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Commentary

Disulfide isomerase family-6 mediates cisplatin resistance by interfering with apoptosis and autophagy

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Cisplatin (cis-diamminedichloroplatinum (II)) is the backbone of chemotherapy, above all in lung cancers (small and non-small cell lung cancer (SCLC and NSCLC)). The drug was known as Peyrone's salt for more than 100 years until it was recognized as an anti-cancer drug through a serendipitous finding in 1969. Cisplatin has been used in cancer medicine since the 1972 [1], albeit, cisplatin-based chemotherapy still provides short-lived progression-free survival in advanced NSCLC (Fig. 1).

Breast cancer susceptibility gene 1 (BRCA1)-customized cisplatin therapy was unsuccessful in two randomized clinical trials in European and Chinese NSCLC patients [2]. The mechanisms of cisplatin resistance have been related to nucleotide excision repair (NER), as well as other DNA repair pathways that includes BRCA1 modulating stress-induced apoptosis signaling cascade constituting H-ras oncogene, mitogen-activated protein kinase 4, JNK, Fas and Fas ligand, and the activation of caspase-9 [1,3,4]. The intrinsic mitochondrial apoptosis pathway is controlled by interactions between the pro-apoptotic and anti-apoptotic members of the BCL2 protein family. One central gene is BCL2L11 (also known as BIM). Tumor cells mostly use the mitogen-activated protein kinase (MAPK) proteasome axis to escape from BCL211 induced apoptosis. The amount of BCL211 expression can control the fate of tumor cells [4]. MAPK pathways modulate cisplatin sensitivity. MAPKs encompass a family of kinases that are divided into three subfamilies: c-Jun N-terminal kinase 1/2 (JNK 1/2), p38 and extracellular-signal-regulated kinase (ERK). The DNA damage response also involves the ATR-Claspin-Chk1 pathway [1,5]. Intriguingly, the endoplasmic reticulum (ER) resident PERK has been shown to regulate ERK phosphorylation and inhibit the ATR-Claspin-Chk1 pathway [6]. Less known is the role of autophagy and its regulation of the response to chemotherapy. Autophagy involves the formation of double-membrane vesicles, known as autophagosomes for cargo delivery to the lysosomes. Membranes from the ER, the outer membrane of mitochondria, the Golgi apparatus, as well as plasma membranes contribute to its formation [7]. In the current *EBioMedicine* article, Bai and colleagues uncover a common mechanism of resistance to cisplatin in NSCLC through the protein disulfide isomerase family-6 (PDIA6), that negatively regulates cisplatin-induced autophagy and apoptosis [8]. PDIA6 is mainly localized in the ER and functions as an oxidoreductase, that catalyzes the formation of disulfide bond and as a chaperone in protein folding. Bai et al. show that PDIA6 is upregulated in NSCLC cells and in patients' tumors, both at mRNA and protein levels. They convincingly show that PDIA6 inhibits cisplatin-induced NSCLC cell apoptosis and autophagy via interacting with MAP 4 K1 to suppress the JNK/c-Jun signaling pathway. The authors show that MAPK has central functions in apoptosis and autophagy [8]. The activation of Jun Bcl-2 phosphorylation activates Beclin1-induced autophagy and caspase-3-mediated apoptosis [4,7].

PDI family members are defined by the presence of one or more thioredoxin domains containing the CXXC motif and catalyze the formation of cysteine disulfide bonds, critical for correct protein folding in the ER. Anterior gradient 2 (a.k.a. AGR2, PDIA17) encodes an ER-resident protein that is overexpressed in various cancers, including NSCLC. AGR2 suppresses p52 activation through inhibition of p38 MAPK. AGR2 promotes lung tumorigenesis and correlates with EGFR ligands (EGF and TGFA) in EGFR-mutant, but not KRAS-mutant NSCLC [9]. Bai et al. have found that PDIA6 is broadly overexpressed in a panel of NSCLC cell lines, including KRAS-mutant cell lines (for example, A549, NCI-H460) [8]. The contribution of the PDIA6/MAP4K1/JNK/c-Jun signaling pathway in KRAS-mutant NSCLC warrants further exploration. The main contribution of the study is to highlight the coordinated intervention of the mitochondrial apoptosis pathway and autophagy in cisplatin resistance. Moreover, the study attempts to illuminate the multiple difficulties in overcoming cisplatin resistance and the limited, short-lived response in the clinical setting [2]. Another unsolved question is that PDIA6 probably remains an undruggable target and the development of small molecular inhibitors could be difficult. It is tempting to surmise that poly (ADP-ribose) polymerases (PARP-1) could overcome PDIA6 cisplatin-mediated resistance. Since c-Jun is a substrate of JNK, it is possible that it regulates NER and PARP-1 phosphorylation. Nevertheless, PARP-1 inhibitors are currently being used for the treatment of ovarian and breast cancer and are in clinical trials for the treatment of lung cancer. Bai et al. show enticing experiments where PDIA6 knockdown resulted in upregulated levels of autophagy proteins, including LC3II, Beclin1, and Atg5 in two NSCLC cell lines (NCI-H520 and Anip973). These findings could pave the way for understanding the potential role of cisplatin and programmed cell death ligand 1 inhibitors in DNA-induced autophagy and signaling through

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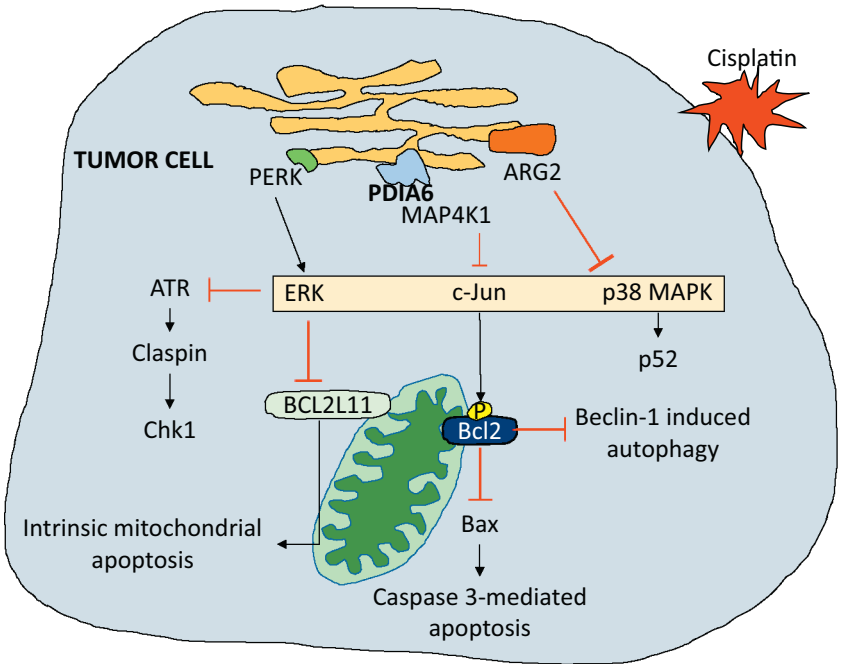

Fig. 1. PDIA6 through c-Jun modulates sensitivity to cisplatin.

the cGAS-STING pathway, as well as the activation of ER-resident PERK that has been found to activate after BRAF or MEK inhibition, leading to more ERK phosphorylation and an increase of autophagy [8]. All in all, autophagy is not very well understood at the clinical level and the stimulation of autophagy in response to treatment could enhance or decrease chemo-resistance and anti-tumor immunity [7].

Disclosure

The authors report no conflicts of interest in this work.

Author contribution

Both authors contributed equally in writing of the commentary.

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