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Review

Cell homeostasis alterations induced by environmental stress

Alica Navrátilová, Marek Kovár, Anna Trakovická, Miroslava Požgajová*
Slovak University of Agriculture in Nitra, Slovak Republic

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The modern lifestyle with high level of industrialization eventuates in the large quantity of environmental pollutants entering the atmosphere, soil and water. Hence, exposure of the organism to these elements occurs primarily through the ingestion of contaminated food and water or through inhalation of polluted air. Environmental contaminants such as heavy metals and other xenobiotics are able to interact with essential cellular components resulting in destabilization of the control machineries required for the normal cell behavior. The main focus of this review is thus to describe the current knowledge of the threat of the toxic environment to fundamental processes of living organisms. Although much has been investigated to date concerning the effect of environmental contamination on all aspects of the organism's biological processes including metabolism, growth, or reproduction, still a lot remains elusive.

Keywords: environmental contamination, heavy metals, cell cycle, ionome, homeostasis

1 Introduction

Under physiological conditions, the major source of reactive oxygen species (ROS) is the respiration process in mitochondria which is normally under tight homeostatic control. The ROS formed as by-products of oxygen metabolism in living cells include hydrogen peroxide, hydroxyl radical and superoxide anion. Although, ROS under normal physiological conditions are involved in some cell signaling pathways, their over-production as a result of an environmental stressors activity like UV, ionizing radiations, pollutants, heavy metals, and xenobiotics contribute to imbalance of the cell homeostasis causing oxidative stress to the cell which in turn gives rise to cell and tissue damage (Pizzino et al., 2017). A consequence of our modern lifestyle is that organism is on daily basis attacked by various impairing agents, oxidants, inducing elevation of ROS by individual cells. Excessive levels of ROS negatively affect important cellular structures such as proteins, lipids, nucleic acids, membranes and organelles. This is associated with severe diseases including cancer, hypertension, cardiovascular diseases, diabetes, chronic obstructive pulmonary disease, asthma, idiopathic pulmonary fibrosis, skin diseases, chronic kidney disease, and various neurodegenerative diseases (Unsal et al., 2020). Hence, environmental contamination and its influence on all aspects of the organism's biological processes is the research focus of many scientific laboratories world-wide.

Environmental contamination

As the contamination of the environment through rapid urbanization and industrialization has markedly enhanced levels of toxic elements in the environment and the common feature of most pollutants and toxicants is their ability to spread to wide distances from the original source, they represent significant risk for ecology, evolution, nutrition and the environment (Maleki et al., 2017; Lazarini et al., 2019). Environmental pollutants such as heavy metals, nanomaterials, polycarbonate plastics, epoxy resins, drug residues and other xenobiotics are accumulated in soils or water and plants grown at such soils occurring mostly in urban, industrial and roadside areas are enriched by these dangerous and toxic elements in concentrations that are harmful for living organisms. The unique properties of soil potentiate its ability to act as a filter and a reservoir for toxic elements including heavy metals, propylbenzenes (PBZs) and trimethylbenzenes (TMBs), nanoplastics, bisphenols and

***Corresponding Author:** Miroslava Požgajová, Slovak University of Agriculture in Nitra, AgroBioTech Research Center, Tr. Andreja Hlinku 2, 949 76 Nitra, Slovak Republic. e-mail: miroslava.pozgajova@uniag.sk

other pollutants of chemical or biological origin (Peng et al., 2021; Sathishkumar et al., 2020; Jiang et al., 2020; Palma-Lara et al., 2020; Eladak et al., 2015). Unfortunately, as to the most prominent features of heavy metals belong non-degradability, high persistence in the ecosystem, and substantial bioaccumulation by living organisms, contamination of the environment by these elements is therefore almost irreversible (Hanfi et al., 2020; Onakpa et al., 2018). Moreover, such polluted soils become inadequate for crop cultivation resulting in severe microclimate changes causing biodiversity degradation and water cycles alterations which in turn lead to floods and erosion. Hence, soil contamination might change the whole ecosystem. It is now more than obvious that the soil quality and its contamination by toxic elements reflects many different factors including historical country development, use of the land, industrialization, population density, climate conditions, biogeography, etc. Transport of toxicants from soils to plants and via the food chain to humans triggers the so-called chronic effect which is related to mutagenic and carcinogenic threat to the organism (Weissmannová and Pavlovský, 2017; Khan et al., 2018; Drzeżdżon et al., 2018). Generally, environmental conditions, availability of micro and macronutrients in nutrition play an inconvertible role in the ability of cells to maintain internal balance.

