tissue showed a relationship of expression of some miRNAs with increased CDDP-induced nephrotoxicity, such as miR-181a (Zhu et al., 2012), -449 (Qin et al., 2016), -146b (Zhu et al., 2016), and -375 (Hao et al., 2017). MiR-181a seems to be induced by CDDP and suppressed in Bcl-2 expression, inducing apoptosis in tubular epithelial cells (Zhu et al., 2012). Bcl-2 is an anti-apoptotic protein, increasing cell resistance to apoptosis and suppressing oxidative processes (Hockenbery et al., 1993). Regarding miR-

Table 1
Studies involving microRNAs and CDDP-induced nephrotoxicity.

Reference	Models / subjects	Tissue / cell / sample type	CDDP treatment	Time of collected sample	Platform	miRNAs deregulated associated CDDP treatment	Main findings
Bhatt et al.(Bhatt et al., 2010) (2010)	*in vivo*: C57BL/6 mice (wild-type and p-53 deficient) *in vitro*: BUMPT-306 cell line	Kidney tissue Mouse proximal tubular cells	Single dose of 30 mg/kg 40 μmol/L for 24h	0, 1, 2 and 3 days after CDDP treatment After CDDP treatment	Real-time PCR	miR-34a	MiR-34a was induced during CDDP treatment *in vitro* and *in vivo*. The induction is p53 dependent, and miR-34a has a protective role against CDDP-induced apoptosis in renal cells.
Han-yu et al.(Zhu et al., 2012) (2012)	HK-2 cell line	Human renal tubular cell line	50 μmol/L for 24h	After CDDP treatment	Real-time PCR and Luciferase reporter assay	miR-181a	CDDP may play a role in nephrotoxicity by up-regulating miR-181a, which suppresses the Bcl-2 expression, inducing apoptosis in tubular epithelial cells.
Joo et al.(Joo et al., 2013) (2013)	Wild-type and Nrf2 knockout mice	Kidney tissue	Single dose of 15 mg/kg	Day 3 after CDDP treatment	Illumina MouseWG-6 Expression BeadChip	miR-125b	Nrf2 knockout mice nullify an adaptive increase of miR-125b by CDDP. Nrf2-dependent induction of miR-125b has a hole in protecting the renal cells from acute injury.
Kanki et al. (Kanki et al., 2014) (2014)	30 Male Sprague-Dawley rats: 20 treatment and 10 control; half of them fed and half fasted. 10 Male Sprague-Dawley rats: 5 treatment and 5 control	Urine and kidney tissue Urine and kidney tissue	Single dose of 6 mg/kg Single dose of 1, 3, and 6 mg/kg	Urine: days 4 to 5 for 17 hours. Kidney: removed on day 5 Urine: 24 hours from 0 to 1 day, 2 to 3 days, and 6 to 7 days; Kidney: removed on days 1, 3, or 7	Real-time PCR	miR-335, miR-378a-5p, miR-183-5p, miR-328a-3p, miR-1839-5p, let-7a-1-3p, miR-93-5p, miR-532-3p, miR-20b-5p, miR-192-5p, miR-17-5p, miR-140-3p, miR-25-3p, miR-340-5p, miR-191a-5p, let-7 g-5p, miR-193-5p, miR-218a-5p, miR-7a-1-3p, miR-130b-3p, miR-30a-5p, miR-26b-3p, miR-744-5p, miR-7a-1-3p, miR-320-3p	25 miRNAs were overexpressed in urine and conversely decreased in kidney tissue in rats treated with 6 mg/kg of CDDP under both fed and fasted conditions. 8 of these miRNAs were dose-dependently and increased in the urine from day 3, maximizing levels on day 5 and decreasing on day 7.
Pavkovic et al. (Pavkovic et al., 2014) (2014)	Male Wistar rats (6 dose of 1 mg/kg, 6 of 3 mg/kg, and 6 control)	Urine and kidney tissue	Single dose of 1 and 3 mg/kg	Days 3, 5, 8, 15, and 26; rats were euthanized, and the kidney was removed on days 3, 5, 8 and 26.	TaqMan® Low Density A Arrays (TaqMan® cards) in urine of 3 mg/kg treated rats	miR-16, miR-20a, miR-20b, miR-21, miR-34a, miR-141, miR-146a, miR-184, miR-185, miR-192, miR-196c, miR-200b, miR-210, miR-223, miR-327, miR-339-3p, miR-15b, miR-193	Considering the miRNAs identified in the urine after administration of 1 mg/kg and 3 mg/kg of CDDP, and those already increased in the presence of only slight histopathological changes in the kidney and were also found increased in urine of Sprague-Dawley rats in Kanki et al., miR-15, miR-16, miR-20a, miR-192, miR-193, and miR-210 may serve as biomarkers for CDDP-induced nephrotoxicity.
Lee et al. (Lee et al., 2014) (2014)	*in vivo:* male C57BL/6 mice *in vitro:* NRK52E cells	Kidney tissue Rat kidney cell line	Single dose of 15 mg/kg, i.p. 30 mmol/L	Days 1, 3, and 5 after CDDP 24, 48, and 72 hours following CDDP treatment	Agilent mouse miRNA microarray in 3 days after CDDP	miR-122, miR-34a	CDDP treatment downregulated miR-122 and up-regulated miR-34a. The decrease in miR-122 induced Foxo3 translation, contributing to tubular cell injury. The increase in miR-34a promoted acetylation of Foxo3 by repressing SIRT1. Dysgerulation of Foxo3 induced and activated by these miRNAs contributes to renal damage by strengthening the p53 signaling pathway.
Qin et al.(Qin et al., 2016) (2016)	NRK-52E cell line	Rat renal tubular cell line	Single dose of 20 μg/mL	24 h after CDDP treatment, miR-449 was inhibited by its sponge transfection	Real-time PCR	miR-449	CDDP treatment up-regulated miR-449 levels. This up-regulation may inhibit SIRT1, which further elevates acetylated p53 and BAX levels, thus activating p53/BAX signaling of the mitochondria apoptosis pathway. miR-449 may be a potential target for treating CDDP-induced nephrotoxicity.

