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ToxPoint: Dissecting Functional RNA Modifications in Responses to Environmental Exposure—Mechanistic Toxicology Research Enters a New Era

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RNA molecules have long been considered as mere intermediate players that bridge 1-way genetic information passing flow from DNA to protein in organisms. The discovery and characterization of regulatory noncoding RNAs (such as microRNAs and long noncoding RNAs) challenged the central dogma of molecular biology and revolutionized the traditional view of RNA function. The recent breakthrough in demonstrating the dynamic and reversible feature of RNA modifications and their vital roles in a variety of biological processes represents another wave in the revolution of understanding RNA biology and function (Shi *et al.*, 2019; Zhao *et al.*, 2017). The recognition of important biological functions of RNA modifications also led to the birth of terms of "RNA epigenetics", "Epitranscriptome", and "Epitranscriptomics" (Roundtree and He, 2016; Saletore *et al.*, 2012).

RNA modifications refer to naturally occurring chemical modifications in nucleotides and ribose of RNA molecules. Since the first RNA chemical modifications were reported in the 1950s, more than 150 types of chemical modifications in RNAs have been identified to date (Boccaletto *et al.*, 2018). Even though the variety of RNA modifications and their occurrence among many different types of RNAs are no less than DNA and protein modifications, our understanding of the mechanisms and biological functions of RNA modifications has lagged far behind of our knowledge of DNA and protein modifications. This is mainly due to the low abundance of RNA modifications and the lack of sensitive techniques to detect and quantitate them. Moreover, even less is known about how environmental exposure affects RNA modifications; and whether and how RNA modifications are linked to adverse health effects of environmental exposure. Decoding functional RNA modifications in response to environmental exposures represents a challenge in mechanistic toxicology research and addresses a significant knowledge gap in understanding the health impact of environmental exposure.

Studies on functional RNA modifications initially focused on transfer ribonucleic acid (RNA) and ribosomal RNA due to the relatively high abundance of modifications in these 2 types of RNAs. The discovery of the first chemical modifications in messenger RNA (mRNA) in the 1970s especially the modification of N^6-methyladenosine (m^6A) gradually shifted the focus of functional RNA modification studies to mRNA modifications. The m^6A is now known as the most prevalent internal modification in eukaryotic mRNAs with an estimated occurring frequency of m^6A around 1–4 per thousand adenosine nucleotides in mammalian mRNAs (Zhao *et al.*, 2017). Thanks to the development of the specific anti-m^6A antibody and advances in high-throughput sequencing technologies, it has been determined that m^6A modification is primarily distributed in 3′-untranslated regions and near stop codons (Meyer *et al.*, 2012). The proteins or the methyltransferases that deposit m6A methylation were discovered in 1990s (Zhao *et al.*, 2017). However, it is the recent discoveries of 2 m^6A demethylases fat mass and obesity-associated protein and alkB homolog 5 that revealed for the first time the reversible and dynamic nature of m^6A modification (Zhao *et al.*, 2017). Moreover, these discoveries also suggested that m^6A could have important biological functions, and thus greatly stimulated and redirected RNA modification studies on m^6A. There is now convincing evidence demonstrating that RNA modifications play critical roles in almost all aspects of RNA metabolism, posttranscriptional regulation of gene expression, many normal physiological processes, as well as pathogenesis (Uddin *et al.*, forthcoming; Zhao *et al.*, 2017).

The advances in RNA modification field over the past decade sets a splendid stage for toxicologists to step up to and study the significance of RNA modifications in responses to environmental exposure. In general, the final consequences of RNA modifications are determined by the coordinated efforts of RNA modification machinery consisting of “writes” (the enzymes that deposit the modifications), “erasers” (the enzymes that remove the modifications), and “readers” (the proteins that mediate the functions of modifications; Shi *et al.*, 2019). Given the demonstrated importance of RNA modifications in regulating gene expression and cellular functions and environmental pollutants as known important etiological factors for many diseases, it is anticipated that environmental exposure could have significant impacts on expression levels and functions of components in RNA modification machinery leading to dysregulation and abnormal function of RNA modifications. Indeed, a recent pioneering study showed that m^6A modification regulates the ultraviolet-induced DNA damage response, facilitating repair and cell survival (Xiang *et al.*, 2017). This finding strongly suggests that RNA modifications may serve as key mediators of adverse health effects of environmental exposure. Further studies are, therefore, badly needed to define: (1) Whether and how does environmental exposure affect the expression levels and activities of “writers” and “erasers” to change abundance and distribution of RNA modifications? (2) Whether and how does environmental exposure affect the expression levels and modified-RNA binding capabilities of “readers” and thus change the outcomes of RNA modifications? (3) Could specific RNA modifications be linked with certain environmental exposures and serve as biomarkers for monitoring and early diagnosis of adverse health outcome of environmental exposure? (4) Are RNA modifications critical driving-forces or mere accompanying phenotypes of adverse health effects of environmental exposure?

In summary, scarce information is currently available regarding the involvement or connections of functional RNA modifications in the adverse health effects of environmental exposure. With the rapid progresses in RNA modification basic mechanistic studies and advances in microarray and high-throughput sequencing technologies, toxicologists are now enabled to take the challenge to elucidate functional RNA modifications in responses to environmental exposure. Elucidating the significance and mechanism of the involvement of functional RNA modifications in the adverse health effects of environmental exposure will likely reveal a new layer of complexity of action of pollutants/toxicants. A new era of mechanistic toxicology research has arrived.

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