Ionome homeostasis

Intake and accumulation of mineral elements by the cell are under control by various regulatory mechanisms as some minerals are part of macromolecules, or serve as co-factors of enzymes, eventually are involved in different biochemical processes as signal molecules. Thus, analyses of the ionome representing the overall content of minerals in the organism provides considerable information about nutritional status of the organism and its nourishment (Salt et al., 2008). Ionomics focuses on quantification of the most elements in the sample, with the aim to understand how physiology, genetics, evolution and the environment influence mutual interactions and changes of the inorganic composition of the organism (Lahner et al., 2003). Genetic screen performed with the gene deletion library of the yeast *Saccharomyces cerevisiae* revealed that at least 619 genes are involved in ionomic processes (Yu et al., 2012). Similar set of experiments was performed with human library of small interfering RNAs transfected to HeLa cells revealing new regulatory proteins involved in ionome homeostasis maintenance (Malinouski et al., 2014). Misbalance in mineral elements homeostasis and utilization leads to health complications such as the lethal Menkes disease resulting from the ATP7A gene mutation which leads to severe decrease in copper content in most tissues. Mutation of the ATP7B gene causes copper accumulation in liver and brain leading to Wilsons disease development (Horn et al., 2020). Other health alterations and diseases have been described as a consequence of misbalance in intake, metabolism, mutual interaction or utilization of minerals in the organism (Cheng et al., 2019; Davenport, 2020; George et al., 2019). This implies that genetic predispositions, on one hand, and food intake with balanced or unbalanced mineral content, as well as environmental conditions, on the other hand, seriously affect population health. Concomitant with this, our recently published data (Pozgajova et al., 2020) demonstrate that acute contamination of the environment with heavy metals such as nickel and cadmium leads to substantial ionome misbalance in the cell. Correlation analyses of mineral content in the cell show strong positive correlation among tested essential elements (Ca^{2+}, Na^{+}, Cu^{2+}, Mg^{2+} and Fe^{3+}) except for K^{+} in the presence of nickel and cadmium in growth media, demonstrating the significant impact of heavy metal treatment on ion homeostasis of the cell. Studies of elemental balance analyses reviewed by Jeyasingh et al. (2017) confirmed the genes-to-ecosystem pattern referring to consequences of the changes among sets of micro and macro elements that influence the physiological adjustments leading to unexpected models in biomass stoichiometry. However, further investigation is required to define the impact of environmental toxicants on internal balance of the cell in more details.

Cell cycle regulation as a target for environmental pollutants

Cell cycle as a fundamental feature of all living organism is a strictly regulated process that ensures growth and development of the organism. Mitosis results in the production of two identical daughter cells from one mother cell (Lee and Bolanos-Garcia, 2014). A specific kind of cell division, meiosis, leads to production of gametes in which the number of chromosomes is reduced to half of the original number, and the genetic material between homologous chromosomes is exchanged. To reduce the number of chromosomes a single round of DNA replication is followed by two sequential rounds of chromosome segregation called meiosis I and meiosis II. Meiosis is crucial for the differentiation of germ cells undergoing the process of haploid cell generation, and to set the foundation for sexual reproduction (Hunt et al., 2009). In healthy cells, under normal living conditions, the cell cycle is regulated by multiple and overlapping series of signaling pathways controlling cell growth, DNA replication and cell division ensuring error-free chromosome segregation into newly formed cells (Kipreos et al., 2019; Dangarh et al., 2020). Although, much

