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Is *in vitro* Cell Culture Suitable for Study of Environmental-Induced Oxidative Stress?

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Introduction

Oxidative stress could be induced by multiple environmental factors. Although *in vivo* tests are usually adopted on the study of environmental toxicology, in order to control the influencing factors better and explore further mechanisms, is *in vitro* cell culture more suitable for the study of environmental-induced oxidative stress?

Oxidative stress is caused by an imbalance between the production of reactive oxygen and the protective ability of biological system which could detoxify the reactive intermediates or easily repair the oxidative damage. Oxidative stress is considered as a critical pathophysiological mechanism in different frequent illnesses, including cardiovascular diseases, cancer, diabetes, rheumatoid arthritis, or neurological disorders [1-5].

Multiple environmental materials could induce oxidative stress [6,7]. For example, the excessive consumption of animal protein and fat combined with few fruits and vegetables could cause the occurrence of some cancers, such as on-Hodgkin lymphoma, prostate, olon, breast and endometrium. Some inducers of oxidative injury are found in polluted air, such as sulphur dioxide able to induce the oxidative damage of protein and DNA-protein crosslinks, and ozone able to elevate the level of 8-isoprostane, a biomarker of oxidative damage related to air pollution, when exposed for a long term. Exposure of cells to ionizing radiation could cause complex cellular responses eventually injuring DNA. The underlying cytotoxic and cellular stress responses to radiation are mediated by signaling pathways, activation of which may be amplified by intrinsic cellular radical production systems. These cellular responses include the activation of plasma membrane receptors, cytoplasmic protein kinases and transcriptional activation. Pesticides induce oxidative stress by resulting in an imbalance between pro-oxidant and antioxidant defense mechanisms in different tissues, including alterations in antioxidant enzymes. Tissue culture studies show that pesticides, especially organophosphate pesticides, induce oxidative stress and affect catalase and superoxide dismutase activities. Toxic effects of several metals including arsenic, antimony, lead, cadmium, chromium, cobalt, beryllium, nickel and vanadium, are related to the cellular redox regulation and induction of oxidative stress. These metals catalyse the formation of ROS which damages key proteins by causing protein denaturation, aggregation, and a failure of the ubiquitin/proteasome system to remove these defective proteins.

The toxic effect and mechanism of environmental toxicants could be researched by *in vivo* and *in vitro* methods. However, in the 20th century, *in vivo* toxicity tests were the major methods which were used in predicting ecological risk of environmental toxicants relied on the testing programs that could detect toxic effects. Extrapolation which was based on largely conservative assumptions or arbitrary uncertainty factors was used on risk assessment from one species to another or from controlled laboratory tests to uncontrolled real-world environments [8]. However, a large number of testing animals are used and killed for toxic studies and the ethical concerns are increased gradually [9,10]. The Cosmetic Directive and the REACH legislation expect to reach the aim of replacement of animals, refinement of animal experiments and reduction of the number of experimental animals (3R principles) which are supported by omics technologies [11]. Furthermore, it is limited to predict the risk of toxicants by the extrapolation from animals to human beings, such as acute toxicity, reproductive toxicity, eye irritation and skin irritation [12-15]. In conclusion, it is costly, time-consuming, unfocused, and contentious assessments that often failed to give public confidence in related regulatory decisions [8].

In the 21st century, advances in biological methods, including transcriptomics, proteomics, metabolomics *in vitro*, and high-throughput technologies, enable us to make further studies on toxic effects and mechanism at the molecular, cell and tissue levels. Analysis of complex data from the toxic studies *in vitro* is more systematic and scientific by using modern computers [8]. It is cheap, timely, reduplicated and even automotive to evaluate toxicology by *in vitro* methods. Culturing cells is the most widely used *in vitro* method in toxicology and co-cultures of cell types are expressing organ-specific functions even better. Human cells and tissues models are more promising tools in toxic studies. Nowadays, human skin models are commercially available and have been used successfully to investigate pharmacology and toxicology of new drugs [16].

Cell models are available for practically all tissues or laboratory animal species. There are few ethical problems, with the notable exceptions of human tissue donation and embryonic stem cells [17]. In modern times, the method of cell culture has been widely used in the studies of oxidative stress induced by environmental factors, which is more controllable, quick and inexpensive. What is more, the allelopathy mechanism of environmental materials is more detailed. For example, the induction of inflammation in human airway epithelial cells by exposure to diesel soot and particles throughout a process mediated by oxidative stress has been shown by *in vitro* studies [18]. The urban particulate matter with an aerodynamic diameter ≤ 2.5 or 10 μm could induce oxidative stress and cause the injury of human umbilical vein endothelial cells by means of evaluating ROS, nitric oxide (NO), NF-κB translocation and cell death, which demonstrated that these particles may participate in the development of cardiovascular and inflammatory diseases [19]. Culturing cell has been widely applied on the study of relation between oxidative stress and diseases such as cancer [20].

The toxic effects of environmental toxicants are closely related

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to the occurrence of oxidative stress. Studies on the mechanism of oxidative stress induced by environmental factors are conducive to further understanding of environmental toxicology. Cell cultures are helpful for quickly and cost-effectively screening chemicals that might induce an adverse effect, elucidating mechanisms of toxicity, and justifying more intensive studies with whole organisms. *In vitro* cell culture is more suitable for the study of environmental-induced oxidative stress. However, more efforts should be taken to establish in vitro cell models and corresponding regulations of the environmental toxicology, which is both challenged and hopeful.

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