Simple models supported by complex and integrated analyses in neurotoxicity studies

Federica Bovio[1], Matilde Forcella[1], Paola Fusi[1#], Alice Simeoni[1], Melissa Ferrian[2], Antonia Franceschi[2], Stefano Porru[2#], Pasquale Melchioretto[3] and Chiara Urani[3#]

[1] Department of Biotechnology and Biosciences, University of Milano-Bicocca, Milan, Italy (federica.bovio@unimib.it)

[2]Department of Diagnostics and Public Health, University of Verona, Italy

[3]Department of Earth and Environmental Sciences, University of Milano-Bicocca, Milan, Italy (chiara.urani@unimib.it)

[#]MISTRAL, Interuniversity Research Centre «Integrated Models of Study for Health Protection and Prevention in Living and Working Environments», University of Brescia, Milano-Bicocca and Verona, Italy

Abstract

Background Neurotoxicity and neurodegenerative studies are challenging, due to the high tissues and system complexity. In this work we present a case-study of an integrated approach by using non-animal methods to be applied in the context of the neurotoxic potential of heavy metals, in particular of cadmium (Cd). Cd is uptaken by ingestion of contaminated food and water, inhalation and dermal contact, and accumulates in tissues with a long biological half-life (up to 30 years) due to the absence of excretory mechanisms. In addition, Cd can disrupt the blood-brain barrier and was found in brain tissues of patients with neuromotor disease.

Methodology We used a human model of neurons (SH-SY5Y cells) exposed to environmentally- and human-relevant Cd concentrations and applied different methods to the mechanistic identification of Cd neurotoxicity. The approach integrates the following methodologies: *1)* morphological analyses, that help to relate structure and function; *2)* chemical analyses (ICP-MS) to relate effects and actual concentrations within the cells and identify uptake kinetics; *3)* transcriptomics analyses to evidence early dysregulated molecular pathways; *4)* biochemical approaches to recognize biomarkers and altered cell functions (e.g., mitochondrial activity).

Conclusions Although 2D models do not completely fit, especially in studies of complex processes, they represent a powerful tool when an integrated approach is applied to achieve a global (dys)functional picture. Indeed, simple models afford to collect a broad spectrum of data and information on biological processes and are helpful approaches for the identification of pathways and mechanisms that could be further deepened through more complex models. New advanced methodologies can benefit from consolidated methods and the crosstalk of different approaches to be subsequently transferred to more complex systems such as 3D, organoids as well as more complex organ-on-chip and microphysiological systems.

Acknowledgments: The authors acknowledge the support of MISTRAL Interuniversity Center and of 2023-ATE-0523 to CU

Disclosure of conflicts of interest: No

Ethical Statements: No