is known about toxic effects of environmental pollutants such as heavy metals on living organisms, their effect on regulation of the cell cycle progression remains unclear. Organisms exposed to oxidative stress exhibit lipid peroxidation, destruction of biological macromolecules, DNA alterations, threatening the genomic stability of a cell and its survival. DNA damage through double-stranded break formation, in turn, leads to genetic instability and chromosomal aberrations (Gobrecht et al., 2017; Srivastava et al., 2014; Zhou et al., 2013). Accordingly, errors in DNA repair mechanism can cause mutations and missegregation of chromosomes leading to uncontrolled cell division or compromised gametes production during meiosis (Beyersmann and Hartwig 2008; Klinakis et al., 2020). One of the most common regulatory mechanisms controlling the cell cycle, possibly altered through environmental toxicants, is reversible protein phosphorylation. Protein kinases catalyze signaling pathways and cell processes affecting transcription, cell cycle progression, differentiation, cytoskeletal reorganization and cell movement, apoptosis, cell response to environmental changes etc. (Johnson, 2009; Harashima et al., 2013). Central regulatory molecules controlling the cell cycle progression are cyclins and cyclin-dependent kinases. The phosphorylation activity of the major regulatory kinase in the model eukaryotic organism *Schizosaccharomyces pombe*, Cdc2, rises at the beginning of premeiotic S-phase and has its peak during karyokinesis. Regulatory molecules cyclin Cdc13 and the kinase activator Cdc25 are both important for progression of the first and second meiotic division and their activity and regulatory function might be directly or indirectly affected by environmental pollutants (MacKenzie and Lacefield, 2020; Bišová et al., 2003). However, meiotic cell division in *S. pombe* is regulated by a variety of other protein kinases involved in multiple signaling pathways that could also be a target of the contamination causing elements (Kovacikova et al., 2013; Rumpf et al., 2010). Additionally, cell division is regulated through checkpoint mechanisms that monitor critical events. They hinder initiation of late events until earlier events have been successfully completed to ensure error-free transmission of genetic information to the progeny (Barnum et al., 2014). These surveillance mechanisms arrest or delay cell cycle progression in case of the genome integrity alterations. In mammals, defects in checkpoint responses cause genomic instability, leading to tumor development, miscarriages or birth defects (Lanz et al., 2019; Waterman et al., 2020). The ascending evidence that carcinogenic toxicants disturb regulation of the DNA repair systems and cell cycle control comes from variety scientific studies. Moreover, it has been described that impairments of diverse mechanisms on different regulatory levels of multi-stage pathways are involved in these processes. For instance, it has been shown that zinc finger proteins are sensitive to toxic metals, cadmium together with other unessential heavy metals trigger DNA integrity alterations, chromosomal abnormalities and cell cycle arrest (Pizzaia et al., 2019; Genchi et al., 2020; Chiu et al., 2010; Morales et al., 2016). Moreover, a recent study of Špačková et al. (2020) shows a negative impact of bisphenol A on the cell cycle progression in the G1 or early S phase in the fission yeast. The authors suggest that the possible mechanism for the cell cycle alteration is the bisphenol A-enhanced ROS production that in turn leads to DNA damage.

Antioxidant defense mechanisms

The toxic danger of many environmental toxicants such as heavy metals (Cd, Pb, Hg, Ge, Co, Cr, or Ni) is related to their ability to be converted by various metabolic pathways present in biological systems to derivatives leading to enhancement of ROS production (Thorpe et al., 2004; Halliwell and Gutteridge, 2015). ROS generation results from the reduction of molecular oxygen. To these short-lived molecules among others belong H_2O_2, $O_{2^{\cdot-}}$ and OH^- (Table1). A physiological production of ROS is ensured by mitochondria through the electron transport chain (ETC) and by the NADPH oxidases (NOXs). Under physiological conditions act ROS as secondary messengers and their production is regulated by enzymatic and non-enzymatic antioxidant systems. The decrease of the antioxidants activity or increase of ROS formation results in oxidative stress (Masselli et al., 2020). Thus, the characteristic feature of the oxidative stress is the cellular redox imbalance which means that the pro-oxidant state exceeds the antioxidant state of the cell. To the major reasons of oxidative stress formation belongs overproduction of ROS via cell exposure to heavy metals or soluble organic compounds, mitochondrial dysfunction, NADPH-oxidases alteration, or disruption