(*continued on next page*)

Table 1 (*continued*)

Reference	Models / subjects	Tissue / cell / sample type	CDDP treatment	Time of collected sample	Platform	miRNAs deregulated associated CDDP treatment	Main findings
Zhu et al.(Zhu et al., 2016) (2016)	*in vivo:* Sprague-Dawley rats.	Serum and kidney tissue	Single dose of 6 mg/kg. To evaluate sensitivity a single dose of 3 mg/kg.	Extraction of serum daily. The extraction of kidney after 5 days.	Microarray: Agilent 2100 system	miR-146b	miR-146b levels increased after CDDP treatment in AKI rats (peak at day 3 and high until day 5) and NRK52E cells, while serum creatinine and blood urea nitrogen levels increased 3-4 days.
	in vitro: NRK52E cell line.	Rat renal tubular epithelial cells	7.5 μM for 6 h.	RNA extraction every 6 h after CDDP treatment	Real- time PCR		In renal tissue of AKI began increasing 4 days after CDDP and gradually decreased 5 days after. miR-146b may suppress ErbB4 and is a potential biomarker for acute kidney injury induced by CDDP.
Wolenski et al. (Wolenski et al., 2017) (2016)	8 male Sprague-Dawley rats (4 rats euthanized 24 hours post-dose, and 4 in 72 hours)	Urine, plasma, and kidney tissue	5 mL of 2 or 5 mg/kg	24 h and 72 h	Next-generation sequencing (miR-seq) – in 72 hours post-dose	**Urine:** **UP:**miR-378a, miR-1839, miR-140, miR-26b, let-7 g, miR-22 **Plasma:** **UP:**miR-34c, miR-128, miR-34a, miR-130b, miR-702, miR-6215, miR-484, miR-134, let-7e, miR-151, miR-191a, miR-431, miR-181b, miR-92b **Kidney:** **UP:** miR-34a, miR-146b, miR-34c **DOWN:** miR-144, miR-451.	miR-378 was the most elevated miRNA (up 6.1-fold), thus it can be a novel urinary biomarker. Comparative analysis of urine and plasma miRNAs demonstrated their utility as biomarkers of kidney injury.
Pavkovic et al. (Pavkovic et al., 2016) (2016)	108 patients with malignant mesothelioma, the sample was extracted before and after treatment	Urine	Intraoperative heated CDDP chemotherapy	Prior chemotherapy and on 9 subsequent time points (4, 8, 12, 24, 48, 72, 96, 120, and 144 h)	SYBR Green-based qPCR	miR-21, miR-200c, and miR-423	miRNAs increased significantly after CDDP treatment in patients. However, there was no relationship of the expression of these miRNAs with the renal toxicity.
	HPTEC cell line	Cells line from normal human kidney tissue	85 μM for 24 h	After CDDP treatment			In the cells, the miRNAs decreased minimally after CDDP administration and increased in medium, strengthening the hypothesis of kidney cells to be the source for these miRNAs release in urine after nephrotoxicity.
Hao et al.(Hao et al., 2017) (2017)	*in vivo*: Mice: kidney proximal tubule-specific Dicer knockout mouse line, and procimal tubule-specific p53 knockout mouse line	Kidney tissue	Single dose of 30 mg/kg	Day 1 and Day 3	TaqMan® Rodent MicroRNA array card A v2.0	miR-375	The overall depletion of miRNAs from proximal tubules does not have significant effects on CDDP-induced nephrotoxicity. MiR-375 is up-regulated in *in vivo* and *in vitro* models of CDDP nephrotoxicity. The induction is mediated by p53 and NF-κB and, upon induction may repress Hnf-1β to increase tubular cells injury and death.
	in vitro: RPTC cell line	Rat kidney proximal tubular cells	20 μM for 16 hours	After CDDP treatment	Luciferase reporter assay		

