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EDITORIAL

Understanding toxicology: mechanisms and applications

Madhav Bhatia

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The goal of the current commentary is to describe the key elements of molecular toxicology and the way to better understand molecular toxicology by analyzing the articles published in Cell Biology and Toxicology during 2014–2015. In this commentary, I would like to discuss my view of the articles published in the journal during this period, and some thoughts for the way forward for the journal.

The journal publishes 6 issues per year, with 4–5 articles in each issue. In the years 2014 and 2015, most of the articles were Original Reports, but there were some Review Articles and Brief Reports as well. In total, 49 articles were published in 2014–2015. I am very impressed with the quality of work published in the journal. Some articles that I found particularly impressive, along with the scientific contribution they make, are summarized below.

Nanosilica is a nanostructured material, consisting of aggregates of primary particles (Kessler 2011). It is as commonly used as E551, an anti-caking agent in food products, and considered "safe" for human/animal consumption. A study published in 2014 (Athinarayanan et al. 2014) investigated its toxic effects on WI-38 (human lung normal fibroblast) cells in terms of cell viability, intracellular ROS levels, cell cycle phase, and the expression levels of metabolic stress-responsive genes. Overall, the results from this study showed that E551 induces a dose-dependent cytotoxicity and changes in ROS levels and alters the gene expression and cell cycle. Treatment with a high concentration of E551 caused significant cytotoxic effects on WI-38 cells. The authors also showed that 2.74–14.45 μg/g silica was found in commercial food products. E551 was isolated from food products. Investigations showed the presence of spherical silica nanoparticles in food, approximately 10–50 nm in size. The study is scientifically sound and has practical implications on the use of nanoparticles in the food industry. In the short time since publication, the article has already been cited 13 times to date (Thomson ISI Web of Science).

Nanoparticles, which are being used in medicine, have adverse effects which have only recently started being recognized but has been shown to be influenced by size, proliferation, and embryonic origin of the cells used for testing (Fröhlich et al. 2012). An impressive article (Prietl et al. 2014) describes the effects of nanoparticles of sizes between 20 and 1000 nm on phagocyte function. Twenty nanometer carboxyl polystyrene (CPS) particles stimulated IL-8 secretion in human monocytes and induced oxidative burst in monocytes. Five hundred- and 1000-nm CPS particles stimulated IL-6 and IL-8 secretion in monocytes and macrophages, chemotaxis towards a chemotactic stimulus of monocytes and phagocytosis of bacteria by macrophages, and provoked an oxidative burst of granulocytes. In the absence of cytotoxicity, 500- and 1000-nm CPS particles appear to influence phagocyte function to a greater extent

M. Bhatia (✉)
Department of Pathology, University of Otago, Christchurch, 2 Riccarton Avenue, PO Box 4345, Christchurch 8140, New Zealand
e-mail: madhav.bhatia@otago.ac.nz

than particles in other sizes. This scientifically sound study, again, has practical implications in view of the increasing use of nanoparticles in medical sciences. This article has been cited 10 times to date (Thomson ISI Web of Science).

Titanium dioxide (TiO_2) is used as a color additive and as a texture and moisture modifier in human food products, and is used in several confectionary foods and toothpastes. TiO_2, however, also causes a dose-dependent disruption of the brush border on the epithelial surface of absorptive cells of the intestine (Koeneman et al. 2010). A paper by Faust et al. (2014) reports the effect of titanium dioxide (TiO_2) on the microvilli of the human, brush border expressing cell line, Caco-2_{BBe1}. Once ingested, nano-scale TiO_2 can interact with epithelia that line the human gastrointestinal tract. Results from this study show that food-grade TiO_2 exposure results in the loss of microvilli from the Caco-2_{BBe1} cell system due to a biological response. Similar to the previous two reports discussed above, this study has significant practical implications, given the wide use of TiO_2 in human food products. This article has been cited 8 times to date (Thomson ISI Web of Science).

Radioprotectors are agents that protect normal cells from radiation injury in cancer patients undergoing radiotherapy (Kamran et al. 2016). Amifostine is an effective radioprotectant, has been approved by the FDA for limited clinical use. However, due to its adverse side effects, it is not routinely used clinically (Kamran et al. 2016). Ormsby et al. (2014) have investigated the effect amifostine on radiation-induced apoptosis. Results in this study show that while amifostine can reduce apoptosis caused by high doses of radiation, it does not mediate the same effect in response to low-dose radiation exposures. These results suggest that there may be a dose threshold at which amifostine protects from radiation-induced apoptosis. Results in this study also highlight the importance of examining a range of radiation doses and time points. This paper is an example of a study well conducted and results well presented and discussed. This article has been cited 8 times to date (Thomson ISI Web of Science).

Toxicity to the frequently used antipyretic drug acetaminophen (paracetamol) in the liver is a well-known problem. It can lead to hepatic failure and involves the metabolic pathways which take place within hepatocytes (Yoon et al. 2016). Leclerc et al. (2015) have investigated acetaminophen toxicity in HepG2/C3a microscale cultures using a system biology model of glutathione depletion. In this study, using an integration of a coupled mathematical and experimental liver on chip approach, the authors were able to correlate in vitro extracellular acetaminophen exposures with an intracellular in silico ROS accumulation. This paper represents clever science, with meaningful results obtained using multidisciplinary approaches, and has been cited 3 times to date (Thomson ISI Web of Science).

