SL06 Modulation of Organic Cation Transport by TKIs

Alex SPARREBOOM
Division of Pharmaceutics, College of Pharmacy, The Ohio State University

Cisplatin and oxaliplatin are among the most widely used anticancer drugs in both children and adults. The clinical use of these agents is associated with dose-limiting damage to kidneys (nephrotoxicity) and peripheral nerves (neurotoxicity), which occur in the majority of patients despite intensive prophylactic measures, and these complications may limit further treatment, cause prolonged complications, or even threaten life. There is no known treatment for prevention of these side effects, and mechanistic details of their etiology remain unclear. We previously reported that the urinary excretion of these platinum-based chemotherapeutics as well as drug-induced damage to renal tubular cells (Filipski et al, *Clin Pharmacol Ther* 2009; Pabla et al, *PNAS* 2015) and dorsal root ganglia (Sprowl et al, *PNAS* 2013) is dependent on organic cation transporter-mediated mechanisms. In mice, this process is regulated by the two closely related organic cation transporters, mOct1 and mOct2, that are functionally redundant and that together fulfill a role equivalent to that of a single organic cation transporter, OCT2, in humans. Recently, we found that the function of mOct2 and OCT2 can be potently antagonized by various tyrosine kinase inhibitors (TKIs), including dasatinib and vandetanib, through a non-competitive mechanism (Sprowl et al, *Nat Commun* 2016). Based on this observation, we hypothesized that tyrosine phosphorylation of OCT2 is essential for its function and that one or more specific kinases are responsible for OCT2 tyrosine phosphorylation. Using mass spectrometry-based proteomics and generation of site-specific mutants, we confirmed that mOct2 and OCT2 are tyrosine phosphorylated, and that this pathway can be modulated by TKIs. An RNAi kinase library screen subsequently identified the Src-family member YES1 as the OCT2-phosphorylating kinase, and the YES1-OCT2 connection was validated with a rescue experiment involving a TKI-resistant YES1 mutant, confirmation of an interaction with YES1 of TKIs with OCT2-inhibitory properties, changes in OCT2 function following in vivo silencing of YES1, and by demonstrating OCT2 inhibitory properties of non-TKI inhibitors of YES1, such as dorsomorphin. We have recently found that a similar regulatory mechanism is operational for several related organic cation transporters, including OCT1, OCT3, and MATE1. In addition, recent studies indicate that certain TKIs can significantly inhibit the OCT3-mediated uptake of the anti-cancer drug doxorubicin into human and murine cardiomyocytes, a prerequisite for drug-induced cardiomyopathy. These findings provide a rationale for the translational development of new targeted interventions using high-dose TKI pulse-exposure to mitigate the debilitating side effects associated with chemotherapeutics.