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Editorial

Epigenetics of Heavy Metal Stress and Response in Plants

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In 1942, Waddington suggested the name 'epigenetics' to describe the studies concerning the relationship between phenotypes and genotypes and the mechanisms underlying this correlation. This is one of the earliest published uses of the term *epigenetics*, referring to studies of the *causal mechanisms* by which *genes of the genotype bring about phenotypic effects* [1]. However, in this first occurrence, *epigenetics* lacks the aspect of inheritance. Indeed, the study on epigenome and epigenetic effects was limited, and the issue of the heritability of the epigenetic state was still uninvestigated. Almost twenty years later, in 1958, Nanney interpreted the cellular epigenetic state under a slightly different light, i.e., the sum of "auxiliary mechanisms with different principles of operation [that] are involved in determining which specificities are to be expressed in any particular cell" [2]. The author introduced the link to heritability and the "localisation" of epigenetic devices into the nucleus.

Nowadays, epigenetics addresses the study of those changes that can be mitotically and meiotically heritable and do not alter the DNA sequence per se. These changes are able to modify gene expression and functions, mainly by changing DNA condensation and accessibility to DNA-binding proteins and components of the transcriptional machinery. Experiments have also shown that histone protein modifications and covalent methylation of cytosine DNA bases are the main actors defining the epigenetic state [3]. Epigenetic mechanisms are therefore involved in fine-tuning plant physiology to the changing environment, connecting plant responses to abiotic and biotic stimuli, and are potentially heritable, contributing to plant adaptation to complex ecosystems [4].

Being sessile and rooted into the soil, plants cannot avoid exposure to adverse edaphic conditions. The presence of inorganic contaminants and the imbalance of micro- and macronutrients greatly impact plant life and reproduction. Collectively called potentially toxic elements (PTE), metals and metalloids are naturally present in soils, do not degrade in the environments, and their concentrations rise usually due to natural causes (e.g., volcanic activity and erosion of metal-rich rocks) and anthropogenic activities (industry and mining, vehicle circulation, agriculture, to mention a few). As an increasing amount of literature deals with the effect of PTE toxicity on the epigenome of plants, two main effects are emerging: on the one hand, PTEs induce modifications of DNA methylation (at promoters and/or gene bodies) and this might be involved in shaping the cell transcriptome to deal with excess or toxic PTEs; on the other hand, upon PTE treatment plant genomes show overall hypermethylation, probably using methylation-mediated chromatin condensation as a DNA-protecting mechanism against PTE genotoxic effects [4,5]. Small interfering RNA have been also proven to mediate de-novo DNA methylation, a phenomenon known as RNA-directed DNA methylation (RdDM). However, its actual involvement in the response to PTEs has been largely underinvestigated, and the effects of this particular mechanism are still underestimated. We would like to point out that while it has been shown that PTEs have effects on global chromatin organisation, it is also evident that DNA epigenetic modifications are extremely variable, and the cause/effect relationship between PTEs and epigenetic modifications is complex to unravel.

Related literature strongly suggests that variables such as the plant species under investigation (sensitive or tolerant to excess PTEs), the metal considered (nutrient or toxic), and the experimental conditions applied (*in vitro* or *in vivo*; seedlings or adult individuals) dramatically influence the results, hindering "common" conclusions on the epigenetic response to PTEs. Particularly, differences are very evident when directly comparing non-tolerant versus tolerant species. Indeed, recent works compare (or contrast) sensitive species with hyperaccumulators, i.e., species able to accommodate extremely high metal concentrations in their above-ground tissues (for a review, refer to [6,7]). Unfortunately, the alignment of obtained results is difficult because of the lack of commonly recognised investigation protocols and the impossibility of applying common treatments due to exceedingly different edaphic requirements of the plant species investigated. This is highlighted by the fact that often opposite plant responses (e.g., increased or decreased widespread DNA methylation) to the same metal

ion are reported in the literature. For instance, cadmium (Cd) induces DNA hypermethylation in Arabidopsis while hypomethylation in rice, in both cases by modulating the expression of proteins involved in DNA modification [8,9]. Intriguingly, reactive oxygen species seem to play a role in mediating PTE signalling, bridging PTE sensing and epigenetic modifications on the overall genome or at specific sites [10,11], by, for instance, influencing the activity of chromatin-remodeller enzymes [4].

A common as much as questionable trend is the adoption of unnatural conditions to evaluate the effects of PTEs (e.g., *in vitro* systems), short experimental periods (usually from hours to few days) and high doses of PTEs (which would be lethal on a long-term basis). Indeed, this undoubtedly simplifies the approach on one side, but on the other hand, tested plants experience conditions that do not adequately reflect the natural environment. This approach enhances the risk of deriving deviating results due to non-specific events that superimpose on the actual cause-effect correlation between PTEs and epigenetic changes.

As stated above, epigenetic marks influencing gene expression and stress responses might be inherited from parental generations to progenies. Transgenerational epigenetic inheritance is also a highly complex process, and its investigation is challenging [12]. Experimentally, extensive resources are required. It is necessary to examine and define the epigenetic pattern induced by PTEs in the parental individuals, differentiating male and female counterparts (that might differently contribute, as observed, for example, in hyperosmotic stress [13]), and monitor the presence and stability in the offspring, even over several consecutive generations, discriminating at the same time random variations [14]. In this context, using model plants with a short life cycle could help, offering the opportunity to analyse multiple successive generations in a reasonable timeframe. Also, the broad genomic and transcriptomic knowledge may be an interesting feature. Indications emerged that the offspring of plants exposed to heavy metal stress are more tolerant to the same metal when compared to the progeny of untreated parents, and this was consistent with specific hypomethylated DNA sites [15,16]. Another interesting subject is the methylation of organellar DNA and its involvement in PTE response in plants. Recent literature on land plants seems to converge, attributing no effect to plastome methylation on plastid-encoded gene expression, even if this is still an unexplored field [17].

The study of the epigenetic-induced tolerance against PTEs sees future applications when considering the possibility to manipulate the epigenome to modulate crop tolerance to PTEs. Such an approach is still in its infancy and research must move from cultivar characterisation to investigation of strategies of epigenetic control of PTE tolerance in plants.

Author Contributions

GG, EF and GDC have conducted the research and contributed to write the manuscript. All authors read and approved the final manuscript. All authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate

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Conflict of Interest

Given Giovanni DalCorso's role as the Editorial Board member in FBS, he was not involved in the peer review of this article and has no access to information regarding its peer review. Full responsibility for the editorial process for this article was delegated to Gustavo Caetano-Anollés. The authors declare no conflict of interest.

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