A brief dive into the phenomenon of cisplatin resistance in non-small-cell lung cancer

BioOpen 2021 – Post-conference article

Maciej Sobczak [ID]

University of Lodz, Faculty of Biology and Environmental Protection, Department of General Biophysics, Pomorska 141/143, 90-236 Lodz, Poland
E-mail: maciej.sobczak@biol.uni.lodz.pl

ABSTRACT

Lung cancer is one of the most lethal types of cancer due to a lack of proper treatment. The rare presence of molecular therapy targets forces the use of platinum-based drugs. Cisplatin, approved by the USA as an anticancer therapy in the 1970s, is still one of the most prominent therapies against lung cancer. Unfortunately, the biggest limitation of cisplatin-based therapy is the development of cisplatin resistance. Cancer cells overcome the vast DNA damage caused by the drug in a variety of ways such as detoxication and extracellular transport of the drug, enhanced repair mechanisms, omitting apoptosis and epigenetic alterations. Chemotherapy resistance is an issue that so far cannot be dealt with. Nevertheless, better understanding of the molecular pathways behind cisplatin resistance brings hope for better therapy outcomes in lung cancer patients.

KEYWORDS: non-small-cell lung cancer, cisplatin, cisplatin resistance

Introduction

Despite the decades of extensive studies on cancer, it remains one of the leading causes of human deaths worldwide. It is estimated that in the United States of America in 2021, over 1.8 million new cancer cases will be diagnosed, while over 608,000 Americans will die from a variety of cancer types. It is expected that almost 25% of cancer-related deaths in both women and men will be caused by lung cancer. Due to that fact, lung cancer is placed among the most lethal cancer types in both sexes (Siegel *et al.* 2021). Although several causes of lung cancer are listed in the literature, tobacco smoking is considered a critical factor for the development of lung cancer. A variety of cancerogenic substances in the tobacco smoke may cause DNA damage, which in turn may cause mutations and therefore lead to cancer initiation and progression (Dela Cruz *et al.* 2011).

Lung cancer can be divided into two subtypes: small-cell lung cancer (SCLC) and non-small-cell lung cancer (NSCLC)

(Zappa and Mousa 2016). Unfortunately, most NSCLC cases (85–90%) lack defined molecular targets for targeted therapies; therefore, platinum-based chemotherapeutics are widely used in NSCLC treatment (Fennell *et al*. 2016).

The commonly known platinum-containing compound cisplatin is frequently used in the approach to cure multiple types of cancer. Due to its alkylating properties, cisplatin prevents DNA strands from uncoiling by forming adducts with guanine nucleotides, which in turn debilitates DNA replication (Wishart *et al*. 2018). In response to cisplatin-related DNA damage, DNA lesion repair machinery is triggered. Therefore, proteins engaged into mechanisms such as nucleotide excision repair (NER) or mismatch repair (MMR) attempt to restore DNA integrity. Depending on the severity of the DNA damage, cells may either undergo cell cycle arrest and repair the DNA, or proceed to cell death (Figure 1) (Galluzzi *et al*. 2012). Although cisplatin has been proven to be at least to some extent successful as an anticancer therapy, there are several limitations to its use. In addition causing to nausea, cisplatin is known to be nephro- and neurotoxic (Fennell *et al*. 2016).

The problem of cisplatin resistance

Possibly the greatest limitation of successful use, not only of cisplatin but many other chemotherapeutics as well, is the development of drug resistance by cancer cells. Cisplatin resistance is a complex phenomenon that integrates a variety of molecular processes in order to ensure cell survival. Cancer cells are able to adapt to some extent to the presence of the drug and overcome its activity by, for example, enzymatic deactivation or a change in the activity of the drug, drug efflux, extensive lesion repair or alterations in epigenetics (Figure 2) (Gąsiorkiewicz *et al*. 2021). The aforementioned strategies will be briefly addressed in the following paragraphs.

Glutathione-dependent resistance

Glutathione (GSH) plays a variety of roles in mammalian cells. Its activity includes inter alia protection from reactive oxygen and nitrogen species, and detoxification of various compounds as
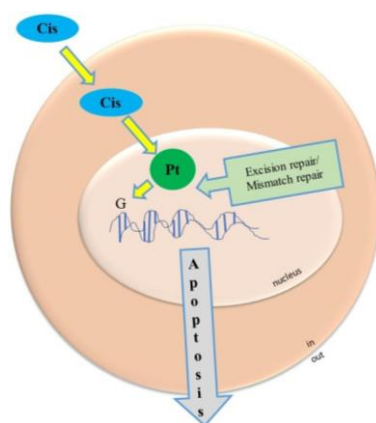
Figure 1. General mechanism of cisplatin response. Cisplatin forms DNA adducts with guanine bases in DNA. Depending on the severity of the DNA lesions, cells may repair the DNA using NER or MMR pathways, or undergo apoptosis. Cisplatin is depicted by blue ellipses and the platinum atom by a green ball.
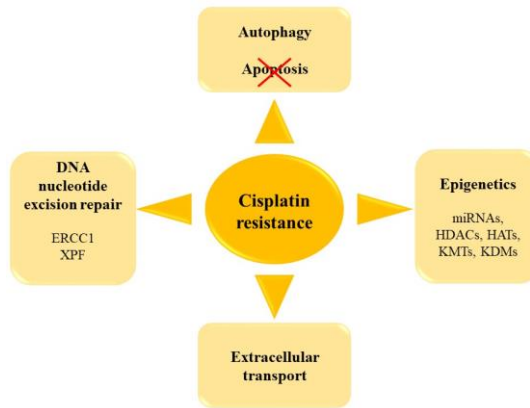
Figure 2. Main cisplatin resistance mechanisms in lung cancer.

