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The rapid development of cisplatin resistance in A2780 human ovarian tumor cells can be prevented by the folate enzyme inhibitor, berberine

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Resistance to the chemotherapy drug cisplatin is a common cause of treatment failure in ovarian cancer. Many studies have focused on agents that might reverse resistance once it has developed. For example, berberine, an isoquinoline alkaloid that interferes with folate cycle enzymes, has been found to induce apoptosis in cisplatin resistant cells. We have pursued an alternative to the resistance reversal strategy: the prevention of the development of resistance. This strategy requires that cells predictably develop resistance to a high dose of cisplatin that effectively inhibits non-resistant tumor cells. For this study, A2780 (Addex) human ovarian tumor cells were cultured in nutrient medium (F12/DMEM plus 7% FBS) alone or with a low, pretreatment dose of 7.5 µM cisplatin (Sigma Aldrich). After 24 hours in pre-treatment conditions, cells were counted and replicate cultures exposed to the high dose of 15 µM cisplatin. After 24 hours in this high dose, cells were counted again. In non-pretreated cells, high dose cisplatin decreasedcell survival to 51.8 (6.5) % of control cultures. In contrast, cisplatin pretreatment resulted in 90.6 (9.7) % survival following the high dose. Thus, this pretreatment resulted in the rapid induction of resistance. We then employed this protocol to test whether berberinecan prevent the development of this resistance. Replicate cultures were pretreated with either 21 µM or 53 µM berberinehydrochloride (Sigma Aldrich) alone or with 7.5 µM cisplatin pretreatment. Pretreatment with berberine alone had no effect on cell sensitivity to high dose cisplatin: 50.3 (6.1) % survived the subsequent high-dose cisplatin, virtually the same response as cultures with no pretreatment. The addition of berberineon the same day as the cisplatin pretreatment prevented resistance and maintained sensitivity similar to that of controls: 45.3 (5.9) % of cells survived following high dose cisplatin. The results suggest that berberine pretreatment prevents the development of cisplatin resistance in this protocol, perhaps by preventing the overexpression of folate cycle enzyme genes. Further studies are underway to investigate whether this is the case.

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Biography:

Paula B Caffrey received her Ph.D. from Rutgers University in 1989. Her graduate research, performed with K. Irwin Keating, explored the interdependence of Se- and Zn- requirements in aquatic systems. As a post doc in Gerald D. Frenkel's labat Rutgers Newark, she studied selenium's effect on drug resistant tumor cells. Following postdoctoral projects at UCSD Cancer Center and GeorgetownMedical School, she resumed her collaboration with Dr. Frenkelas a Research Associateat Rutgers from 1995-2007. They developed models of drug resistant ovarian cancer to identify agents that can prevent this resistance. Their findings resulted in a Phase 1 clinical trial at the New Jersey Cancer Institute. Since 2007, Dr.Caffrey has held the position of Assistant Professor at the California University of Pennsylvania, where she mentors research students and continues collaboration with Dr. Frenkelonthe prevention of drug resistance inSCLC lung cancer and ovarian cancer.