Caption: CDDP: cisplatin; miRNA: microRNA; Nrf2: nuclear factor-erythroid 2-related factor 2; SIRT1: Sirtuin 1.

Table 2
Main miRNAs suggested as possible biomarkers of CDDP-induced nephrotoxicity.

miRNA	Study that identified the miRNA	Mechanism/reason why can be a biomarker
34a	Bhatt et al. (Bhatt et al., 2010) (2010) Lee et al. (Lee et al., 2014) (2014) Pavkovic et al. (Pavkovic et al., 2014) (2014) Wolenski et al. (Wolenski et al., 2017) (2016)	Altered in rat urine. Controversial role: identified as protective against renal injury (*via* p53) and as an inducer of nephrotoxicity (by acetylation of Foxo3 and repressing SIRT1).
146b	Pavkovic et al. (Pavkovic et al., 2014) (2014) Wolenski et al. (Wolenski et al., 2017) (2016) Zhu et al. (Zhu et al., 2016) (2016)	Up-regulated in the urine and kidney of rats and contributes to renal injury of CDDP *via* downregulation of ErbB4.
378a	Wolenski et al. (Wolenski et al., 2017) (2016) Kanki et al. (Kanki et al., 2014) (2014)	Up-regulated in the urine of rats with renal injury and suggested as a biomarker of CDDP-induced toxicity. This miRNA was the most elevated in study of Wolenski.
192	Kanki et al. (Kanki et al., 2014) (2014) Pavkovic et al. (Pavkovic et al., 2014) (2014)	Up-regulated in the urine of rats with renal injury and suggested as a biomarker of CDDP-induced toxicity.
193	Kanki et al. (Kanki et al., 2014) (2014) Pavkovic et al. (Pavkovic et al., 2014) (2014)	Up-regulated in the urine of rats with renal injury and suggested as a biomarker of CDDP-induced toxicity.

Caption: CDDP: cisplatin; miRNA: microRNA; SIRT1: Sirtuin 1.

