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Editorial Overview: Oxidative Toxicology: From molecules, to cells, to tissues

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This review comes from a themed issue on **Oxidative Toxicology: From molecules, to cells, to tissues**

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Professor Dimitrios Kouretas was born in Patras, Greece, in 1962. He studied pharmacy (1985) and received his PhD in biochemistry (1989). He spent the period 1990-1992 at Harvard Medical School, USA, as postdoctoral fellow. His field of research is the mechanisms of antioxidants in health and disease. He has published more than 180 peer-reviewed articles with more than 5500 citations with an h-index of 40. He is a professor of physiology-toxicology in the Department of Biochemistry-Biotechnology, University of Thessaly, Greece, from 2001. He is a member of experts in European Commission (SCHERR).

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Dr. Roede is an assistant professor and associate director of the toxicology graduate program in the Skaggs School of Pharmacy and Pharmaceutical Sciences at the University of Colorado. He obtained his PhD from the University of Colorado and conducted a postdoctoral fellowship under the guidance of world-renowned oxidative stress expert, Dr. Dean P. Jones. Dr. Roede's research program is focused on understanding how toxicants impact cellular redox signaling and control and how this mechanism plays a role in the development of neurodegenerative disease.

In the present special issue of *Current Opinion in Toxicology* entitled 'Oxidative Toxicology', 12 interesting opinion articles have approached this broad topic under four pillars. Firstly, three articles highlight the significance of biomarkers, which might be a wide range of molecules able to depict the outcome of several compounds and treatments in the field of oxidative toxicology. Furthermore, the interconnection between redox biology and toxicology is described in three additional articles stressing that these two scientific areas are associated not only with the pathology of several diseases but also with the alleviation of some of their symptoms. Finally, five additional reviews included in this special issue examine the action of several toxic agents in the frame of reduction and oxidation reactions, whereas one article discusses the association of toxicology with free radical generation during physiological treatments, such as exercise and administration of dietary antioxidant compounds.

Veskoukis et al., in their article, have presented a battery of translational biomarkers for measuring the antioxidant, antimutagenic, and antitoxic capacities of plant compounds at three biological levels, namely, *in vitro*, cell culture, and *in vivo*. By defining the biomarker issue (i.e. the rationale of adopting biomarkers to address scientific queries) and the widely used term redox biomarkers, Professor Kouretas' group has contributed to the establishment of a trajectory to holistically assess the biological action of polyphenolic compounds in the frame of oxidative toxicology. Thus, they propose a practice that can be applied in a wide range of experimental approaches in biomedical sciences, and it can provide mechanistic answers regarding the activity of physical substances in the redox continuum. Similarly, Pikula et al. have also pinpointed that oxidative stress metabolites of plants can be used as biomarkers in the field of ecotoxicology. They state that environmental pollutants increase the intracellular formation of reactive oxygen species (ROS) that in turn trigger various defense mechanisms against oxidative stress. As defined by Veskoukis et al., ROS molecules generated following cell oxidative damage, as well as the activity and concentration of antioxidants, can be used as redox biomarkers. Therefore, the article of Pikula et al. presents an overview of the novel use of microalgal oxidative stress biomarkers for the study of toxic

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Professor Tsatsakis is the director of the Department of Toxicology and Forensic Sciences, Medical School, University of Crete. He has published well over 1000 works, over 500 of them in ISI journals, and he is holder of several patents. The main research interests of Professor Tsatsakis include biomonitoring and risk assessments of xenobiotics and links of chronic exposure to them, at low doses, with health problems and diseases. Dr Tsatsakis is Foreign Member of the National Academy of Sciences of Russia, Fellow of Academy of Toxicological Sciences (USA), Honorary Member of EUROTOX, and Honorary Doctor of Mendeleev University; Far East Federal University; and Carol Davila University. He has served as the EUROTOX President.

activity of common xenobiotics. Additionally, in the manuscript by Costa et al., these authors approach the notion of biomarkers at the molecular level. Their review refers to the specific genetic polymorphisms that can alter the function of antioxidant enzymes involved in pesticide metabolism. The assessment of exposure to pesticides remains difficult, although the pathogenesis of chronic diseases related with pesticide exposure involves various mechanisms, including oxidative stress. Further, the production of free radicals is capable of inducing genomic damage; thus, this article reviews the potential role of genetic polymorphisms in the enhancement of pesticide-induced oxidative stress.