well as extracellular transport of harmful agents (Pizzorno 2014). The latter function of GSH is facilitated by glutathione-S-transferase (GST), which promotes the formation of GSH-drug complexes. Next, the complexes are removed from the cells via ATP-binding cassette transporters (ABC transporters) such as ABCC1, ABCC2 and ABCB1 (Lan *et al*. 2018). While most of the efficiency in counteracting cisplatin takes place due to drug efflux, some of its activity to form DNA adducts is diminished by the formation of GSH-drug complex. Increased efficacy of complex formation has been observed upon increased expression of the P1-1 variant of GST (Peklak-Scott *et al*. 2008).

Autophagy-related cisplatin resistance

A variety of cell-stressing factors including cisplatin may lead to the autophagy of cancer cells. Autophagy allows a cell to recycle energy extracted from digesting its own components in order to cope with stressors. As autophagy is considered an anti-chemotherapeutic measure, cisplatin-resistant cells tend to exhibit a high level of autophagy (Gąsiorkiewicz *et al*. 2021), which suggests the potential involvement of autophagy in the origin of cisplatin

resistance. Additionally, autophagy can be induced by hypoxic conditions. It is a common condition for solid tumours to lack a proper oxygen supply due to insufficient vascularization of the tumour site; therefore, those starving cancer cells redirect their metabolism into autophagy (Yun and Lee 2018). Hypoxia-induced metabolic and genetic changes desensitize cancer cells to cisplatin treatment in comparison to cells with a proper oxygen supply. Under hypoxic conditions, cancer cells are less likely to undergo apoptosis due to inhibition of Bax protein translocation to the mitochondria. Moreover, under hypoxic conditions, expression of the pro-apoptotic mediators BNIP3 and BNIP3L is reduced in cisplatin-treated lung cancer cells. The opposite effect is observed when cells are subjected to either hypoxia or cisplatin alone. Additionally, the simultaneous presence of hypoxia and cisplatin treatment robustly elevates expression of the autophagy markers Beclin-1, p-Beclin-1, LC3-II and p65 (Wu *et al*. 2015). Therefore, hypoxia-induced autophagy may support cisplatin resistance by redirecting cancer cells from DNA damage-triggered apoptosis into autophagy that supports cancer cell survival.

Nucleotide excision repair in cisplatin-resistant cells

As mentioned previously, NER is the main DNA damage repair mechanism involved in dealing with cisplatin-induced DNA adducts. Although the exact mechanism by which the NER pathway influences cisplatin resistance remains unknown, some proteins involved in the process have been identified. Two components of the NER machinery, endonuclease XPF accompanied by ERCC1 protein, have been acknowledged to enhance cisplatin-induced DNA damage in drug-resistant cancer cells (Rocha *et al*. 2018). Knockdown of either of the proteins results in increased cisplatin toxicity in NSCLC cells. Moreover, simultaneous knockdown of both proteins results in a cumulative cytotoxic effect (Arora *et al*. 2010). Notably, histone deacetylases (HDACs) may be involved in the regulation of ERCC1 expression in lung cancer. The introduction of HDAC inhibitors (iHDACs) increases the acetylation of E2F1, which promotes association of E2F1 with the promoter region of miR-149. The miRNA recognizes and binds the 3' UTR region of ERCC1, decreasing its expression and thus promoting cisplatin toxicity in NSCLC cells (He *et al*. 2020).

Epigenetic alterations in cisplatin resistance

Histone-modifying enzymes, such as histone acetyltransferases (HATs), deacetylases (HDACs), methyltransferases (KMTs) and demethylases (KDMs), play a role in NSCLC development. In particular, some of these enzymes have been involved in the development of cisplatin resistance: BRCA1/2, HDAC6, KAT5, KAT3A, KAT2B, KAT13B, KAT13D, KMT6 (O'Byrne *et al*. 2011). For example, ubiquitin-specific peptidase 10 (USP10) has been found to stabilize HDAC6, thus promoting its hyper-activity. Moreover, both enzymes are overexpressed in lung cancer. USP10 knockdown leads to increased cisplatin toxicity in a p53-deficient murine xenograft model (Hu *et al*. 2020). Besides epigenetic writers and erasers, miRNAs play a variety of regulatory roles crucial for tumour progression and survival as well as in the development of cisplatin resistance (Fadejeva *et al*. 2017). miR-29c expression is decreased in tumour samples taken from NSCLC patients. Interestingly, the miRNA acts as a cisplatin resistance suppressor, by specific inhibition of AKT2, a key signal transducer in the PI3K/AKT pathway (Sun *et al*. 2018).

Conclusions

The phenomenon of cisplatin resistance or chemotherapy resistance in general is a complicated issue. Despite years of extensive studies, the problem remains elusive and successful anticancer therapy is still non-existent. Besides the off-target toxicity, the main problem of chemotherapy resistance is the multitude of potential cellular pathways and mechanisms that may substitute those that are targeted and inhibited with specific compounds. Nonetheless, the better the understanding of the molecular mechanisms behind cisplatin resistance, the better the potential outcomes and survival chances for cancer patients.

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