449, Qin et al. (Qin et al., 2016), showed that the up-regulation of this miRNA might inhibit the expression of a protein that protects renal proximal tubular cells, Sirtuin 1 (SIRT1), which further elevates acetylated p53 and BAX, thus activating the mitochondria apoptosis pathway. MiR-146b may contribute to CDDP-induced renal damage by downregulation of ErbB4 (Zhu et al., 2016) (also known as human epidermal growth factor receptor 4 – HER4), a member of epidermal growth factor receptor (EGFR) family (Raab and Klagsbrun, 1997), which is critical for kidney development. A recent study showed that miR-375 had its expression induced in CDDP-treated renal cells, and its inhibition decreased the CDDP-induced apoptosis in these cells, suggesting that miR-375 is a pro-apoptotic miRNA induced by p53 and the transcription nuclear factor NF-κB (Hao et al., 2017). NF-κB mediates inflammation, cell death, proliferation and differentiation under various conditions (Karin, 2006; Perkins, 2007). The induction of miR-375 may repress the transcription factor Hnf-1β (Hao et al., 2017), which drives the expression of genes for renal development, maturation and function of renal epithelial cells (Igarashi et al., 2005; Naylor and Davidson, 2014).

MiR-122 and miR-34a were also associated with nephrotoxicity following the administration of CDDP in mice and renal cells. The downregulation of miR-122 by CDDP contributed to tubular cell injury by increasing Foxo3 translation, while the upregulation of miR-34a after CDDP may contribute to nephrotoxicity by repressing SIRT1. SIRT1 promotes the acetylation (activation) of Foxo3. Foxo3 induced and activated by these dysregulated miRNAs may contribute to renal damage by increasing the p53 signaling pathway (Kanki et al., 2014).

Other studies also performed on renal cells and tissue showed a protective role of miRNAs in CDDP-induced renal injury, such as miR-34a (Bhatt et al., 2010), -125b (Joo et al., 2013) and -155 (Pellegrini et al., 2014). Although the study of Lee et al. (Bhatt et al., 2010) showed that miR-34a may contribute to acute tubular injury, Bhatt et al. (Joo et al., 2013), showed that miR-34a was induced *via* p53 and has a protective role. MiR-125b is transcriptionally increased by nuclear factor-erythroid 2-related factor 2 (Nrf2), which induces the expression of antioxidant genes and is important for the protection of many organs from oxidative stress (Aleksunes et al., 2010). MiR-155 potential target c-Fos (Pellegrini et al., 2014), when combined with Jun proteins can inhibit anti-apoptotic proteins, such as Bcl2 and Bcl-xL (Eferl and Wagner, 2003).

By analyzing all these studies involving miRNAs and CDDP-induced nephrotoxicity, we can observe that only a few miRNAs were involved in more than one study: miR-20b, -21, -34a, 130b, -140, -146b, -191a, -192, -193, -378a, -1839, and let-7 g. MiR-20b was identified in urine and kidney tissue of rats and was associated with nephrotoxicity by Kanki et al. (Kanki et al., 2014) and Pavkovic et al. (Pavkovic et al., 2014); however, Pavkovic et al. (Pavkovic et al., 2014) did not suggest further investigations of this miRNA as a biomarker of renal damage. MiR-21 was also identified in Pavkovic et al. (Pavkovic et al., 2014); however, another study performed by the same author found no relationship of nephrotoxicity and this miRNA after the administration of CDDP in cancer patients (Pavkovic et al., 2016).

Pavkovic et al. (Pavkovic et al., 2014), suggested as possible biomarkers of nephrotoxicity miR-192 and -193, which were also altered in Kanki et al. (Kanki et al., 2014). MiR-1839, -140, -191a, -130b, let-7 g, and -378a were not upregulated only in the urine of rats in Kanki et al. (Kanki et al., 2014), but also in the urine, plasma or kidney of rats treated with CDDP in Wolenski et al. (Wolenski et al., 2017), miR-378a was the most elevated miRNA and the only suggested as a urinary biomarker. MiR-34a and -146b were significantly altered after CDDP infusion in two studies, Kanki et al. (Kanki et al., 2014) and Wolenski et al. (Wolenski et al., 2017), and other authors also studied them. MiR-34a was shown to be a miRNA induced by CDDP that performs a protective role in renal cells (Bhatt et al., 2010), and was also identified as a promoter of Foxo3 acetylation by repressing SIRT1, thus contributing to renal damage (Lee et al., 2014); miR-146b was shown to contribute to CDDP renal injury *via* downregulation of ErbB4 (Zhu et al., 2016). Table 2 shows the main miRNAs suggested as possible biomarkers of CDDP-induced nephrotoxicity. Fig. 2 shows the mechanisms already studied to explain how some of them induce renal damage.

