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► To cite this version:

Maria Castedo, Florine Obrist, Guido Kroemer. Cisplatin resistance coupled to enhanced sensitivity to metabolic interventions. *Molecular & Cellular Oncology*, 2018, 5 (6), pp.e1526004. <10.1080/23723556.2018.1526004>. <hal-04702742>

HAL Id: hal-04702742

<https://hal.science/hal-04702742v1>

Submitted on 19 Sep 2024

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AUTHOR'S VIEWS



Cisplatin resistance coupled to enhanced sensitivity to metabolic interventions

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ABSTRACT

Specific metabolic alterations have recently been observed in cisplatin-resistant cancers. As a result, cisplatin resistance can be overcome by co-administration of pyridoxine, and cisplatin-resistant cancer cells become exquisitely sensitive to killing by inhibitors of poly(ADP-ribose) polymerase, starvation, and antimetabolites targeting nucleotide biosynthesis.

ARTICLE HISTORY

Received 25 June 2018
Revised 13 September 2018
Accepted 14 September 2018

KEYWORDS

chemotherapy; DNA damage response; non-small cell lung cancer

One of the major problems of anticancer chemotherapy resides in the capacity of neoplastic cells to partially survive a sort of Darwinian selection that, coupled to their intrinsic genomic instability,¹ allows for the persistence and later expansion of treatment-resistant clones. Thus, even in the event of an initial cancer regression, fatal relapse is a close-to-ineluctable event when non-small cell lung cancers (NSCLC) or ovarian cancers are treated with cisplatin-based chemotherapies.²

There are multiple mechanisms through which cancer cells acquire cisplatin resistance.³ One of the main mechanisms apparently resides in a major rewiring of tumor cell metabolism, consisting for example in a decrease in the expression of the pyridoxal kinase (PDXK) or an increase in the expression of its counterenzyme pyridoxal phosphatase (PDXP), resulting in reduced phosphorylation of the vitamin B6 precursor pyridoxal within the cancer cells and a consequent decrease in the intracellular concentration of active vitamin B6 (pyridoxal phosphate). Of note, low expression of PDXK is a negative prognostic marker in NSCLC.⁴ Moreover, high doses of pyridoxine can be used to improve the outcome of cisplatin-based chemotherapies in preclinical models.⁵

Another metabolically relevant mechanism of cisplatin resistance consists in the induction of a chronic DNA damage response coupled to the enzymatic overactivation of poly(ADP-ribose) polymerase (PARP), hence yielding cells that contain abnormally high levels of poly(ADP-ribose) (PAR)-modified proteins.⁶ Indeed, the presence of immunohistochemically detectable PAR is a negative prognostic marker in NSCLC.^{7,8} Moreover, the inhibition of PARP with small molecules improves cisplatin responses in preclinical models, suggesting that this enzyme constitutes yet another actionable target for treating cancer.⁹

In the course of our long-term project on cisplatin resistance mechanisms, we recently discovered yet another set of metabolic vulnerabilities that are coupled to cisplatin

resistance.¹⁰ Indeed, when we compared the capacity of cisplatin-resistant cancer cells to resist to various culture conditions, we observed that chemotherapy-resistant human NSCLC cells readily succumbed to culture in serum- and nutrient-free conditions (in vitro starvation) while parental, cisplatin-sensitive control cells conserved their viability.¹⁰ When such cells were implanted into immunodeficient mice, both parental and cisplatin-resistant NSCLC cells developed tumors that progressed at a comparable pace. However, periodic starvation of the mice (24 hours twice per week) reduced the growth of cisplatin-resistant cancers without affecting that of the parental, cisplatin-sensitive tumors.¹⁰ These findings suggest that cisplatin resistance is coupled to an increased reliance on external nutrients that might be therapeutically exploited.

We therefore explored the capacity of different nutrients to avoid the death of cisplatin-resistant NSCLC cells in vitro. An initial screen using different sugars and amino acids led us to the discovery that L-glutamine was sufficient to rescue cisplatin-resistant NSCLC cells from death induced by starvation. Moreover, L-glutamine depletion alone could sensitize cisplatin-resistant NSCLC cells to cell death induction. Hence, L-glutamine apparently is a nutrient that determines the cisplatin sensitivity of NSCLC cells (as well as ovarian cancer cells, as we could confirm). Surprisingly, however, the doses of L-glutamine required for this rescue effect were rather low, in the micromolar (rather than millimolar) range, arguing against a merely bioenergetic role of L-glutamine supplementation. To engage in anaplerotic reactions (i.e. to fuel the Krebs cycle) intracellular L-glutamine must be converted to L-glutamate (which is the precursor of the anaplerotic substrate α -ketoglutarate). This amidohydrolase reaction is catalyzed by glutaminase. Of note, pharmacological inhibition or RNA interference-mediated depletion of glutaminase failed to abolish the rescue effect of L-glutamine on starved cisplatin-

