

Faces of Autophagy Inhibition in Cisplatin Therapy

Subjects: Pharmacology & Pharmacy

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Cisplatin treatment promotes autophagy in both cisplatin-sensitive and cisplatin-resistant cells. Consequently, inhibition of autophagy can be considered a strategy for improving cisplatin chemosensitivity. This is the positive side, which is called Yang. However, the functional activity of cisplatin-induced autophagy is related to different genetic phenotypes and tumor types as well as the microenvironment of the tumor. In addition, preclinical studies have found that pharmacological autophagy inhibitors are not uniformly effective in enhancing the effectiveness of cisplatin and may also exacerbate the side effects of cisplatin toward normal tissue. This is the negative side, which is called Yin.

Keywords: autophagy ; chloroquine ; cisplatin ; p53 ; resistant

1. Introduction

Cisplatin (cis-diamminedichloroplatinum (II)) was first approved for clinical use by the FDA in 1978 and has continued to be used as a first-line chemotherapeutic agent for the treatment of approximately 50% of solid tumors, including lung, head and neck, breast, testicular, ovarian, prostate, and bladder cancers ^{[1][2]}. Cisplatin was initially synthesized by Michel Peyrone in 1845 and therefore was initially called Peyrone's salt. In testing the effects of platinum compounds on *E. coli* proliferation, Rosenberg and his group found that cisplatin also has inhibitory effects on sarcoma 180 and L1210 leukemia cells ^{[3][4]}. Prior to this time, chemotherapeutic drugs in the clinic were all natural or synthetic organic compounds, and cisplatin became the first antitumor candidate containing heavy metal elements. After approximately 15 years of preclinical experimentation, through 1975, clinical trials led by the J.M. Hill laboratory confirmed the antiproliferative activity of cisplatin against multiple solid tumors ^[5]. Although cisplatin has a wide range of antitumor activity, its side effects continue to limit its therapeutic use and efficacy. In the clinic, patients treated with cisplatin often experience symptoms of renal tubular necrosis (nephrotoxicity), hearing loss or cochlear damage (ototoxicity), and peripheral sensory neuropathy (neurotoxicity) ^[6]. These side effects appear more frequently with increasing doses of the drug. In addition to side effects, patients with solid tumors will frequently develop resistance to cisplatin, forcing physicians to consider other treatment options. As cisplatin resistance is often associated with cross-resistance to other commonly used cytotoxic chemotherapeutic drugs, such as doxorubicin and etoposide, this results in a reduction in treatment options ^[7]. There are many factors leading to cisplatin resistance, including alterations in DNA metabolism, epigenetic and transcriptional modifications, activation of drug efflux systems, and subcellular drug localization and translocation ^[8].

The mechanisms mediating the antitumor actions of cisplatin have been studied for decades, with DNA being the primary drug target. Once inside the cell, cisplatin undergoes aquation to form $[\text{Pt}(\text{NH}_3)_2\text{Cl}(\text{OH}_2)]^+$ and reacts with DNA to form monoadducts, interstrand, intrastrand or DNA-protein cross-links, affecting the DNA double helix structure and nucleosomes of cancer cells ^{[9][10]}. This leads to replication and transcriptional repression, and DNA double-strand breaks (DSBs), which then initiate DNA repair. Once DNA repair fails or is overwhelmed by excessive DNA damage, cell death is triggered ^[11]. An increased capacity to repair DNA is considered as the most significant feature of platinum-resistant cells ^{[12][13]}.

The central downstream event following cisplatin interaction with cellular DNA is apoptosis ^{[14][15][16]}. The intrinsic pathway of cisplatin-induced apoptosis involves the promotion of oxidative stress, whereby cisplatin-treated cells accumulate excessive reactive oxygen species (ROS) (hydroxyl radicals and superoxide). Abnormally accumulated ROS damages mitochondrial respiratory function, leading to mitochondrial dysfunction ^[17]. ROS, influencing the pro-apoptotic protein Bax, also cause damage to mitochondrial DNA and a reduction in mitochondrial membrane potential, which promotes mitochondrial destruction. Cytochrome c and caspase 9 are then released by damaged mitochondria and evoke a cascade of caspase cleavage reactions ^[18].

The extrinsic pathway of cisplatin-induced apoptosis is mediated via a type-II membrane protein that activates the Fas receptor in conjunction with the Fas ligand, thereby promoting the formation of the apoptosome complex by the Fas-associated death domain and pro-caspase 8. This apoptosome complex activates caspase 3, caspase 6, and caspase 7,

ultimately leading to apoptosis [19]. In addition, cisplatin generally arrests cells in the G1/S or G2 phase of the cell cycle, providing time for repair of damaged DNA prior to DNA synthesis. When cells fail to repair DNA damage at the cell cycle checkpoints, they are forced to re-enter the cycle prematurely, progressing to apoptosis [20][21]. As a “gatekeeper”, the activation of p53 also contributes to cisplatin-induced tumor cell apoptosis [22]. In addition, the p21, MDM2, GADD45 [23], MAPK pathway [24], and PI3K/Akt pathways [25], which are related to p53 and cell cycle regulation, have all been shown to be involved in cisplatin-induced apoptosis.