Table 1 Types of reactive oxygen species (ROS)

Radicals:	
Superoxide	$O_{2^{\cdot-}}$
Hydroxyl	$^{\cdot}OH$
Peroxyl	$RO_{2^{\cdot}}$
Alkoxyl	$RO^{\cdot}$
Hydroperoxyl	$HO_{2^{\cdot}}$
Non-radicals	
Hydrogen peroxide	H_2O_2
Hypochlourus acid	$HOCl^-$
Singlet oxygen	$^1O_2$
Peroxynitrit	$ONOO^-$

of intracellular calcium homeostasis. Another ROS generation enhancement occurs through the redox sensitive signaling pathway-mediated activation of inflammatory cells such as mitogen-activated protein (MAP) kinases, activator protein 1 (AP-1), and activation of the nuclear factor kappa B (NF-kB) which in turn changes the pro-inflammatory gene expression and increases production of cytokines (Møller et al., 2014).

As oxidative stress is considered as a general pathophysiological mechanism it is associated with lots of health threatening conditions including cardiovascular and neurodegenerative diseases, diabetes or cancer. Over time, cells have evolved numerous biological molecules to handle the living in an oxidizing atmosphere (Figure 1). To the most powerful enzymatic protection belong superoxide dismutases (SODs), catalase (CAT), glutathione reductase (GR), or cellular glutathione (GSH) (Erlich et al., 2020).

Many plant derived antioxidants including vitamin C, vitamin E (mainly α-tocopherol), carotenoids, flavonoids, etc. serve as second line antioxidant defense machinery. To the prominent discharger of singlet oxygen belongs β-carotene. Vitamin C and GSH have been described as prominent $O_{2}^{\cdot-}$ and HO scavengers. Flavonoids and vitamin E prevent cell membrane damages as they are capable of peroxyl radicals displacement therefore avoiding lipid peroxidation (Gupta and Sharma 2006). The role of biological antioxidants, including ascorbic acid, glutathione, α-tocopherol (vitamin E), or carotenoids, together with antioxidant enzymes catalase and glutathione peroxidase (GTX) is to react with oxidants and help to detoxify ROS (Kapoor et al., 2019). Additionally, cells have evolved diverse biochemical mechanisms of self-adaptation to various stresses. It has been reported that eukaryotic organisms exposed to environmental challenges respond by activating stress-dependent gene expression programs through several mitogen-activated protein (MAP)s kinase pathways. Phosphorylated MAP kinase triggers phosphorylation of specific transcription factor (TF) facilitating changes in the gene expression program by adapting the complex RNA polymerase II (Pol II) transcriptional machinery into particular sets of genes (Salat-Canela et al., 2017). Recently a non-coding RNA (ncRNA) system modulating protein levels in response to stress has been described showing that the non-coding transcripts have the potential to influence multiple pathways and thus regulate specific stress responses adding extensions to the core MAPK signaling pathway (Leong et al., 2014). Other cellular responses to the increased ROS production leading to oxidative stress induced DNA damage include activation of ataxia telangiectasia mutated (ATM) which in addition to p53 phosphorylation mediates retinoblastoma protein (pRb) phosphorylation and thereby regulates the cell cycle progression in B65 neuroblastoma cells (Pizarro et al., 2009). However, increased ROS levels exceeding the antioxidant cell capacity induce cells to be exposed to oxidative stress, which in turn can impair cellular components including lipids, proteins, and DNA, and ultimately be the cause of cell death (Cheng et al., 2021).

