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## Epigenetics in an ecotoxicological context

Q1 Michiel B. Vandegehuchte\*, Colin R. Janssen

Laboratory of Environmental Toxicology and Aquatic Ecology, Ghent University (UGent), Jozef Plateaustraat 22, 9000 Gent, Belgium

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## ABSTRACT

Epigenetics can play a role in interactions between chemicals and exposed species, between species and abiotic ecosystem components or between species of the same or another population in a community. Technological progress and advanced insights into epigenetic processes have led to the description of epigenetic features (mainly DNA methylation) in many ecologically relevant species: algae, plants, several invertebrates and fish. Epigenetic changes in plants, insects and cladocerans have been reported to be induced by various environmental stress factors including nutrition or water deficiency, grazing, light or temperature alterations, social environment, and dissolved organic matter concentrations. As regards chemicals, studies in rats and mice exposed to specific pesticides, hydrocarbons, dioxins, and endocrine disrupting chemicals demonstrated the induction of epigenetic changes, suggesting the need for further research with these substances in an ecotoxicological context. In fish and plants, exposure to polycyclic aromatic hydrocarbons, metals, and soluble fractions of solid waste affected the epigenetic status. A novel concept in ecotoxicological epigenetics is the induction of transgenerational stress resistance upon chemical exposure, as demonstrated in rice exposed to metals. Evaluating epigenetics in ecotoxicological field studies is a second relatively new approach. A cryptic lineage of earthworms had developed arsenic tolerance in the field, concurrent with specific DNA methylation patterns. Flatfish caught in the framework of environmental monitoring had developed tumours, exhibiting specific DNA methylation patterns. Two main potential implications of epigenetics in an ecotoxicological context are (1) the possibility of transgenerationally inherited, chemical stress-induced epigenetic changes with associated phenotypes and (2) epigenetically induced adaptation to stress upon long-term chemical exposure. Key knowledge gaps are concerned with the causality of the relation between epigenetic and phenotypic changes, the persistence of transgenerational effects, the implications at population level and the costs of tolerance. Epigenetic changes following exposure to multiple stressors constitute another promising area of further research.

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## 1. Introduction

Epigenetics has been in the picture of ecotoxicology research in recent years, resulting in both review and focus papers on the implications of epigenetics for ecotoxicology and the impact of environmental stressors on the epigenome [1–3]. However, thanks to the fast pace of epigenetics research and technology, many new findings and novel insights in the field of ecotoxicological epigenetics emerged during the past few years. Some of those are not covered by the above-mentioned papers. Therefore, the goal of this review is to present the current state of the field on epigenetics in an ecotoxicological context.

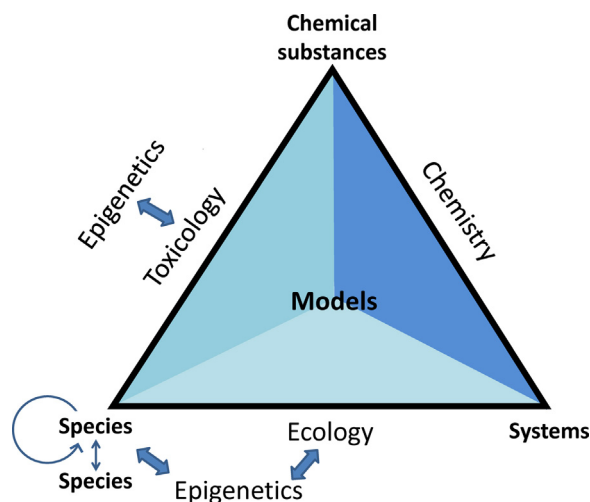
## 2. Ecotoxicology and epigenetics

Ecotoxicology has been defined as ‘the science of contaminants in the biosphere and their effects on constituents of the biosphere, including humans’ [4]. In this review, we will focus on the effects in non-human species. Epigenetics in this context is still very much an emerging research field. Indeed, the bulk of epigenetics toxicology