Macroautophagy (which will be referred to as autophagy) is a critical process in eukaryotic cells whereby superfluous organelles, misfolded proteins, and other cellular debris are cleared, restoring a state of cellular equilibrium [26]. This process is an evolutionarily conserved process whereby cellular debris or toxic cellular components are engulfed by the autophagosome, a double-layered membrane structure, and transported to acidic lysosomes, where they undergo degradation and recycling [27]. Autophagy occurs in cells under nutrient-poor conditions, responding to the decline in external energy sources. Therefore, autophagy is generally considered to reflect a survival-promoting function. However, if autophagy is continuously or overly activated, cell death will be triggered. Upon cisplatin treatment, autophagy induction has been detected in both cisplatin-sensitive and cisplatin-resistant cancer cells. In fact, the basal level of autophagy was significantly elevated in cisplatin-resistant cells [28][29][30][31].

Defective apoptosis is one cause of cisplatin resistance, which confers a survival advantage to tumor cells. This defect facilitates the generation of cellular stress-mediated autophagy, which precedes or effectively blocks the apoptotic cascade. A large number of studies have shown that when cisplatin-induced autophagy is inhibited in cancer cells, the manner of cell death switches to apoptosis [28]. Therefore, taken together, cisplatin-induced autophagy is often considered one of the primary factors thwarting its chemotherapeutic effects. However, the role of autophagy is often far more complex than has been appreciated.

In addition to autophagy and apoptosis, the tumor cell response following cisplatin treatment can include cellular senescence, as in some cases, persistent DNA damage leads to long-term growth arrest [32]. Although senescence was previously considered an irreversible response after chemotherapy, recent studies from a number of laboratories have shown that tumor cells have the capacity to escape from this therapy-induced senescence [33].

2. The Yin and Yang Faces of Autophagy Inhibition in Cisplatin Therapy

2.1. A Beneficial Treatment Strategy of Autophagy Inhibition Combined with Cisplatin Is Closely Related to Tumor Types

CQ and HCQ are quinoline derivatives that exhibit a variety of activities and are able to cross cell membranes by passive diffusion. These drugs accumulate and are subsequently protonated in acidic vesicles such as lysosomes. This accumulation leads to a weakened acidic environment, thereby disrupting the endolysosomal system [34]. The fusion of lysosomes and autophagosomes is a critical step for the completion of autophagy, sometimes referred to as autophagic flux. CQ interferes with the fusion process and is therefore considered to be an effective inhibitor of late-stage autophagy [35]. The combination of CQ with cisplatin has been reported to not only increase the chemotherapeutic efficacy of cisplatin-sensitive cancer cells [35] but also to effectively improve the chemosensitivity of cisplatin-resistant cancer cells (Table 1). For example, as listed in Table 1 below, CQ increased cisplatin sensitivity by inhibiting autophagy in cisplatin-resistant A549 (A549/cisplatin) [36], endometrial cancer [37], urothelial carcinoma [38], epithelial ovarian cancer [39], esophageal cancers [29], and neuroblastoma [40]. Apart from the generally recognized autophagy inhibitory effect, recent studies have also reported autophagy-independent activities of CQ against breast cancer [41], as well as increased cisplatin sensitivity to laryngeal tumor cells by promoting repolarizing tumor-associated macrophages from M2 to M1 in vivo and in vitro [42].

Table 1. Effect of CQ or HCQ on cisplatin-treated cancer cells.

Cancer Types	In Vitro Study Models	In Vivo Study Models	Effect of CQ or HCQ on Cisplatin Sensitivity	Reference
NSCLC	A549/cisplatin cells	-	Increased	[36]
	H460 cells	-	No effect	[43]
Endometrial cancer cells	Ishikawa/cisplatin cells	-	Increased	[37]

Cancer Types	In Vitro Study Models	In Vivo Study Models	Effect of CQ or HCQ on Cisplatin Sensitivity	Reference
Urothelial carcinoma cells	RT-112/cisplatin cells	-	Increased	[38]
Ovarian cancer	A2780-CP20/cisplatin cells	An orthotopic mouse model established with A2780-CP20 cells and a drug-resistant patient-derived xenograft model	Increased	[39]
	ARHI-low expressed SKOV3 cells	-	No effect	[44]
Esophageal cancers	EC109/cisplatin cells	Nude mice xenografted with EC109/cisplatin cells	Increased	[29]
Neuroblastoma cells	Cisplatin-resistant model SK-N-BE(2)Cres cells	-	Increased	[40]
Oral squamous cell carcinoma	SCC-4 cells and SCC-4/cisplatin cells	-	Increased in SCC-4 cells, no effect in SCC-4/cisplatin cells	[45]
Pediatric medulloblastoma cells	DAOY and ONS76 cells	-	no effect	[46]
Breast cancer cells	67NR and 4T1 cells	-	no effect	[41]

The above studies appear to suggest that the combination of CQ and cisplatin is indeed a potential approach to overcoming cisplatin resistance, where this sensitizing effect is largely relevant to specific tumor types. For instance, in patients with cisplatin-resistant oral squamous cell carcinoma, inhibition of autophagy does not seem to be an ideal treatment. A recent study showed that although CQ increased the apoptosis rate of cisplatin-treated SSC-4 cells, it had a very limited effect on the apoptosis of cisplatin-resistant SSC-4 cells (only about a 5–7% increase) [45].

