A single treatment of Selenate, a repositioning drug, specifically sensitizes P-gp-overexpressing resistant cancer cells

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We investigated possible conditions or drugs that might enhance the sensitivity of anti-mitotic drug-resistant cancer cells. We particularly focused on identifying mechanisms or drugs that could sensitize P-glycoprotein (P-gp)-overexpressing resistant KBV20C cancer cells. Our approach utilized repositioning drugs, which are already used in clinics, because once their sensitization mechanisms on resistant cancer cells are known, they would be readily applied without further toxicity studies. Selenium-derived drugs such as selenate, selenite, selenomethionine (SeMet), methyl-selenocysteine (MSC), and methaneselenic acid (MSA) have been shown to have anti-cancer properties clinically. The type of selenium-derived drug that can specifically sensitize P-gp-overexpressing resistant KBV20C cancer cells was investigated for further application in the clinical settings. We recently reported five selenium-derived drugs that could sensitize both resistant KBV20C and KB parent sensitive cancer cells without P-gp inhibition. Among these five drugs, our study highlights the unprecedented finding of the selective sensitization ability of selenate against P-gp-overexpressed resistant KBV20C cells. Detailed analysis indicates that selenate is a resistant cancer cell-specific sensitizing drug that increases apoptosis via G2-phase cell cycle arrest. These results may help improve chemotherapeutic treatments based on selenium-derived drugs for cancer patients who develop resistance to anti-mitotic drugs.

Keywords: selenite; selenium-related drugs; drug repositioning; P-gp; anti-mitotic drugs resistant cancer; G2-arrest

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Cancer cells resistant to anti-mitotic drugs and overexpressing P-glycoprotein (P-gp)

Anti-mitotic drugs target microtubules and prevent their polymerization or depolymerization, in order to inhibit mitosis. Paclitaxel, docetaxel, vincristine, vinorelbine, vinblastine, and halaven are some examples of anti-mitotic drugs [1, 2]. While anti-mitotic drugs are widely used to treat cancer, cancer cells can develop resistance in various ways. One such mechanism is via overexpression of P-gp on cell membranes. P-gp is a membrane channel that can pump out anti-mitotic drugs and thus avoid drug-induced toxicity [1-3]. Identifying sensitization mechanisms or drugs for cancer cells that overexpress P-gp would lead to better treatment of patients who develop resistance to anti-mitotic drugs.

Sensitization mechanisms or drugs for resistant cancer cells overexpressing P-gp

Cancer cells that overexpress P-gp and are resistant to anti-mitotic drugs can be sensitized via a few mechanisms and drugs, which are summarized in Fig. 1. First, sensitization drugs should be non-substrates for P-gp-mediated efflux (Fig. 1A-B). It is also important that
they have similar IC50 in sensitive (parents) and resistant cancer cells, as described for Drug A (Fig. 1A), in order to minimize toxicity in clinical applications. As seen in Fig. 1B, Drug B has a stronger sensitization effect in resistant cells and would be a valuable drug for treating cancer cells that overexpress P-gp. Therefore, more investigation is required to identify drugs that can be specifically toxic to these cancer cells.

Resistant cancer cells can be sensitized by P-gp inhibitors, which inhibit the membrane efflux of anti-mitotic drugs. When P-gp inhibitors are co-treated with anti-mitotic drugs, the cellular accumulation of anti-mitotic drugs results in increased toxicity for the resistant cancer cells, as described by Drug C (Fig. 1C). Verapamil is an example of a P-gp inhibitor [4, 5]. However, in terms of clinical applications, P-gp inhibitors show significant toxicity against normal cells [4]. A single treatment can sensitize P-gp overexpressed resistant cancer cells to both apoptosis and P-gp inhibition, as described in Fig. 1D. As seen in Fig. 1D, if Drug D has both P-gp inhibitory and apoptotic activity, it can be effective not only as a single treatment but also in combination with anti-mitotic drugs.

Identification of novel sensitization mechanisms of repositioning drugs in P-gp-overexpressing resistant cancer cells

Drug repositioning is the application of known drugs to new indications [6, 7]. It is a powerful tool for identifying effective treatment options for new diseases in a timely manner. The urgent need for pharmacological treatments for P-gp-overexpressing resistant cancers can be efficiently addressed once novel mechanisms are identified for repositioning drugs. We hypothesized that repositioned drugs can be applied to human patients at a relatively fast pace, especially for patients resistant to conventional treatment.

Based on experimental candidate approaches found in the literature, we have tried to identify novel repositioning drugs and their mechanisms for application to P-gp overexpressed resistant cancer, including increased sensitization-efficacy of
repositioned drugs when used in single treatment or in combination with anti-mitotic drugs.

