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Editorial: Model organisms in predictive toxicology 2022

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Editorial on the Research Topic
Model organisms in predictive toxicology 2022

Various chemicals, including pharmaceuticals, pesticides, microparticles, and heavy metals, are persistent in the environment (Brack et al., 2022). Predicting the toxicities of these chemicals is critical for human health and assessment of environmental risk (Michelangeli et al., 2022; Pognan et al., 2023). Next-generation technologies have developed novel *in silico* and *in vitro* approaches for risk assessments (Cavasotto and Scardino, 2022; Jeong et al., 2022). However, *in vivo* phenotypic assessments using model organisms, including fishes, rodents, and monkeys, are still indispensable for predicting toxicology and elucidating adverse outcome pathways (Komada et al., 2017; Donovan et al., 2018; Alsakran and Kudoh, 2021; Hoffmann et al., 2021; Khabib et al., 2022; Nishimura and Kurosawa, 2022).

Wang et al. demonstrated that ibrutinib, a clinical drug used in patients with B-cell malignancies, caused impairment of vascular development in zebrafish larvae. It reduced the proliferation and increased the apoptosis of vascular endothelial cells in zebrafish larvae. Additionally, ibrutinib decreased the expression of vascular endothelial cell growth factor receptors, which may have a possible role in the impairment of vascular development. Although ibrutinib has been used as a selective inhibitor of Bruton's kinase (BTK), its toxicological effect on vascular development may not be mediated via the inhibition of BTK, since vascular development is not impaired by other BTK inhibitors or knockdown of BTK in zebrafish. Furthermore, zebrafish has also been used to develop selective BTK inhibitors (Sousa et al., 2022).

Komoike et al. showed that exposure of zebrafish embryos from 6 to 72 h post fertilization (hpf) stage to lead (Pb) at 100 ppb, which is below the occupational regulatory standard concentrations, increased the expression of oxidative stress related genes at 72 hpf. This resulted in edema and inflation defects in the swim bladder at 7 days post fertilization. These results corroborated with those of previous studies (Park et al., 2020; Wang et al., 2022), thereby, suggesting that zebrafish are useful for investigating the adverse developmental effects of trace pollutants such as Pb. As Pb easily binds to oxygen and sulfur atoms in proteins to form a stable complex and accumulates in the zebrafish body, the developmental effects of Pb at concentrations lower than 100 ppm need to be analyzed.

Using rainbow trout, Mallik et al. performed a pharmacokinetic analysis and biosafety evaluation of florfenicol, a synthetic veterinary antimicrobial agent approved by the Food and Agriculture Organization. Florfenicol has been widely used in veterinary medicine to

treat and prevent diseases, and residues in food from animals treated with florfenicol can adversely affect human health (Guidi et al., 2017). In Atlantic salmon aquaculture, florfenicol is typically administered at 10 mg/kg body weight for 10 consecutive days (Horsberg et al., 1996). Mallik et al. analyzed the pharmacokinetics and biosafety of rainbow trout treated with various doses of florfenicol and recommended the use of 10 mg/kg body weight. Further *in vivo* studies are required to determine the dose of veterinary antimicrobial substances that have positive effects on animals but no adverse effects on both animals and humans who consume food products from the animals.

The antioxidant system plays a critical role in the body's response to chemical exposure (Espinosa-Diez et al., 2015). Nuclear factor erythroid 2-related factor 2 (Nrf2) is a key transcription factor that regulates antioxidant genes (Bellezza et al., 2018). Mice have been successfully used in studies to analyze the role of Nrf2 in regard to the toxicity of many chemicals (Mutter et al., 2015).

Wang et al. examined the role of Nrf2 in the nephrotoxicity of colistin, an antibiotic known as polymyxin E. Although colistin is effective against multidrug-resistant gram-negative bacteria, its nephrotoxicity limits its use (Ordooei Javan et al., 2015; Trimble et al., 2016). Using mice, Wang et al. revealed that colistin-induced nephrotoxicity via suppression of Nrf2 was mediated by the activation of histone deacetylase 1 (Hdac1). Furthermore, co-treatment with 7-hydroxycoumarin ameliorated colistin-induced nephrotoxicity via the inhibition of Hdac1 activity. However, the mechanisms by which colistin and 7-hydroxycoumarin regulate Hdac1 warrant further investigation.

Ding et al. analyzed the role of Nrf2 in lung damage in mice exposed to ambient fine particulate matter (PM2.5) and found that lung damage was ameliorated in *Nrf2* knockout mice. In the study, it was demonstrated that endoplasmic reticulum stress caused by exposure to PM2.5, was decreased in *Nrf2* knockout mice, possibly through the suppression of Cyp2e1. The role of Nrf2 in chemical exposure and disease varies depending on the context (Menegon et al., 2016; Cheryl et al., 2021). Further studies are required to elucidate the molecular mechanisms underlying the context-dependent roles of Nrf2.

Assessment of drug-induced QT interval prolongation is a critical step in drug development (Komatsu et al., 2019). Monkeys have been widely used to assess drug-induced QT interval prolongation because they are more sensitive than dogs in this assessment, and the concentration-QT relationship is transferable to humans (Holzgrefe et al., 2014; Dubois et al., 2016). Izumi-Nakaseko et al. analyzed the effect of atrioventricular block on *dl*-sotalol-induced QT interval prolongation. They revealed that monkeys with chronic atrioventricular block could be used as a proarrhythmic model to detect drug-induced QT interval prolongation, although it takes several months to complete pathological remodeling after the onset of atrioventricular block in monkeys.

The integration of *in vivo*, *in vitro*, and *in silico* models with new methodologies is fundamental for accurately predicting chemical toxicity (Knudsen et al., 2021). Considering the different physiology, body size and sensitivities to different toxicants, it is important to investigate chemical toxicities using a variety of model organisms. Therefore, the development of novel approaches to predict toxicology using model organisms warrants further investigation.

Author contributions

All authors listed have made a substantial, direct, and intellectual contribution to the work and approved it for publication.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

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