The methylome of *Biomphalaria glabrata* and other mollusks: enduring modification of epigenetic landscape and phenotypic traits by a new DNA methylation inhibitor

Nelia Luviano[1], Marie Lopez[2], Fleur Gawehns[3], Cristian Chaparro[1], Paola Arimondo[4], Slavica Ivanovic[5], Patrice David[6], Koen Verhoeven[5], Céline Cosseau[1], and Christoph Grunau[1]

[1]Universite de Perpignan Via Domitia
[2]Institut des Biomolecules Max Mousseron
[3]Netherlands Institute of Ecology
[4]Institut Pasteur
[5]Netherlands Institute of Ecology Department of Terrestrial Ecology
[6]Centre d'Ecologie Fonctionnelle et Evolutive

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Abstract

5-methylcytosine (5mC) is an important epigenetic mark in eukaryotes. Little information about its role exists for invertebrates. How 5mC contributes to phenotypic variation in invertebrates can be investigated by experimental alteration of methylation patterns. Here, we apply new non-nucleoside DNA methyltransferase inhibitors (DNMTi) to introduce global changes into the methylome of mollusk species. Flavanone inhibitor Flv1 was highly efficient in reducing 5mC in the freshwater snails *Biomphalaria glabrata* and *Physa acuta*, and to a lesser degree, probably due to lower stability in sea water, in the oyster *Crassostrea gigas*. Flv1 has no toxic effects and significantly decreased the 5mC level in the treated *B. glabrata* generation and in its untreated offspring. Drug treatment triggers significant variation in the morphometric traits in both generations. An epigenotyping by sequencing method corroborates hypomethylation effect of Flv1 in both *B. glabrata* generations and identifies one Differential Methylated Region (DMR) out of 8, found both in Flv1-exposed snails and its progeny, demonstrating a multigenerational effect of an induced epimutation. By targeted bisulfite sequencing, we confirmed hypomethylation in a locus associated with reduced gene expression.

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