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Quantitative Adverse Outcome Pathway Modeling: An ODE-Based Framework Applied to Platinum-Induced Nephrotoxicity

Abstract

The Adverse Outcome Pathway (AOP) framework describes biological mechanisms connecting molecular initiating events (MIEs) through intermediate key events (KEs) to adverse outcomes (AOs). Despite its broad adoption, establishing a robust quantitative AOP (qAOP) modeling framework to enable accurate predictive risk assessment remains challenging. Here, we introduce an ordinary differential equation (ODE)-based qAOP framework designed to quantitatively describe KEs and their relationships over time. Bayesian inference and cross-validation techniques are employed for parameter estimation, model calibration, and validation. To demonstrate this framework, we focus on platinum-induced nephrotoxicity, a significant limitation in chemotherapy. Two complementary ODE-based qAOP models were developed: one utilizing newly generated in vitro data from RPTEC/TERT1 cells and another built upon published in vivo rat kidney data exposed to cisplatin. Analysis of these models revealed distinct immune system dynamics, highlighting how rapid clearance of necrotic cells initially protects against immediate kidney

damage, whereas sustained inflammation contributes to cumulative nephrotoxicity. Moreover, we perform quantitative in vitro to in vivo extrapolation (QIVIVE) to link the two models. With this approach, in vivo adverse outcome predictions can be made in the future not only for platinum- based compounds but also for the safety assessment of other chemicals and drugs, reducing the need for animal testing.