*Abbreviations:* A, adenine; AFLP, amplified fragment length polymorphism; AHR, aryl-hydrocarbon receptor; As, arsenic; B[a]P, benzo[a]pyrene; BPA, Bisphenol A; C, cytosine; Cd, cadmium; CpA, cytosine-phosphate-adenine; CpG, cytosine-phosphate-guanine; Cr, chromium; Cu, copper; *cyp19a*, cytochrome P450, family 19, subfamily A; DEET, *N,N*-Diethyl-*meta*-toluamide; DEHP, di-2-ethylhexyl phthalate; DNMT1, DNA methyltransferase 1; *Dnmt2*, DNA methyltransferase 2, also known as also known as tRNA aspartic acid methyltransferase 1; G, guanine; GNMT, glycine N-methyltransferase; H, adenine or thymine or guanine; Hg, mercury; LC-MS, liquid chromatography coupled to mass spectrometry; MBD, methyl-CpG-binding domain; MeDIP, Methylated DNA immunoprecipitation; miRNA, microRNA; MS-AFLP, methylation specific amplified fragment length polymorphism; MSAP, methylation-sensitive amplification polymorphism; PAH, polycyclic aromatic hydrocarbon; PC, Principal Coordinate; PCB, Polychlorinated biphenyl; REACH, Registration, Evaluation and Authorisation of Chemicals; SAH, S-adenosylhomocysteine; SAM, S-adenosylmethionine; T, thymine; TCDD, 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin; tRNA, transfer RNA; UPLC-MS/MS, ultra performance liquid chromatography coupled to tandem mass spectrometry; USA, United States of America.

Q2 \* Corresponding author. Tel.: +32 9 264 37 07; fax: +32 9 264 37 66.

E-mail addresses: [Michiel.Vandegehuchte@UGent.be](mailto:Michiel.Vandegehuchte@UGent.be),  
[michielvandegehuchte@gmail.com](mailto:michielvandegehuchte@gmail.com) (M.B. Vandegehuchte).1383-5718/\$ – see front matter © 2013 Published by Elsevier B.V.  
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**Fig. 1.** Ecotoxicology is the study of interactions between chemical substances, species and systems (components of an ecosystem). Models are needed to describe and predict the overall results of these complex interactions. Epigenetics can interfere with interactions between chemical substances and species, as well as with interactions among and within species and between species and ecosystems. Therefore, epigenetic factors need to be taken into consideration when designing such models. Redrafted from [8].

research involves studies in humans, rodent models or human cell lines. For recent reviews about these types of studies, the reader is referred to e.g. Kim et al., Collotta et al. or Cheng et al. [5–7].

An ecotoxicologist studies the relationships between chemical substances, exposed species and ecosystems [8]. Thus, ecotoxicological research integrates aspects of chemistry, ecology and toxicology, thereby making use of models (Fig. 1).

Epigenetics can interact with all biological aspects of ecotoxicology. The most obvious is the toxicological interaction: chemical substances are known to affect the epigenetic status of exposed species. Many examples of such chemicals are summarised in previous reviews and include nanomaterials, benzene, endocrine disrupting chemicals such as diethylstilbestrol, dioxins or pesticides and metals [1,5]. Recent findings on the epigenetic aspects of interaction between species and chemical substances will be discussed in Section 3.3.

However, epigenetics may also play a role in the interaction between species and ecosystems or ecosystem components. It is well known that nutritional factors can cause epigenetic alterations [9]. For any animal species, food is an important ecosystem component. Taking into account the relationship between epigenetics and chemicals, one could hypothesise that alterations in environmental food quality or quantity entailing epigenetic modifications could result in a shift of sensitivity to chemicals in exposed populations. Other examples of epigenetic effects of environmental stress exposure will be discussed in Section 3.2.