On the basis of the second pillar as described previously, diverse pathologies induced by toxicants, such as neurodegeneration, are an outcome of disruption in redox signaling and control of cellular processes, indicating anew the interrelation between redox biology and toxicology. For example, Aivazidis et al. provide examples of the mechanistic interaction between oxidative stress and proteostasis network (PN) alterations. The article from Professor Roede's group discusses the toxicant-mediated PN disruptions focusing on environmental metals and pesticides. Additionally, they emphasize the need to distinguish whether the presence of protein aggregations are contributory to phenotypes related to neurodegeneration, or if they are a byproduct of PN deficiencies. In addition, Li et al. highlight the putative role of Nrf2 in the incidence of the nonalcoholic fatty liver disease. It is common knowledge that Nrf2 is one of the most fundamental transcription factors regulating adaptive antioxidant and xenobiotic stress responses. Nonalcoholic fatty liver is characterized by excessive triglyceride accumulation in hepatic cells, and there is scarce evidence that Nrf2 activators could be beneficial if administered in the proper phase of the disease. Hence, Nrf2 could be regarded as a promising biomarker for the onset of the disease, although the impact of its activators on amelioration of hepatic steatosis and inflammation still seems to be controversial. Alcoholic liver disease (ALD) is another pathology related to impaired antioxidant defense. Ali et al. highlight that lipid peroxidation, which is a consequence of oxidative stress, plays key role in ALD. Ethanol consumption is highly related to impaired antioxidant action since it induces pathogenic lesions on protein, DNA, and lipids throughout the cellular environment. Ali et al. describe recent studies and approaches relating cellular mechanisms of lipid peroxidation to the pathogenesis of ALD, formulating a series of articles in the present special issue regarding oxidative toxicology and pathogenesis.

The third structural pillar of the special issue is related to the redox basis of action of several toxic agents. Arsenic, as presented by Roggenbeck et al., is usually ingested in its inorganic form and is linked to diverse pathologies in many organ systems. Its detoxification involves alternating oxidations and reductions of arsenic, and although its metabolism pathways have been in depth studied, the interplay between microbiome and the host is rather neglected. Therefore, Roggenbeck et al. stress that there is a need to shed light on microbiome-host arsenic-interactions, which will potentially foster the development of novel targeted strategies to relieve or prevent arsenic- and redox-associated pathologies. In addition, the group of Professor Poulas presents an interesting article reviewing the less detrimental effects of electronic nicotine delivery systems (ENDS, or electronic cigarettes) on human health compared to conventional cigarettes. Andrikopoulos et al. focus on oxidative stress and alterations in antioxidant activity caused by ENDS' aerosols or liquids in oral cavity and lung tissues. They report that ENDS induces less oxidative stress at the molecular level compared to cigarettes, indicating that their toxicity is confined by restricting the action of harmful oxidative molecules. Furthermore, Allawzi et al. review the toxic mechanisms of bleomycin, which is a substance used to model pulmonary fibrosis, acute respiratory

distress syndrome, and pulmonary hypertension secondary to interstitial lung disease. This molecule acts by inducing oxidative damage, which then leads to subsequent inflammation and fibrosis mediated by generation of both extracellular and intracellular ROS. The authors focus on the role of extracellular redox environment in bleomycin toxicity, with attention to the generation of extracellular ROS, alterations in the redox state of extracellular thiols, and the central role of the extracellular isoform of superoxide dismutase in the development of bleomycin-induced injury and fibrosis stressing the redox background of bleomycin toxicity. Moreover, the article by Cagle et al. focuses on reactive aldehydes that are the end products of several oxidative decomposition reactions. Polyunsaturated lipids are usually the main molecules to generate aldehydes, including 4-hydroxy-2-nonenal and malondialdehyde. Overproduction of such metabolites generates reactive species and/or causes aggregation of proteins, hence considered a potential etiological factor in neurodegeneration. To this end, specific scavengers could prove a novel therapeutic approach to relevant pathologic conditions, such as Parkinson's disease. Finally, Mendoza and Brown review toxicity induced by engineered nanomaterials (ENMs), which are incorporated into a wide range of biomedical and consumer products. It has been found that ENMs act as toxic agents by inducing redox-related cytotoxicity in high acute doses, as expected. However, ENMs are also harmful in low, nontoxic concentrations via induction of oxidative stress. Therefore, the authors review the physicochemical properties and mechanisms associated with ENM-driven oxidative stress, highlighting the need for research investigating effects on the redox proteome that may lead to cellular dysfunction at low or chronic doses of ENMs.

Finally, Yfanti et al. study the generation of toxic concentrations of reactive oxygen and nitrogen species (RONS) following a physiological treatment, namely, exercise. It is established that RONS can be toxic agents against macromolecules by oxidatively modifying them, thereby compromising their normal function. Furthermore, they can also be harmful macroscopically since their overproduction has been correlated with impaired exercise performance. The review of Professor Jamurtas' group specifically focuses on the effects of vitamin C, vitamin E, polyphenols, and N-acetylcysteine on the detrimental action of exercise-derived RONS and the protective effect of nutrition. Furthermore, they present data with respect to the effects of protein supplementation and more specifically, whey protein, which has drawn the attention lately due to its antioxidant properties and its putative beneficial action on exercise performance.

The opinion articles that comprise this special issue form a mosaic of ideas regarding the redox-related base of toxicology. They manifest the broad array of applications that oxidations and reductions have on the molecular mechanisms of differential toxic agents and on the onset of several diseases (e.g. ALD) and physiological treatments (i.e. exercise and nutrition). Finally, the biomarker issue is a crucial indicator of both toxicity and alleviation of its detrimental outcome, thus, offering the opportunity to holistically approach the research challenges of oxidative toxicology.