For cells that are inherently sensitive to cisplatin, the outcomes for CQ in combination with cisplatin seem to be more relevant to the tumor types. For example, in cisplatin-sensitive glioblastoma, pediatric medulloblastoma cell lines, atypical teratoma/rhabdomyosarcoma cell lines [46], low ARHI-expressing ovarian cancer SKOV3 cells [44], p53 wild-type lung cancer H460 cells [43] and p53-null mouse breast cancer 67NR and 4T1 cells [41], CQ had no significant effect on the activity of cisplatin (**Table 1**).

In addition to CQ, Bafilomycin-A1 and PI3K inhibitors (3-MA and wortmannin) are also common inhibitors of autophagy and have been reported to increase the chemosensitivity of cisplatin in different tumor cells in a large number of studies, which have been summarized in many reviews [28]. Nevertheless, there are also exceptions. An example is that the 3-MA showed no effect on the cell proliferation rate in cisplatin-treated nasopharyngeal carcinoma CNE1 cells [47]. More interesting examples are cisplatin-resistant gastric cancer KATO-III cells, for which studies have shown that the resistance is independent of MRP1 and MDR1 and rather linked to Aldoketoreductase1 C1 and C3 (AKR1C1 and AKR1C3). When AKR1C1 and AKR1C3 were inhibited, the combination of 3-MA paradoxically decreased the cell death rate of KATO-III induced by cisplatin [48].

Based on the data presented above using combinations of autophagy inhibitors with cisplatin, although most of the reported cisplatin-resistant cells demonstrated sensitization from the combination treatments, inefficient or even ineffective outcomes were also evident. Moreover, most of the experimental data were generated solely in in vitro cellular models. Furthermore, the paradigm that “autophagy is a drug resistance mechanism” may have occasionally resulted in a less than objective interpretations of the data.

In addition to these more classical autophagy inhibitors, there are some compounds and nanomaterials that have also been found to overcome cisplatin resistance by disrupting autophagy. U0126, a MAPK inhibitor, enhanced cisplatin-induced apoptosis by inhibiting autophagy in cisplatin-resistant ovarian cancer cells [49] and NSCLC cells [50]. Some natural products have also been found to promote the activity of cisplatin by regulating autophagy (**Table 2**). For example, astragaloside IV (AS-IV) derived from *Astragalus membranaceus* sensitizes cisplatin-resistant NSCLC cells to cisplatin by inhibiting ER stress and autophagy [51]. However, the role of autophagy induced by natural products in combination with cisplatin is not consistent. For instance, *Gardenia jasminoides* (GJ), a medicinal herb abundant with flavonoids, in

combination with cisplatin paradoxically activated cytotoxic autophagy in glioblastoma multiforme [52]. In addition, the combination of autophagy-inhibiting nanoparticles or materials with cisplatin enhanced the chemosensitivity or reduced the resistance to cisplatin. For instance, a nanoparticle-based co-delivery system (siBec1@PPN) is centered on the efficient co-delivery of Beclin1 siRNA (Beclin1 is an autophagy initiation factor) and cisplatin to enhance the inhibitory effect on cisplatin-resistant A549 cells by inhibiting autophagy in vivo and in vitro [53]. Compared with the poly lactic acid (PLA) + cisplatin nanoparticles (CDDP-PLA NPs), the PLA + cisplatin-CQ nanoparticles (CDDP/CQ-PLA NPs) reduced autophagy and enhanced the ROS and apoptosis of Cal-27 cells [54].

Table 2. Role of autophagy in synergistic effects of natural products and cisplatin.

Compound	In Vitro Study Models	In Vivo Study Models	The Role of Autophagy in Cisplatin Only-Treated Models	Effect of Combination Treatment on Autophagy	Reference
Astragaloside IV (AS-IV) derived from <i>Astragalus membranaceus</i>	Cisplatin-resistant NSCLC cell lines	-	Unknown	Decreased autophagy levels	[51]
Hederagenin, a triterpenoid derived from <i>Hedera helix</i>	NSCLC cell lines NCI-H1299 and NCI-H1975	NCI-H1299 cells xenograft model	Unknown	Decreased autophagy levels	[55]
Acetyl-11-keto- β -boswellic acid (AKBA), a pentacyclic triterpenes, from <i>Boswellia serrata</i>	NSCLC cell lines A549	-	Unknown	Decreased autophagy levels	[56]
Andrographolide (Andro), one of the major active components in <i>Andrographis paniculata</i>	Cisplatin-resistant A549 cells	A549/cisplatin cells xenograft model	Unknown	Decreased autophagy levels	[57]
	Colon cancer cells HCT-116 (p53 wild type and p53-null)	-	Cytoprotective autophagy (both cell lines)	Decreased autophagy levels	[58]
Morin hydrate, a bioflavonoid, isolated from the Moraceae family	HepG2 cell	HepG2 xenograft nude mice	Unknown	Decreased autophagy levels	[59]
	Cisplatin-resistant HepG2 cells	Cisplatin-resistant HepG2 xenograft nude mice	Unknown	Decreased autophagy levels	[60]
Gardenia jasminoides (GJ) is a medicinal herb abundant with flavonoids	Glioblastoma multiform U87MG and U373MG cells	-	Unknown, but induced cytotoxic autophagy when combined with GJ	Increased cytotoxic autophagy levels	[52]