Identification of sensitization drugs for P-gp-overexpressing resistant KBV20C cancer cells

In order to identify sensitization mechanisms and drugs, we compared two cell lines, anti-mitotic drugs-sensitive KB (parent) and -resistant KBV20C cells. The KBV20C-resistant cell line highly expresses P-gp proteins\[9\], which actively pump out anti-mitotic drugs. While our findings regarding sensitization mechanisms and drugs are limited to the resistant cell line KBV20C, most of the previous studies on KBV20C have shown consistent results in P-gp overexpressed resistant cancer cell lines.

Our approach to repositioning drugs and P-gp overexpressed resistant KBV20C cells demonstrated novel findings\[5, 9, 10\]. For example, the anti-malarial drugs primaquine and mefloquine can sensitize both sensitive KB and resistant KBV20C cancer cells at similar IC50 values\[9\], as shown in Fig. 1A. A single treatment of thiouridazine was demonstrated to markedly sensitize KBV20C resistant cancer cells compared to their effects on drug-sensitive KB parent cells\[10\], as described in Fig. 1B. In addition, primaquine, mefloquine, and thiouridazine highly sensitize KBV20C-resistant cells to anti-mitotic drugs. Considering that they could inhibit P-gp activity in the resistant KBV20C cells\[9, 10\], we concluded that the mechanisms underlying sensitization in resistant KBV20C cells involve both apoptosis and P-gp inhibition, as described in Fig. 1D.

Sensitization effect of selenium-derived drugs against resistant KBV20C and sensitive KB cells

The importance of selenium-derived drugs in cancer therapy has been previously suggested\[11, 12\]. Selenate, selenite, selenomethionine (SeMet), methyl-selenocysteine (MSC), and methaneselenic acid (MSA) are the most commonly studied and well-known selenium-derived drugs used to treat cancer in humans. However, the efficacy of these drugs in treating cancer has not been compared. Therefore, we investigated which members of the selenium-derived family could be used in the treatment of P-gp-overexpressing resistant KBV20C cells, and whether their sensitivity was greater in resistant than that in sensitive parent KB cells.

The sensitizing effects of all five drugs on KBV20C cells were comparable to their effects on sensitive parent KB cells\[13\], as described in Fig. 1A. The selenium-derived drugs were found to be effective against drug-resistant cancer cells at low concentrations. Although all five drugs have different structural modifications, they demonstrated a similar sensitization effect in both the sensitive and resistant cells, suggesting that selenium-derived drugs are stable sensitization-targeting molecules in resistant cancer cells. Since it is important that sensitization mechanisms among drug derivatives remain unaltered for generalization, selenium-derived drugs can be considered good targeting drugs for resistant cancer cells. We also observed that these drugs did not inhibit P-gp activity in resistant KBV20C cells, suggesting that the mechanism of sensitization of resistant KBV20C cells involves other cellular pathways, which are assumed to be similar to those involved in KB cell sensitization.

Better sensitization effect of selenate against resistant KBV20C than that against sensitive KB cells

In our studies, we also aimed to assess which members of the selenium-derived family produced the greatest sensitization effects. Interestingly, we found that among the five selenium-related drugs (selenate, selenite, SeMet, MSC, and MSA), selenate highly sensitized drug-resistant KBV20C cells, as compared to sensitive KB cells, by activating the apoptotic pathway\[13\]. Selenate-induced toxicity was associated with an increase in G2-phase cell cycle arrest in KBV20C cells, suggesting that the selenate-induced increase in apoptosis resulted from cell cycle arrest in resistant KBV20C cells. Considering that increased G2 arrest was found to positively correlate with increased apoptosis in resistant rather than sensitive cells, screening for G2 arrest can be utilized to find specific drugs targeting P-gp-overexpressing resistant cancer cells.

Contribution of our findings to clinical application

Taken together, our results highlight the novel selective sensitization of selenate. In addition, other selenium-derived drugs, including selenite, SeMet, MSC, and MSA, have been shown to be potentially useful in the treatment of P-gp-overexpressing resistant cancer. Since their toxicity is already well-defined, these drugs are readily applied for clinical settings. In addition, since these drugs do not possess P-gp inhibitory activity, we can assume that normal cells are spared after prolonged treatment with these drugs. Our study contributes to the development of selenium-based therapy for cancer patients previously resistant to anti-mitotic drugs.

Conflicting Interests

The authors have declared that no competing interests exist.

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Abbreviations

P-gp: P-glycoprotein; SeMet: selenomethionine; MSC: methyl-selenocysteine; MSA: methaneselenic acid; IC50: half maximal inhibiting concentration.

References