Nitric oxide and cisplatin resistance: NO easy answers

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Cisplatin is one of the most widely used chemotherapeutic drugs for treating cancer. Initially, platinum-based therapies are very effective in treating a wide array of cancers; however, recurrence and resistance remain the major limitation to curative therapies (1). Although cisplatin resistance is clearly multifactorial in nature, increased levels of cellular thiols are often associated with the cisplatin-resistant phenotype (2). Cellular thiols, which include glutathione (GSH), can sequester cisplatin, leading to a reduction in the levels of cisplatin–DNA damage. DNA is the therapeutic target of cisplatin, and efficacy is a function of cisplatin–DNA adducts inhibiting DNA replication and transcription, ultimately resulting in apoptosis. Reduced efficacy of the cisplatin is often observed in cells with increased GSH levels. Modulating the levels of intracellular thiols has been demonstrated to influence cisplatin cytotoxicity in numerous studies (3). In a report by Bratasz et al. (4) in a recent issue of PNAS, the authors exploited GSH overexpression using a nitric oxide (NO)-prodrug in a cisplatin-resistant ovarian cancer model to potentially counteract and target cisplatin-resistant cells.

NO has proven to be an important component in numerous signaling pathways and elicits a wide variety of biological effects (5). The regulation and cellular effects of both endogenous and exogenous NO production have been studied in great detail. The development of NO-donating small-molecule prodrugs has resulted in the detailed characterization of the NO response in many aspects of cardiovascular biology (6).

More recently, NO and NO-prodrugs have been assessed for activity in the prevention and treatment of cancer (Fig. 1). Varied results have been reported in numerous cell cancer models. In general, when observed, the cytostatic activity of NO-donating compounds is attributed to the NO-moiety or a function of the metabolism of the prodrug. These conclusions are based on the lack of cytostatic activity with the parental compounds. Perhaps more relevant to the single-agent therapy is the potential of NO and NO-prodrugs to synergize with traditional chemotherapeutic agents in treating cancer. One study used tissue culture media saturated with NO gas and demonstrated that sensitivity to the cytotoxic activity of cisplatin was increased dramatically and that the effect could be mimicked with a subset of chemical NO donors (7). Interestingly, no toxicity was associated with any of the NO treatments in the absence of cisplatin, and the authors discounted intracellular thiols as mediating the cisplatin-sensitization effect. More recent analysis of NO-prodrugs specifically designed to interact with glutathione S-transferase (GST) also demonstrated synergism with cisplatin, an effect attributed to increased cellular accumulation of cisplatin and potentially activation of the mitogen-activated protein kinase (MAPK) pathway (8). The effect of NO on MAPK was originally determined in vascular smooth muscle cells (9) and more recently in colon cancer cells where cytostatic activity was demonstrated to involve MAPK (10). Consistent with the above analyses, a series of NO-donating aspirin derivatives revealed that the aspirin or nonsteroidal anti-inflammatory drug released could not account for the cytostatic activity (11).

Considering the numerous and conflicting reports on the effect of NO and NO-prodrugs on pathways relevant to cancer, the bioactivation of these compounds becomes critical. Some of the variation in activity can be attributed to the rate and duration of NO production as well as the individual cell type being studied. The NO-aspirin derivatives are perhaps the most well studied where slow release of NO by NCX-4016 and other NO-prodrug derivatives appears to be more effective in eliciting the desired responses for cancer chemotherapy. Metabolism of NO-aspirin derivatives typically involves cleavage of the ester linker via a nonspecific esterase to release the aspirin derivative and a nitrooxymethyl derivative (HBN). The NO-containing HBN can then be metabolized further by GST to form an HBA–GSH adduct with concomitant release of NO3 (12). In addition, other detoxification pathways likely contribute to the metabolism of these agents. The end result of this activation and metabolism is the generation of NO and salicylic acid, and the use of reduction potential via the GST/GSH pathway, each of which could potentially influence cell proliferation and sensitivity to chemotherapeutic agents. These pathways and interactions are

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Nitric oxide-donating compounds induce oxidative stress and initiate apoptosis.