One final issue that the researchers suggest is worthy of additional attention is the “switch” between the roles played by autophagy in different tumors. As mentioned earlier, although in many if not most cases where cisplatin-induced autophagy has been detected the autophagy was functionally cytoprotective, particularly in cisplatin-resistant cells, the non-protective form of autophagy (i.e., where autophagy inhibition failed to influence cisplatin sensitivity) has also been observed, particularly in cisplatin-sensitive cells [43][44][41]. However, interestingly, re-expression of ARHI in SKOV3 cells allowed for CQ to suppress cisplatin sensitivity [44], whereas knockdown of p53 in H460 cells resulted in enhanced cisplatin sensitivity [43], which is what the researchers refer to as the “autophagic switch”. This again argues that studies to improve the efficacy of chemotherapy by altering autophagy function should first distinguish the role of autophagy in specific models. In the absence of such a strategy, experimental conclusions in preclinical models may prove to be flawed, while translation of the work could be compromised.

2.2. Does Autophagy Inhibition Have the Potential to Exacerbate the Toxicity of Cisplatin to Normal Tissue?

The above extensive literature strongly suggests that inhibition of autophagy could, in fact, prove to be an effective strategy for combating cisplatin resistance in the clinic. However, this approach does not fully consider, for example, the troublesome issue of cisplatin toxicity to the kidneys. Cisplatin nephrotoxicity is related to the excretion of cisplatin, which occurs through the kidney tubular epithelial cells. Asymptomatic elevation of serum creatinine levels or even acute tubular injury requiring dialysis therapy occurs with cisplatin chemotherapy in the clinic. Patients who present with this condition

often need to have their medication doses reduced to avoid further kidney damage, resulting in under-treatment of the disease [61]. Renal injury is often accompanied by other complications such as water and nitrogenous waste retention and is associated with a poorer patient prognosis [62]. Recent studies have shown that proximal tubule-specific autophagy-deficient mice are more susceptible to kidney injury after cisplatin treatment than wild-type mice [63]. This may be related to autophagy protecting the proximal tubular cells from mitochondrial oxidative stress and protecting the proximal tubular cells from DNA damage. Furthermore, autophagy also protects the proximal tubular cells from ischemic injury [64]. Zhang et al. reported that the mechanism of cisplatin nephrotoxicity may be related to the inhibition of autophagy by the activation of protein kinase C δ [65]. Li et al. found that 3-dehydroxyceanothetic acid 2-methyl ester (3DC2ME) isolated from the roots of jujube (*Ziziphus jujuba*, Rhamnaceae) protected against cisplatin-induced renal epithelial LLC-PK1 cell injury via autophagy modulation [66]. Retinoic acid, a major derivative of vitamin A, attenuates cisplatin-induced acute kidney injury by activating autophagy [67]. Numerous reports have demonstrated a protective effect of autophagy against cisplatin-induced renal cell injury [68]. Thus, prolonged coadministration of high doses of CQ or other autophagy inhibitors may exacerbate the nephrotoxicity of cisplatin. An example of this outcome can be taken from a study of amniotic fluid stem cells (AFSC) by Minocha et al., who found that AFSC reduced cisplatin-induced renal apoptosis in rats and served to protect against acute kidney injury, but CQ counteracted the renal protective effect of the AFSC [69]. The protective effect of autophagy was also demonstrated in cisplatin-induced damage to the cochlear cells [70]. In addition, the current research also demonstrates the importance of autophagy in enhancing the therapeutic potential of stem cell therapy in attenuating cisplatin-associated liver injury [71]. The two-sided nature of autophagy inhibition during cisplatin treatment suggests the necessity of elucidating the pattern of autophagy in therapy and finding ways to target the delivery of autophagy inhibitors to lesions while mitigating nephrotoxicity as well as other normal tissue injury associated with the administration of cisplatin in cancer therapy.