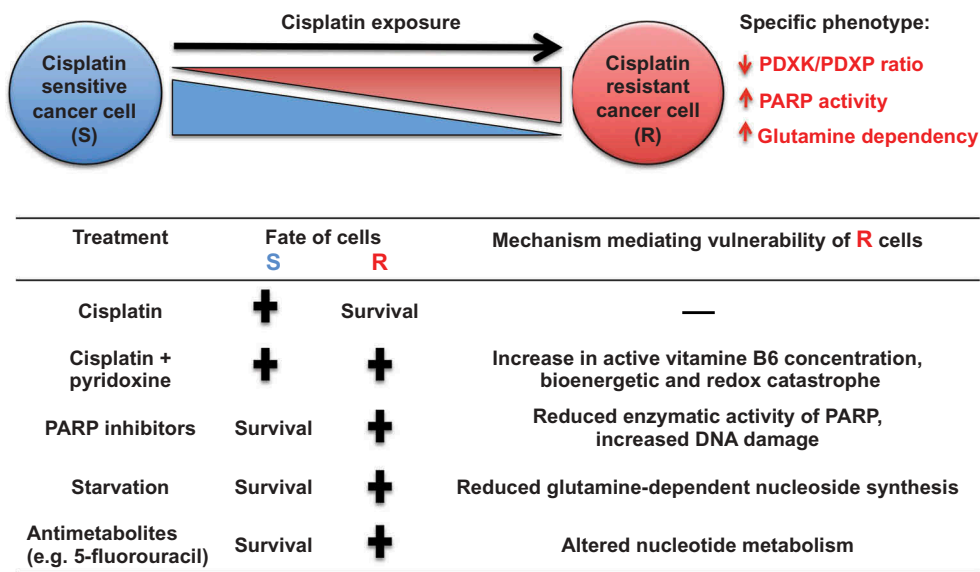


Figure 1. Metabolic vulnerabilities of cisplatin-resistant cancer cells. Shown are the mechanisms that explain the particular vulnerability of cisplatin-resistant cells to combination therapy with cisplatin plus pyridoxine (a vitamin B6 precursor), use of poly(ADP-ribose) polymerase (PARP) inhibitors, starvation and antimetabolites targeting nucleotide biosynthesis such as 5-fluorouracil. PDXK, pyridoxal kinase; PDXP, pyridoxal phosphatase.

resistant NSCLC cells. Thus, the impact of L-glutamine on cisplatin resistance cannot be explained by anaplerotic (bioenergetic) reactions.¹⁰

Intrigued by these observations, we performed extensive mass spectrometric metabolomics including targeted metabolomics analyses to discover that starvation of cisplatin-resistant cells led to a depletion of several intracellular nucleotides that were replenished by the addition of L-glutamine. Importantly, addition of a pool of nucleosides (adenosine, guanosine, uridine and cytidine) fully rescued cisplatin-resistant cells from starvation-induced death. Moreover, anticancer agents that target nucleoside metabolism such as 5-fluorouracil (an inhibitor of thymidylate synthase), clofarabine and gemcitabine (two inhibitors of ribonucleotide reductase) abolished the rescue effect of L-glutamine on starved cisplatin-resistant cells in short-term experiments. These antimetabolites were also particularly efficient against cisplatin-resistant tumor in preclinical studies. Thus, 5-fluorouracil could reduce the growth of cisplatin-resistant, but not cisplatin-sensitive, NSCLC tumors in vivo, in a xenograft model.¹⁰

Altogether, the aforementioned results suggest that cisplatin resistance is coupled to an increased susceptibility of cancers to starvation, likely due to a sort of “glutamine addiction”. More importantly from the therapeutic point of view, cisplatin resistance leads to an enhanced vulnerability of the malignant cells to antimetabolites targeting nucleotide biosynthesis (Figure 1). It will be important to extend these notions to multidrug regimens in which cisplatin-based chemotherapy, pyridoxine (vitamin B6), PARP inhibitors and antimetabolites are combined among each other concomitantly or sequentially. We anticipate that such combination therapies might offer a unique

opportunity to avoid the development of cisplatin resistance and to achieve anticancer effects against cisplatin-resistant tumors.

Acknowledgments

GK is supported by the Ligue contre le Cancer (équipe labellisée); Agence National de la Recherche (ANR) – Projets blancs; ANR under the frame of E-Rare-2, the ERA-Net for Research on Rare Diseases; Association pour la recherche sur le cancer (ARC); Cancéropôle Ile-de-France; Chancellerie des universités de Paris (Legs Poix), Fondation pour la Recherche Médicale (FRM); a donation by Elior; European Research Area Network on Cardiovascular Diseases (ERA-CVD, MINOTAUR); Fondation Carrefour; Institut National du Cancer (INCa); Inserm (HTE); Institut Universitaire de France; LeDucq Foundation; the LabEx Immuno-Oncology; the RHU Torino Lumière; the Seerave Foundation; the SIRIC Stratified Oncology Cell DNA Repair and Tumor Immune Elimination (SOCRATE); the SIRIC Cancer Research and Personalized Medicine (CARPEM).

Funding

This work was support by the Ligue contre le Cancer (équipe labellisée); Agence National de la Recherche (ANR) – Projets blancs; ANR under the frame of E-Rare-2, the ERA-Net for Research on Rare Diseases; Association pour la recherche sur le cancer (ARC); Cancéropôle Ile-de-France; Chancellerie des universités de Paris (Legs Poix), Fondation pour la Recherche Médicale (FRM); a donation by Elior; European Research Area Network on Cardiovascular Diseases (ERA-CVD, MINOTAUR); Fondation Carrefour; Institut National du Cancer (INCa); Inserm (HTE); Institut Universitaire de France; LeDucq Foundation; the LabEx Immuno-Oncology; the RHU Torino Lumière; the Seerave Foundation; the SIRIC Stratified Oncology Cell DNA Repair and Tumor Immune Elimination (SOCRATE); the SIRIC Cancer Research and Personalized Medicine (CARPEM).

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