The involvement of miRNA in CDDP-induced ototoxicity was also observed. This involvement was studied by a research performed to assess the pathway of the protective effect of Ginkgolide B (GB) against hearing impairment. CDDP was administrated to House Ear Institute-Organ of Corti 1 (HEI−OC1) cells and significantly decreased miR-214 expression, GB treatment significantly increased miR-214, which decreases p53 and, consequently, reduced NOX4 and $p66^{shc}$ downstream (Ma et al., 2016). NOX4 is a primary member of the NOX family and is involved in the cytotoxicity induced by CDDP (Kim et al., 2010); activated $p66^{shc}$ regulates state redox within mitochondria, generating ROS (Bhat et al., 2015; Natalicchio et al., 2015). Based on this result, miR-214 may be considered as a protector miRNA in CDDP-induced ototoxicity. Another miRNA was identified as a protector against ototoxicity, miR-182. Overexpression of miR-182 before the CDDP treatment

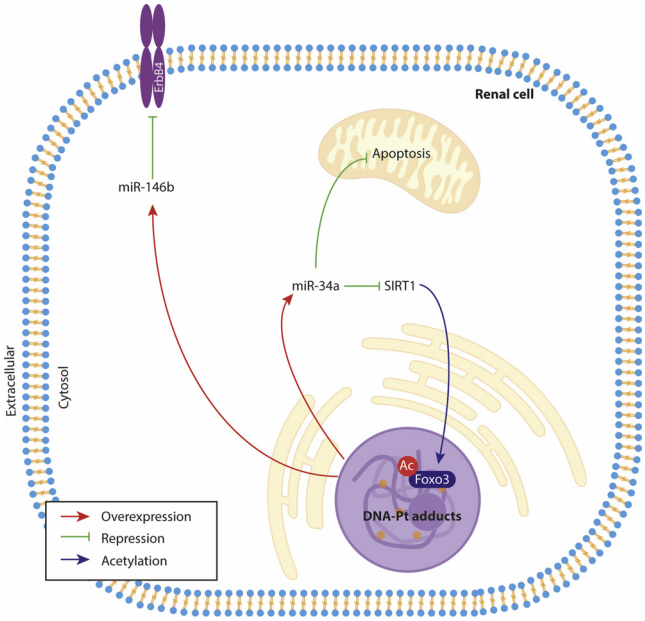

Fig. 2. Proposed mechanisms for induced renal damage by the possible miRNAs biomarkers of CDDP-induced nephrotoxicity. The overexpression of miR-146b suppresses the ErbB4 expression, involved in kidney development. The induction of miR-34a *via* p53 protects CDDP-induced apoptosis in renal cells; on the other hand, CDDP can up-regulate miR-34a, which promotes the acetylation of Foxo3 by repressing SIRT1.

was found to inhibit the expression of Foxo3a, a pro-apoptotic transcription factor, in hair cell nuclei (Li et al., 2016).

MiRNAs polymorphisms are also a relatively new subject of investigations in the pharmacogenomics field. MiR-polymorphisms (genetic variants in the miRNA regulatory pathway) occur at or near a miRNA binding site of a functional gene, which interferes on the miRNA expression and function (Mishra et al., 2008). These variants can occur in the 3′-UTR of a miRNA target gene, in the genes involved in miRNA biogenesis and pri-, pre-, and mature-miRNA sequences. A genetic variant that affect the biogenesis of the miRNA can affect several genes, while a variant in the 3′-UTR is probably more specific and causes fewer consequences (Mishra and Bertino, 2009).