Finally, there may be interplay between epigenetics and species–species interactions. When considering interactions within one species, the most striking example is epigenetic inheritance, i.e. the transgenerational transfer of epigenetic information through the germ line, even when the external trigger that caused an epigenetic alteration has disappeared. Examples are known in rice *Oryza sativa* exposed to metals, the fruit fly *Drosophila* exposed to the antibiotic G418 and rats exposed to e.g. dioxins, plastics components, pesticides or jet fuel hydrocarbons [10–13]. Epigenetic effects of interactions between different species have been shown or suggested in food web-associated relations between e.g. caterpillars and *Arabidopsis*, mammal herbivores and Spanish violets or fish kairomones and water fleas [3,14,15]. The most recent studies will be discussed in more detail in Section 3.2.

### 3. Field update on epigenetics in an ecotoxicological context

#### 3.1. Epigenetic findings in environmentally relevant species

Epigenetic machinery and characteristics are known to vary between species. A famous example is the model nematode *Caenorhabditis elegans*, which lacks DNA methylation or a conventional DNA methyltransferase, epigenetic marks and enzymes that have been found in most invertebrates studied until now. Nonetheless this species is an interesting study object in epigenetics, with recent reports of a transgenerational histone methylation footprint and piwi-interacting RNAs triggering multigenerational gene silencing, also depending on chromatin factors [16–18]. In this section, an overview of recently discovered epigenetic features in various ecotoxicologically interesting species will be given (summarised in Table 1).

For *Chlorella* sp. and *Chlamydomonas reinhardtii*, two unicellular green algae which are commonly used in ecotoxicological research, e.g. using growth inhibition as endpoint [19], DNA methylation has been analysed by deep bisulphite sequencing [20,21]. The *C. reinhardtii* genome exhibited one of the highest methylation levels known, with approximately 90% methylation of cytosine–phosphate–guanine–sites (CpG sites) in gene bodies. Interestingly, there was a large drop in methylation at promoters near the transcription start site, where CpG methylation levels were negatively correlated to transcription of the gene. *Chlorella* sp. exhibited lower CpG methylation levels of 4–5%, without the clear drop near the transcription start site, but with higher methylation in exons compared to introns. However, *C. reinhardtii* had higher levels of CHG and CHH methylation (H representing A, T or C) throughout the genome than *Chlorella* sp., in which CHG methylation was confined to repeats.

The spike moss *Selaginella moellendorffii* has very little methylation in gene bodies, whereas its transposable elements were methylated in the CpG (up to 70%) and to a lesser extent in the CHG and CHH context [20]. The DNA methylation pattern in two more advanced plants, rice *Oryza sativa* and poplar *Populus trichocarpa*, was remarkably different. Although their repeats were methylated in a similar way, these plants exhibited extensive CpG methylation in gene bodies, with clear drops at the transcription start site as well as the transcription termination site [20,21]. At both sites, the methylation level varied inversely with gene transcription, suggesting a silencing function of the methylation at these sites [20].

Invertebrates are a very diverse group, to which many ecotoxicological test species belong. Thanks to recent research, some invertebrate species now also have the potential to be used in epigenetic studies. *Oxytricha trifallax* is a ciliate with two types of nuclei: a germ line micronucleus and a macronucleus; the latter is derived from the micronucleus but contains much less genomic information. The formation of this macronucleus was shown to depend on maternal RNA templates and on cytosine methylation and hydroxymethylation [22,23]. DNA methylation and hydroxymethylation in this ciliate was only found during macronucleus formation in sequences that were subsequently eliminated.

Although the most studied nematode, *C. elegans*, is devoid of DNA methylation as mentioned earlier in this section, this is not true for all members of the Nematoda phylum. *Trichinella spiralis*, a parasitic nematode, possesses several genes with homology to known DNA methyltransferases, e.g. in *Homo sapiens*, *Mus musculus*, *Gallus gallus*, *Danio rerio* [24]. DNA analysis by deep bisulphite sequencing, ultra performance liquid chromatography coupled to tandem mass spectrometry (UPLC-MS/MS) and Methylated DNA Immunoprecipitation (MeDIP) coupled with PCR revealed cytosine methylation in this species. Adult and muscle-larvae stages

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