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DNA Methylation 6mA and Histone Methylation Involved in Multi-/Trans-Generational Reproductive Effects in Caenorhabditis elegans Induced by Atrazine

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Abstract : Atrazine (ATR), a widely used triazine herbicide, is an environmental endocrine disruptor that can cause health problems. However, whether there are multi/trans-generational reproductive impacts of ATR have not been studied to our best knowledge. Therefore, in this study, Caenorhabditis elegans was used as a preferable model organism to identify the multi/trans-generational reproductive toxicity of ATR. L1 larvae were exposed to different concentrations (0.0004–40 mg/L) of ATR for 48 h. Successive generations (F1 to F5) were fed without ATR and consecutive exposure. The results showed that ATR exposure during P0 decreased fecundity, including a reduction in fertilized eggs, oocytes, and ovulation rate, delayed gonadal development, and decreased the relative area of the gonad arm and germ cell number. Furthermore, continuous ATR exposure (P0–F5) causes a significant increase in reproductive toxicity in subsequent generations, although no significant toxicity occurred in the P0 generation after exposure to environmental-related concentrations, suggesting that ATR exposure might have cumulative effects. Likewise, parental exposure to ATR caused transgenerational toxicity impairments. Interestingly, reproductive toxicity not development toxicity was transmitted to several generations (F1–F4), and the F2 generation showed the most notable changes. QRT-PCR results showed that genes related to DNA methylation 6mA (damt-1, nmad-1) and histone H3 methylation (mes-4, met-2, set-25, set-2, and utx-1) can also be passed on to offspring. The function of H3K4 and H3K9 methylation were explored by using loss-of-function mutants for set-2, set-25, and met-2. Transmissible reproductive toxicity was absent in met-2(n4256), set-2(ok952), and set-25(n5021) mutants, which suggests that the histone methyltransferases H3K4 and H3K9 activity are indispensable for the transgenerational effect of ATR. Finally, the downstream genes of DNA methylation and histone H3 methylation were determined. ATR upregulated the expression of ZC317.7, hsp-6, and hsp-60. Mitochondrial stress in parental generation dependent transcription 6mA modifiers may establish these epigenetic marks in progeny.

Keywords : ATR, Caenorhabditis elegans, multi-/trans-generation, reproductive toxicity
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