References

1. Ghosh, S. Cisplatin: The first metal based anticancer drug. *Bioorg. Chem.* 2019, 88, 102925.
2. Chen, S.H.; Chang, J.Y. New Insights into Mechanisms of Cisplatin Resistance: From Tumor Cell to Microenvironment. *Int. J. Mol. Sci.* 2019, 20, 4136.
3. Rosenberg, B.; Van Camp, L.; Grimley, E.B.; Thomson, A.J. The inhibition of growth or cell division in *Escherichia coli* by different ionic species of platinum(IV) complexes. *J. Biol. Chem.* 1967, 242, 1347–1352.
4. Rosenberg, B.; VanCamp, L.; Trosko, J.E.; Mansour, V.H. Platinum compounds: A new class of potent antitumour agents. *Nature* 1969, 222, 385–386.
5. Hill, J.M.; Loeb, E.; MacLellan, A.; Hill, N.O.; Khan, A.; King, J.J. Clinical studies of Platinum Coordination compounds in the treatment of various malignant diseases. *Cancer Chemother. Rep.* 1975, 59, 647–659.
6. Santos, N.; Ferreira, R.S.; Santos, A.C.D. Overview of cisplatin-induced neurotoxicity and ototoxicity, and the protective agents. *Food Chem. Toxicol.* 2020, 136, 111079.
7. Johnson, S.W.; Laub, P.B.; Beesley, J.S.; Ozols, R.F.; Hamilton, T.C. Increased platinum-DNA damage tolerance is associated with cisplatin resistance and cross-resistance to various chemotherapeutic agents in unrelated human ovarian cancer cell lines. *Cancer Res.* 1997, 57, 850–856.
8. Galluzzi, L.; Senovilla, L.; Vitale, I.; Michels, J.; Martins, I.; Kepp, O.; Castedo, M.; Kroemer, G. Molecular mechanisms of cisplatin resistance. *Oncogene* 2012, 31, 1869–1883.
9. Kartalou, M.; Essigmann, J.M. Recognition of cisplatin adducts by cellular proteins. *Mutat. Res.* 2001, 478, 1–21.
10. Danford, A.J.; Wang, D.; Wang, Q.; Tullius, T.D.; Lippard, S.J. Platinum anticancer drug damage enforces a particular rotational setting of DNA in nucleosomes. *Proc. Natl. Acad. Sci. USA* 2005, 102, 12311–12316.
11. Jung, Y.; Lippard, S.J. Direct cellular responses to platinum-induced DNA damage. *Chem. Rev.* 2007, 107, 1387–1407.
12. Wynne, P.; Newton, C.; Ledermann, J.A.; Olaitan, A.; Mould, T.A.; Hartley, J.A. Enhanced repair of DNA interstrand crosslinking in ovarian cancer cells from patients following treatment with platinum-based chemotherapy. *Br. J. Cancer* 2007, 97, 927–933.
13. Makovec, T. Cisplatin and beyond: Molecular mechanisms of action and drug resistance development in cancer chemotherapy. *Radiol. Oncol.* 2019, 53, 148–158.
14. Boulikas, T.; Vougiouka, M. Cisplatin and platinum drugs at the molecular level. (Review). *Oncol. Rep.* 2003, 10, 1663–1682.
15. Dasari, S.; Tchounwou, P.B. Cisplatin in cancer therapy: Molecular mechanisms of action. *Eur. J. Pharmacol.* 2014, 740, 364–378.