Melatonin is produced by the pineal gland and has been shown to possess antioxidant, anti-inflammatory, and antitumor properties, in addition to its role as regulator of biological rhythms. Pancreatic stellate cells (PSCs) play an important role in pancreatic fibrosis, a consistent histological feature of two major diseases of the pancreas - chronic pancreatitis and pancreatic cancer. In health, PSCs maintain normal tissue architecture via regulation of the synthesis and degradation of extracellular matrix proteins (Apte et al. 2012). Santofimia-Castaño et al. (2015) have shown that melatonin induces calcium mobilization and influences cell proliferation independently of MT1/MT2 receptor activation in rat PSCs in culture. Results in this study suggest that pharmacological concentrations of melatonin modulate the proliferation of PSCs. On the basis of their results, the authors suggest that melatonin induces Ca^{2+} mobilization and the activation of components of cell survival/death pathways that, in turn, regulate cell survival. This is a systematic study, which is well performed and well presented, with the key message of the paper presented in the form of a summary figure.

Methanol poisoning can cause significant death and disability, particularly in situations of contamination of illicit or homemade alcoholic beverages. If treatment is inadequate or delayed, mortality exceeding 40 % as well as visual impairment and motor and cognitive disorders may occur (Roberts et al. 2015). Methanol is metabolized to formaldehyde and formic acid, and it is these metabolites that make it neurotoxic in humans. A study by Zerin et al. (2015) reports effects of formaldehyde on mitochondrial dysfunction and apoptosis in SK-N-SH neuroblastoma cells. In this study, the authors compared the cytotoxicity of methanol and its metabolites and found that while methanol and formic acid did not affect cell viability, formaldehyde (200–800 μg/mL) was strongly cytotoxic. Mitochondrial membrane potential (MMP) was dose-dependently reduced by formaldehyde. Inhibition of mitochondrial respiratory enzymes, including NADH dehydrogenase, cytochrome c

oxidase, and oxidative stress-sensitive aconitase was also observed, in a dose-dependent manner, following treatment with formaldehyde. Formaldehyde also caused a dose-dependent increase in nuclear fragmentation and in the activities of the apoptosis-initiator caspase-9 and apoptosis-effector caspase-3/-7. Results of this study suggest that alteration of mitochondrial energy metabolism and mitochondrial membrane potential and oxidative stress may be the major causes for the activation of the caspase cascade that results in nuclear fragmentation and apoptosis. This study provides novel insights into the mechanism of methanol toxicity. This is yet another example of a well-performed and well-presented study.

Air pollution is a major public health problem and is the ninth leading risk factor for cardiopulmonary mortality (Kurt et al. 2016). A review article (Maynard 2015) summarizes our current understanding of the effects on health of ambient particles. This review also provided novel insights for future research. There is a lot we know now about the particulate matter (PM), but there is still a lot that is yet to be understood, including active components of ambient PM. In the short time since its publication, this article has already been cited twice (Thomson ISI Web of Science).

Suggestions for the way forward In my review of the articles published in Cell Biology and Toxicology in 2014 and 2015, I found that the work published in the journal represents strong science. Most of the articles deal with mechanisms of toxicity of chemicals, with several of the published articles having practical implications as well, as they deal with chemicals used as drugs/food additives. The one published review article on environmental toxicology was of indeed of high quality (Maynard 2015). It would be a good idea to invite other experts in the area of cell biology and toxicology to contribute review articles. Ideally, one review article in each issue (or every alternate issue) would, in my view, stimulate readers' interest and complement the work published in original reports. Similarly, editorials provide novel insights on specific subject areas. I am pleased to see editorials published in the journal in 2016 (e.g., Wang 2016; Mikó et al. 2016). Wang (2016) describes the cell biology and toxicology profile of cabozantinib, which was recently approved by the FDA for the treatment of advanced renal cell carcinoma in patients who have received prior anti-angiogenic therapy. Mikó et al. (2016) describe microbiome from a translational perspective. The human body has symbiotic, commensal, and pathogenic bacteria in large numbers, living in the cavities (e.g., gut, genitals, and airways) or on the surface (skin). Microbiome plays a key role since the beginning of life and genetics, prenatal environment and delivery mode can shape the newborn microbiome at birth. Prenatal and postnatal factors shape the development of the microbiome and have implications on health outcomes later on in life (Tamburini et al. 2016). In a concise manner, the review by Mikó et al. (2016) summarizes our current understanding of microbiome studies and inventions and their impact on personalized medicine and human nutrition. These editorials represent timely contributions to the literature with significant translational potential and I would strongly suggest continuing with this practice.

In summary, Cell Biology and Toxicology is making an important contribution to the scientific community by publishing research in the area of cell biology and toxicology. Most of the publications—original papers, review, and editorials—deal with mechanistic toxicology of commonly used chemicals—drugs, food items/additives, and other agents—and therefore have significant potential for practical application. I wish my best for the future of the journal.

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