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EDITORIAL

Highlight report: cytoprotective signaling in toxicology

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Cytoprotective signaling—a topic at the forefront of biological research—has been a focus of our journal over the past years. When cells are exposed to increasing concentrations of chemicals, three concentration ranges can be typically differentiated (Waldmann et al. 2014; Rempel et al. 2015). The first is the range of tolerance, where concentrations are so low that no cellular responses are induced. In the second concentration range, cell stress is evident as cellular functions are compromised, but the cells respond by activating complex mechanisms, which aim to re-establish the prior equilibrium. Very often, the activated response is sufficient to prevent cell death, suggesting that responses in this concentration range may also be sufficient to avoid adverse effects in vivo. Under these circumstances, stress responses can be interpreted as adoptive. In contrast, cell function may be compromised to such an extent that leads to adverse in vivo effects. The absence or presence of these adverse effects may depend on the cell type and the specific chemical used. Currently, the relationship between stress responses and adversity often remains unclear. The third range encompasses cytotoxic concentrations, where adaptive or stress response mechanisms decompensate. Consequently, it is not surprising that many studies in the past years focus on concentration range 2 to better understand the mechanisms and relevance of stress signaling.

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One cutting-edge topic within this field remains the Keap1-Nrf2 pathway, originally discovered by Paul Talalay in 1988 (Talalay et al. 1988). Nrf2 binds Keap1 via two sites called the hinge and latch domains (Baird and Dinkova-Kostova 2011; Marchan and Bolt 2013). After binding, Nrf2 is ubiquitinated and degraded (Slocum and Kensler 2011). Chemicals may disrupt the interaction between Nrf2 and Keap1 which brings about the translocation of Nrf2 to the nucleus, where it initiates the transcription of cytoprotective genes (Balogun et al. 2003; Dinkova-Kostova et al. 2002). A recently published example of a chemical that could disrupt the Nrf2-Keap1 interaction is the isothiocyanate, sulforaphane, a hydrolysis product of glucosinolates found in broccoli (Piberger et al. 2014). Sulforaphane has been shown to induce the Nrf2/Keap1 signaling pathway and is discussed as a possible anticarcinogenic compound. Nrf2 also represents a control factor of skin sensitization (Vander Veen et al. 2013), where Nrf2-deficient mice show a stronger response in the local lymph node assay, suggesting that the Nrf2/Keap1 axis mitigates sensitization. Moreover, the Nrf2 heme oxygenase pathway has recently been shown to confer neuroprotection against paraquat-induced Parkinsonism (Li et al. 2012).

A second field addressing the stress responses of cells exposed to chemicals is the upregulation of detoxifying or downregulation of activating metabolism (Godoy et al. 2013; El-Sherbeni and El-Kadi 2014; Abdelhamid et al. 2013; Grinberg et al. 2014). Metabolism still represents one of the major challenges for in vitro system development (Hammad 2013; Reif 2014; Godoy 2010, 2011). For instance, cultivated primary cells typically downregulate drug-metabolizing enzymes (Zellmer et al. 2010; Ghallab 2013, 2014). In addition, stem cell-derived cells used in toxicity testing usually do not express high enough levels of drug-metabolizing enzymes (Godoy et al. 2015; Baxter

et al. 2015; Brulport et al. 2007). A further difficulty is that stress responses in cultivated cells may differ from those seen in vivo (Heise et al. 2012). For example, cell culture conditions may induce more robust anti-apoptotic mechanisms than those generated in vivo (Godoy et al. 2009, 2010). Therefore, the interpretation of stress responses with respect to adversity in vivo still remains a major challenge.

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