16. Fuertes, M.A.; Castilla, J.; Alonso, C.; Perez, J.M. Cisplatin biochemical mechanism of action: From cytotoxicity to induction of cell death through interconnections between apoptotic and necrotic pathways. *Curr. Med. Chem.* 2003, 10, 257–266.
17. Kim, R.; Tanabe, K.; Uchida, Y.; Emi, M.; Inoue, H.; Toge, T. Current status of the molecular mechanisms of anticancer drug-induced apoptosis. The contribution of molecular-level analysis to cancer chemotherapy. *Cancer Chemother. Pharm.* 2002, 50, 343–352.
18. Bai, L.; Wang, S. Targeting apoptosis pathways for new cancer therapeutics. *Annu. Rev. Med.* 2014, 65, 139–155.
19. Tchounwou, P.B.; Dasari, S.; Noubissi, F.K.; Ray, P.; Kumar, S. Advances in Our Understanding of the Molecular Mechanisms of Action of Cisplatin in Cancer Therapy. *J. Exp. Pharmacol.* 2021, 13, 303–328.
20. Koberle, B.; Grimaldi, K.A.; Sunters, A.; Hartley, J.A.; Kelland, L.R.; Masters, J.R. DNA repair capacity and cisplatin sensitivity of human testis tumour cells. *Int. J. Cancer. J. Int. Du Cancer* 1997, 70, 551–555.
21. Basu, A.; Krishnamurthy, S. Cellular responses to Cisplatin-induced DNA damage. *J. Nucleic Acids* 2010, 2010, 201367.
22. Zhou, J.; Kang, Y.; Chen, L.; Wang, H.; Liu, J.; Zeng, S.; Yu, L. The Drug-Resistance Mechanisms of Five Platinum-Based Antitumor Agents. *Front. Pharmacol.* 2020, 11, 343.
23. DeHaan, R.D.; Yazlovitskaya, E.M.; Persons, D.L. Regulation of p53 target gene expression by cisplatin-induced extracellular signal-regulated kinase. *Cancer Chemother. Pharm.* 2001, 48, 383–388.
24. Basu, A.; Tu, H. Activation of ERK during DNA damage-induced apoptosis involves protein kinase Cdelta. *Biochem. Biophys. Res. Commun.* 2005, 334, 1068–1073.
25. Peng, D.J.; Wang, J.; Zhou, J.Y.; Wu, G.S. Role of the Akt/mTOR survival pathway in cisplatin resistance in ovarian cancer cells. *Biochem. Biophys. Res. Commun.* 2010, 394, 600–605.
26. Mizushima, N.; Komatsu, M. Autophagy: Renovation of cells and tissues. *Cell* 2011, 147, 728–741.
27. Xie, Z.; Klionsky, D.J. Autophagosome formation: Core machinery and adaptations. *Nat. Cell Biol.* 2007, 9, 1102–1109.
28. Gasiorkiewicz, B.M.; Koczurkiewicz-Adamczyk, P.; Piska, K.; Pekala, E. Autophagy modulating agents as chemosensitizers for cisplatin therapy in cancer. *Investig. New Drugs* 2021, 39, 538–563.
29. Yu, L.; Gu, C.; Zhong, D.; Shi, L.; Kong, Y.; Zhou, Z.; Liu, S. Induction of autophagy counteracts the anticancer effect of cisplatin in human esophageal cancer cells with acquired drug resistance. *Cancer Lett.* 2014, 355, 34–45.
30. Gao, J.; Wang, W. Knockdown of galectin-1 facilitated cisplatin sensitivity by inhibiting autophagy in neuroblastoma cells. *Chem.-Biol. Interact.* 2019, 297, 50–56.
31. Wang, Z.; Liu, G.; Jiang, J. Profiling of apoptosis- and autophagy-associated molecules in human lung cancer A549 cells in response to cisplatin treatment using stable isotope labeling with amino acids in cell culture. *Int. J. Oncol.* 2019, 54, 1071–1085.
32. Hernandez-Segura, A.; Nehme, J.; Demaria, M. Hallmarks of Cellular Senescence. *Trends Cell Biol.* 2018, 28, 436–453.
33. Saleh, T.; Bloukh, S.; Carpenter, V.J.; Alwohoush, E.; Bakeer, J.; Darwish, S.; Azab, B.; Gewirtz, D.A. Therapy-Induced Senescence: An “Old” Friend Becomes the Enemy. *Cancers* 2020, 12, 822.
34. Homewood, C.A.; Warhurst, D.C.; Peters, W.; Baggaley, V.C. Lysosomes, pH and the anti-malarial action of chloroquine. *Nature* 1972, 235, 50–52.
35. Kimura, T.; Takabatake, Y.; Takahashi, A.; Isaka, Y. Chloroquine in cancer therapy: A double-edged sword of autophagy. *Cancer Res.* 2013, 73, 3–7.
36. Circu, M.; Cardelli, J.; Barr, M.P.; O’Byrne, K.; Mills, G.; El-Osta, H. Modulating lysosomal function through lysosome membrane permeabilization or autophagy suppression restores sensitivity to cisplatin in refractory non-small-cell lung cancer cells. *PLoS ONE* 2017, 12, e0184922.
37. Fukuda, T.; Oda, K.; Wada-Hiraike, O.; Sone, K.; Inaba, K.; Ikeda, Y.; Miyasaka, A.; Kashiwayama, T.; Tanikawa, M.; Arimoto, T.; et al. The anti-malarial chloroquine suppresses proliferation and overcomes cisplatin resistance of endometrial cancer cells via autophagy inhibition. *Gynecol. Oncol.* 2015, 137, 538–545.
38. Schlutermann, D.; Skowron, M.A.; Berleth, N.; Bohler, P.; Deitersen, J.; Stuhldreier, F.; Wallot-Hieke, N.; Wu, W.; Peter, C.; Hoffmann, M.J.; et al. Targeting urothelial carcinoma cells by combining cisplatin with a specific inhibitor of the autophagy-inducing class III PtdIns3K complex. *Urol. Oncol.* 2018, 36, 160.e1–160.e13.
39. Hwang, J.R.; Kim, W.Y.; Cho, Y.J.; Ryu, J.Y.; Choi, J.J.; Jeong, S.Y.; Kim, M.S.; Kim, J.H.; Paik, E.S.; Lee, Y.Y.; et al. Chloroquine reverses chemoresistance via upregulation of p21(WAF1/CIP1) and autophagy inhibition in ovarian cancer. *C*

