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EDITORIAL

The cytoprotective and the dark side of Nrf2

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In 1988, Paul Talalay and colleagues described a protein with highly reactive cysteine residues that protects against chemical carcinogenesis (Talalay et al. 1988) This led to the discovery of an elaborate network of highly inducible, cytoprotective proteins that are controlled by the Keap1-Nrf2 pathway (Itoh et al. 1999; Dinkova-Kostova et al. 2002; Kobayashi et al. 2004; Wakabayashi et al. 2004; Motohashi and Yamamoto 2004; Zhang and Hannink 2003; Balogun et al. 2003; McMahon et al. 2003; Zhang et al. 2004; Kwak et al. 2003). In the following decades, the Keap1-Nrf2-signaling axis became one of the most studied topics in toxicology. Therefore, it comes as no surprise that two of the most discussed invited reviews published in the Archives of Toxicology highlight the importance of this pathway (Baird and Dinkova-Kostova 2011; Slocum and Kensler 2011) (Table 1). Nrf2 is bound by Keap1 via two binding sites, the so-called hinge and latch domains. Following binding, Nrf2 is ubiquitinated and degraded by the proteasome, which controls Nrf2 basal levels. Chemicals or cell stress may disrupt the interaction between Nrf2 and Keap1 leading to inefficient ubiquitination of Nrf2. Instead, Nrf2 accumulates and translocates to the nucleus where it induces transcription of a number of cytoprotective genes.

In their comprehensive review, Baird and Dinkova-Kostova (2011) present different models of regulation, such as the 'sequester and release model' for Keap1-Nrf2, the role of cullin 3 during dissociation, the hinge and latch model, sensing of inducers by Nrf2 and the role of phosphorylation. Moreover, a comprehensive overview of cytoprotective Nrf2 target genes and the chemistry of inducers are provided. In a complementary review, Slocum and Kensler (2011) focus on genetic mouse models of the Keap 1-Nrf2 pathway and its role in carcinogenesis of the colon, bladder, lung, stomach, skin, liver and breast. Upregulation of Nrf2 signaling provides tumor cells with a survival advantage in adverse environments (Slocum and Kensler 2011). Moreover, Nrf2 also upregulates the expression of the multidrug-resistant protein-3 (MRP3), which exports a variety of cytostatic drugs, including chlorambucil, cisplatin, doxorubicin and etoposide.

Further influential articles published in the Archives of Toxicology in recent years focus on nanotoxicity (Kim et al. 2012; Landsiedel et al. 2012; Nunes et al. 2012; Trpkovic et al. 2012; Gebel 2012; Oesch and Landsiedel 2012), the use of stem cells in toxicology (Wobus and Löser 2011; Krug et al. 2013; Seiler et al. 2011), carcinogenesis (Bernstein et al. 2011; Golka et al. 2011; Burns and Korach 2012; Pavanello and Lotti 2012; Brambilla et al. 2011), metal toxicology (Chasapis et al. 2012), neurotoxicity (Soderlund 2012; Carvalho et al. 2012; Mariussen 2012), in silico and in vitro methods (Karp and Caspi 2011; Godoy et al. 2013; Mehling et al. 2012; Geenen et al. 2012) and oxidative stress (Matés et al. 2012). The editors hope that this choice meets the current needs of our readers, and encourage them to suggest further

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Table 1 Overview of the most discussed review articles

Key message	No. of citations	Reference
Chemicals react with cysteine residues of Keap1. This leads to stabilization and nuclear translocation of the transcription factor, Nrf2. Finally, cytoprotective Nrf2-dependent genes become expressed	89	Baird and Dinkova-Kostova (2011)
An expert panel estimated the time necessary to achieve full replacement of animal testing. Time frames of 7–9 and 5–7 years are discussed for skin sensitization and toxicokinetics, respectively. However, a timeline cannot be estimated for repeated-dose toxicity, carcinogenicity and reproductive toxicity	63	Adler et al. (2011)
Inorganic selenium interacts with endogenous –SH groups, thus explaining some of its toxicological effects. The potential use of organoselenium as a therapeutic has not yet been sufficiently explored	52	Nogueira and Rocha (2011)
Many studies with Nrf-2 knockout mice demonstrate its key role in carcinogenesis of the colon, bladder, lung and stomach, and its relevance to inflammation control	39	Slocum and Kensler (2011)
Gas or liquid chromatography coupled to mass spectrometry allows the quantification of thousands of metabolites. However, despite intensive research in the field of metabolomics, no metabolites have been successfully introduced into routine clinical practice. This review critically discusses the state of the art in the field of inborn errors of metabolism, cardiovascular disease and cancer	38	Mamas et al. (2011)
The micronucleus assay is used to detect aneugens and clastogens. The 'cytokinesis-block micronucleus assay' evaluates nucleoplasmic bridges, cell division inhibition, nuclear buds, apoptosis and necrosis. This review gives an overview of current protocols, high-throughput methods and the biological background of the micronucleus assay	36	Kirsch-Volders et al. (2011)
This review provides an overview of standardized methods to analyze the antioxidative capacity of chemicals, with particular focus on food constituents	35	Gülçin (2012)
Cell signaling activated by nanoparticles includes P38, JNK, NF kappa B and Nrf2 and is associated with the capacity to induce cytotoxicity	30	Marano et al. (2011)
The surface modifications of nanocrystal quantum dots, and not their core metalloid complex, are responsible for most of the observed toxic effects	27	Hoshino et al. (2011)
This review discusses the possibilities and limitations of in vitro testing for the evaluation of human health risks	25	Clift et al. (2011)

The number of citations that are current as of October 14, 2013

cutting-edge topics, and of course the authors who will contribute to future comprehensive and insightful review articles.

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