A functional SNP in Has-miR-196a2 (rs11614913) was associated with severe toxicity induced by platinum-based chemotherapy in NSCLC patients. In the study performed by Xiaoying et al. (Zhan et al., 2012), the patients were treated with chemotherapy regimens involving more than one antineoplastic, being one of these CDDP 75 mg/m^2 or carboplatin AUC 5. Severe overall toxicity required the presence of severe hematologic toxicity (leukocytopenia, neutropenia, anemia, or thrombocytopenia) or gastrointestinal toxicity (nausea or vomiting). The risk of severe overall toxicity was significantly higher in individuals with homozygous CC ($p = 0.02$; odds ratio (OR) = 1.73; 95% confidence interval (CI) 1.10–2.71) compared with T allele carriers (TT/CT). However, the genetic variant had no significant association with leukocytopenia, neutropenia, anemia, thrombocytopenia, or hematologic and gastrointestinal toxicity. In the association with specific treatment, among the patients receiving CDDP regimen, the severe overall toxicity was also higher in homozygous CC ($p = 0.008$; OR = 2.04; 95% CI 1.20–3.48). MiR-196a target regulation molecules including Homeobox B8 (HOXB8), High Mobility Group AT-Hook 2 (HMGA2), annexin A1, and the CC genotype, increase the binding efficiency to its target mRNA (Hu et al., 2008). This study showed the potential influence of miR-polymorphisms in CDDP-induced toxicity; however, further studies must be performed on patients using CDDP as the only chemotherapy treatment, as well as evaluating more toxicities.

5.3. Potential utility of epigenetic biomarkers in toxicity induced by cisplatin

The need for new biomarkers for CDDP-induced toxicity is real, since these toxicities result in the interruption of treatment or decreased doses of CDDP in many cancer patients, and until now, we have no effective biomarkers of the main toxicities.

Traditional markers for renal damage usually are not sensitive, since some of them are only altered after the kidney injury is extensive, and unspecific due to several other physiological processes, it may change their baseline levels. This lack of sensitivity and specificity can lead to false positive or false negative results, causing the late detection of a renal lesion or false conclusions (Herrera-Perez et al., 2016). The most commonly used biomarkers for assessing CDDP-induced nephrotoxicity are serum creatinine and urea; however, they may be influenced by various physiological processes, such as protein synthesis and degradation (Gautier et al., 2010), and dehydration (Mendelssohn et al., 1999).

Studying epigenetic biomarkers is a challenge since these are not constitutive biomarkers like genetic ones, being necessary to detect them at specific moments. There are very few research on DNA methylation as possible biomarkers of toxicities induced by CDDP. However, a study already showed that DNA methylated in white blood cells can be used as a biomarker to predict chemotherapy toxicity in cancer patients (Flanagan et al., 2013). Studies involving CDDP-induced toxicities and DNA methylation are scarce and did not focus on new epigenetic biomarkers, unlike miRNAs, which are much more studied for this purpose.

Identifying miRNAs as new biomarkers of CDDP-induced toxicity is a challenge since many studies present conflicting results. To circumvent this challenge, comparing the results found by other studies and the identified miRNAs in specific organs is necessary. Additionally, further research are needed to assess the specificity of the miRNAs selected in the cited studies for CDDP-induced nephrotoxicity and other toxicities. Human studies are also needed to confirm if the expression of miRNAs is altered in the biological fluids of those subjects with toxicities caused by chemotherapy, since the identification of mechanisms that regulate these toxicities and the monitoring of the expression of one or more specific miRNAs may offer new methods to optimize CDDP treatment.

We must emphasize that a single biomarker is not enough to perform an early and specific detection, but a group of biomarkers are necessary to improve the sensitivity and specificity of the test, and to associate the genes with the pathophysiology of the disease to be detected. The validation in different studies is also a strong indication that a miRNA can be a good biomarker. Considering this discussion, the miRNAs miR-34a, -146b, -378a, -192, and -193 represent an attractive study group to evaluate potential biomarkers of detection of CDDP-related nephrotoxicity.

Based on new epigenetic biomarkers, the distinction between patients who tolerate intensive CDDP treatment from those patients who are more susceptible to toxicities may result in a clinical improvement, providing an opportunity to intervene or tailor the treatment without sacrificing efficacy.

Conflict of interest statement

None.

Authors' contributions

All authors contributed to the conception of the article, writing, and revision of the final manuscript and agree on its submission to this journal.

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