40. Gunda, V.; Pathania, A.S.; Chava, S.; Prathipati, P.; Chaturvedi, N.K.; Coulter, D.W.; Pandey, M.K.; Durden, D.L.; Challa, K.B. Amino Acids Regulate Cisplatin Insensitivity in Neuroblastoma. *Cancers* 2020, 12, 2576.
41. Maycotte, P.; Aryal, S.; Cummings, C.T.; Thorburn, J.; Morgan, M.J.; Thorburn, A. Chloroquine sensitizes breast cancer cells to chemotherapy independent of autophagy. *Autophagy* 2012, 8, 200–212.
42. Guo, Y.; Feng, Y.; Cui, X.; Wang, Q.; Pan, X. Autophagy inhibition induces the repolarisation of tumour-associated macrophages and enhances chemosensitivity of laryngeal cancer cells to cisplatin in mice. *Cancer Immunol. Immunother. Clin* 2019, 68, 1909–1920.
43. Patel, N.H.; Xu, J.; Saleh, T.; Wu, Y.; Lima, S.; Gewirtz, D.A. Influence of nonprotective autophagy and the autophagic switch on sensitivity to cisplatin in non-small cell lung cancer cells. *Biochem Pharm.* 2020, 175, 113896.
44. Washington, M.N.; Suh, G.; Orozco, A.F.; Sutton, M.N.; Yang, H.; Wang, Y.; Mao, W.; Millward, S.; Ornelas, A.; Atkinson, N.; et al. ARHI (DIRAS3)-mediated autophagy-associated cell death enhances chemosensitivity to cisplatin in ovarian cancer cell lines and xenografts. *Cell Death Dis.* 2015, 6, e1836.
45. Magnano, S.; Hannon Barroeta, P.; Duffy, R.; O'Sullivan, J.; Zisterer, D.M. Cisplatin induces autophagy-associated apoptosis in human oral squamous cell carcinoma (OSCC) mediated in part through reactive oxygen species. *Toxicol. Appl. Pharm.* 2021, 427, 115646.
46. Levy, J.M.; Thorburn, A. Modulation of pediatric brain tumor autophagy and chemosensitivity. *J. Neuro-Oncol.* 2012, 106, 281–290.
47. You, Y.; Yang, W.; Qin, X.; Wang, F.; Li, H.; Lin, C.; Li, W.; Gu, C.; Zhang, Y.; Ran, Y. ECRG4 acts as a tumor suppressor and as a determinant of chemotherapy resistance in human nasopharyngeal carcinoma. *Cell. Oncol.* 2015, 38, 205–214.
48. Phoo, N.L.L.; Dejkriengkraikul, P.; Khaw-On, P.; Yodkeeree, S. Transcriptomic Profiling Reveals AKR1C1 and AKR1C3 Mediate Cisplatin Resistance in Signet Ring Cell Gastric Carcinoma via Autophagic Cell Death. *Int. J. Mol. Sci.* 2021, 22, 12512.
49. Wang, J.; Wu, G.S. Role of autophagy in cisplatin resistance in ovarian cancer cells. *J. Biol. Chem.* 2014, 289, 17163–17173.
50. Ko, J.C.; Tsai, M.S.; Chiu, Y.F.; Weng, S.H.; Kuo, Y.H.; Lin, Y.W. Up-regulation of extracellular signal-regulated kinase 1/2-dependent thymidylate synthase and thymidine phosphorylase contributes to cisplatin resistance in human non-small-cell lung cancer cells. *J. Pharmacol. Exp. Ther.* 2011, 338, 184–194.
51. Lai, S.T.; Wang, Y.; Peng, F. Astragaloside IV sensitizes non-small cell lung cancer cells to cisplatin by suppressing endoplasmic reticulum stress and autophagy. *J. Thorac. Dis.* 2020, 12, 3715–3724.
52. Kim, H.I.; Hong, S.H.; Ku, J.M.; Kim, M.J.; Ju, S.W.; Chang, S.W.; Cheon, C.; Ko, S.G. Gardenia jasminoides Enhances CDDP-Induced Apoptosis of Glioblastoma Cells via AKT/mTOR Pathway While Protecting Death of Astrocytes. *Nutrients* 2020, 12, 196.
53. Lin, Y.X.; Wang, Y.; An, H.W.; Qi, B.; Wang, J.; Wang, L.; Shi, J.; Mei, L.; Wang, H. Peptide-Based Autophagic Gene and d Cisplatin Co-delivery Systems Enable Improved Chemotherapy Resistance. *Nano Lett.* 2019, 19, 2968–2978.
54. Li, Q.; Liu, X.; Yan, W.; Chen, Y. Antitumor effect of poly lactic acid nanoparticles loaded with cisplatin and chloroquine on the oral squamous cell carcinoma. *Aging* 2020, 13, 2593–2603.
55. Wang, K.; Liu, X.; Liu, Q.; Ho, I.H.; Wei, X.; Yin, T.; Zhan, Y.; Zhang, W.; Zhang, W.; Chen, B.; et al. Hederagenin potentiated cisplatin- and paclitaxel-mediated cytotoxicity by impairing autophagy in lung cancer cells. *Cell Death Dis.* 2020, 11, 611.
56. Lv, M.; Zhuang, X.; Zhang, Q.; Cheng, Y.; Wu, D.; Wang, X.; Qiao, T. Acetyl-11-keto-beta-boswellic acid enhances the cisplatin sensitivity of non-small cell lung cancer cells through cell cycle arrest, apoptosis induction, and autophagy suppression via p21-dependent signaling pathway. *Cell Biol. Toxicol.* 2021, 37, 209–228.
57. Mi, S.; Xiang, G.; Yuwen, D.; Gao, J.; Guo, W.; Wu, X.; Wu, X.; Sun, Y.; Su, Y.; Shen, Y.; et al. Inhibition of autophagy by andrographolide resensitizes cisplatin-resistant non-small cell lung carcinoma cells via activation of the Akt/mTOR pathway. *Toxicol. Appl. Pharm.* 2016, 310, 78–86.
58. Zhou, J.; Hu, S.E.; Tan, S.H.; Cao, R.; Chen, Y.; Xia, D.; Zhu, X.; Yang, X.F.; Ong, C.N.; Shen, H.M. Andrographolide sensitizes cisplatin-induced apoptosis via suppression of autophagosome-lysosome fusion in human cancer cells. *Autophagy* 2012, 8, 338–349.
59. Pal Singh, M.; Pal Khaket, T.; Bajpai, V.K.; Alfarraj, S.; Kim, S.G.; Chen, L.; Huh, Y.S.; Han, Y.K.; Kang, S.C. Morin Hydrate Sensitizes Hepatoma Cells and Xenograft Tumor towards Cisplatin by Downregulating PARP-1-HMGB1 Mediated A