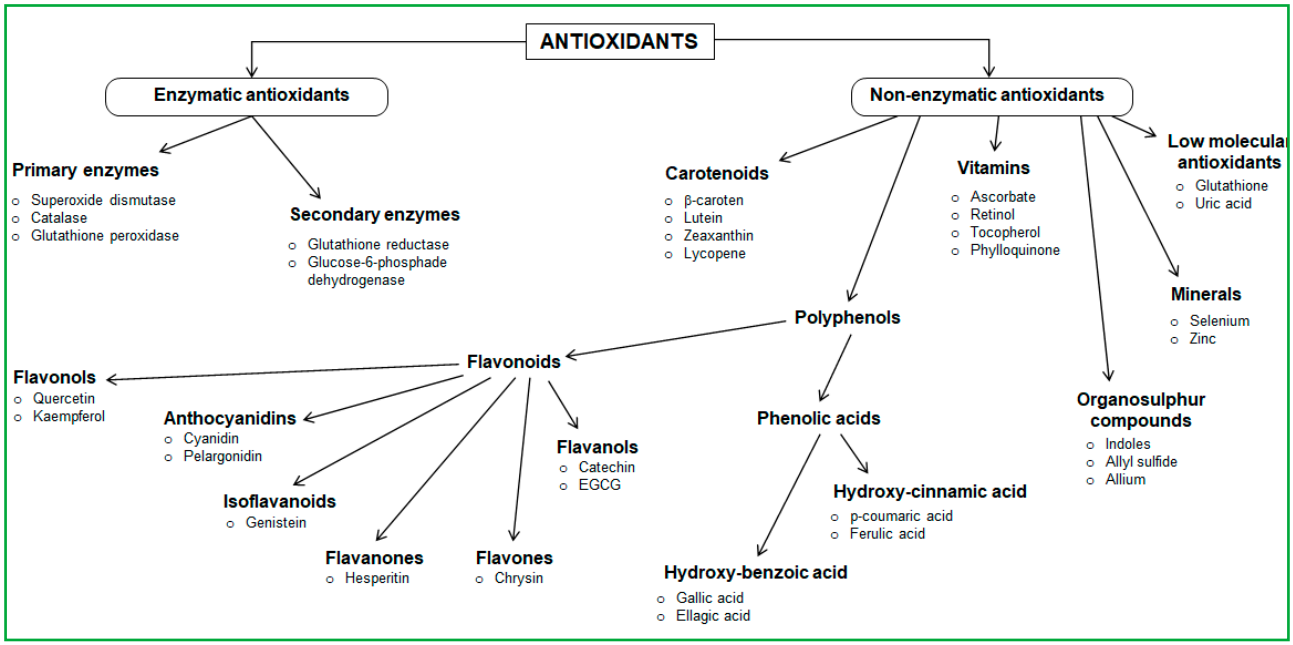

Figure 1 Schematic illustration of enzymatic and non-enzymatic antioxidant defense components

2 Conclusions

Environmental contaminants as for example heavy metals are able to interact with essential cellular components resulting in destabilization of the control machineries required for the normal cell behavior. These elements have the ability to bind to functional sites of regulatory proteins, such as, enzymes that are normally occupied by biologically important molecules, resulting in conformational changes of biologically active molecules, proteins, and nucleic acids. (Diaconu et al., 2020). The mechanisms of cell uptake of toxic elements and the defense against the entry of heavy metals into the organism are the subject of intense study (Beyersmann and Hartwig, 2008; Zhao et al., 2014; Gostinčar and Gunde-Cimerman, 2018; Srivastava et al., 2014) however, still a lot remains to be clarified. There is also much unexplained in terms of the effects and consequences of increased heavy metal intake on intracellular homeostasis and homeostasis of biologically essential minerals in the organism. Hence, studies concerning the uptake, removal and/or detoxication of environmental pollutants from the organism require further investigation to reduce and understand their effects on living systems. Moreover, as there are areas worldwide with high levels of various environmental pollutants the need to monitor the levels of these injurious elements in food crops rises to eliminate intake of large quantities of these toxicants.

Future perspectives

Soil, water, and air contamination is the major concern of the modern times. The regeneration of polluted soils is difficult, long-lasting and expensive process. It can be performed with the use of different methods depending on the type of contamination, the soil properties, and the economic cost. For example, application of plants and nanoparticles capable of heavy metals accumulation is one possible option, or soil supplementation with biologically active compounds, including polyphenols, melatonin, or carotenoids, is another option that can be used for heavy metals sequestration. High consideration is nowadays given to the ways of how to minimize the threat posed by environmental contaminations, with respect to the human's adaptability to them. Further research is however needed to elucidate both direct and indirect possibilities of the environmental toxicity mitigation

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