60. Singh, M.P.; Cho, H.J.; Kim, J.T.; Baek, K.E.; Lee, H.G.; Kang, S.C. Morin Hydrate Reverses Cisplatin Resistance by Impairing PARP1/HMGB1-Dependent Autophagy in Hepatocellular Carcinoma. *Cancers* 2019, 11, 986.
61. de Jonge, M.J.; Verweij, J. Renal toxicities of chemotherapy. *Semin. Oncol.* 2006, 33, 68–73.
62. Mehta, R.L.; Kellum, J.A.; Shah, S.V.; Molitoris, B.A.; Ronco, C.; Warnock, D.G.; Levin, A.; Acute Kidney Injury, N. Acute Kidney Injury Network: Report of an initiative to improve outcomes in acute kidney injury. *Crit. Care* 2007, 11, R31.
63. Takahashi, A.; Kimura, T.; Takabatake, Y.; Namba, T.; Kaimori, J.; Kitamura, H.; Matsui, I.; Niimura, F.; Matsusaka, T.; Fujita, N.; et al. Autophagy guards against cisplatin-induced acute kidney injury. *Am. J. Pathol.* 2012, 180, 517–525.
64. Kimura, T.; Takabatake, Y.; Takahashi, A.; Kaimori, J.Y.; Matsui, I.; Namba, T.; Kitamura, H.; Niimura, F.; Matsusaka, T.; Soga, T.; et al. Autophagy protects the proximal tubule from degeneration and acute ischemic injury. *J. Am. Soc. Nephrol. JASN* 2011, 22, 902–913.
65. Zhang, D.; Pan, J.; Xiang, X.; Liu, Y.; Dong, G.; Livingston, M.J.; Chen, J.K.; Yin, X.M.; Dong, Z. Protein Kinase Cdelta Suppresses Autophagy to Induce Kidney Cell Apoptosis in Cisplatin Nephrotoxicity. *J. Am. Soc. Nephrol. JASN* 2017, 28, 1131–1144.
66. Lee, D.; Kang, K.B.; Kim, H.W.; Park, J.S.; Hwang, G.S.; Kang, K.S.; Choi, S.; Yamabe, N.; Kim, K.H. Unique Triterpenoid of Jujube Root Protects Cisplatin-induced Damage in Kidney Epithelial LLC-PK1 Cells via Autophagy Regulation. *Nutrients* 2020, 12, 677.
67. Wu, J.; Zheng, C.; Wan, X.; Shi, M.; McMillan, K.; Maique, J.; Cao, C. Retinoic Acid Alleviates Cisplatin-Induced Acute Kidney Injury Through Activation of Autophagy. *Front. Pharmacol.* 2020, 11, 987.
68. Wang, Y.; Liu, Z.; Shu, S.; Cai, J.; Tang, C.; Dong, Z. AMPK/mTOR Signaling in Autophagy Regulation During Cisplatin-Induced Acute Kidney Injury. *Front. Physiol.* 2020, 11, 619730.
69. Minocha, E.; Sinha, R.A.; Jain, M.; Chaturvedi, C.P.; Nityanand, S. Amniotic fluid stem cells ameliorate cisplatin-induced acute renal failure through induction of autophagy and inhibition of apoptosis. *Stem Cell Res. Ther.* 2019, 10, 370.
70. Yu, D.; Gu, J.; Chen, Y.; Kang, W.; Wang, X.; Wu, H. Current Strategies to Combat Cisplatin-Induced Ototoxicity. *Front. Pharmacol.* 2020, 11, 999.
71. El Nashar, E.M.; Alghamdi, M.A.; Alasmari, W.A.; Hussein, M.M.A.; Hamza, E.; Taha, R.I.; Ahmed, M.M.; Al-Khater, K. M.; Abdelfattah-Hassan, A. Autophagy Promotes the Survival of Adipose Mesenchymal Stem/Stromal Cells and Enhances Their Therapeutic Effects in Cisplatin-Induced Liver Injury via Modulating TGF-beta1/Smad and PI3K/AKT Signaling Pathways. *Cells* 2021, 10, 2475.