Concept Clearance

Branch: Genes Environment and Health Branch

Council Period: 201805

Concept Title: Functional RNA Modifications Environment and Disease (FRAMED)

Introduction

Chemical modifications of proteins, DNA and RNA nucleoside moieties play critical roles in regulating gene expression. These modifications are central to the field of functional RNA and emerging evidence suggests these modifications have substantive roles in basic biological processes. These include: embryonic stem cell differentiation, excitotoxic cell death, development, intergenerational inheritance of acquired traits, regulation of RNA stability, temperature adaptation, meiotic progression, and regulation of RNA-RNA and RNA-protein binding interactions. A small number of covalent RNA modifications have been studied extensively, and recent evidence suggests that other newly discovered RNA modifications have interesting biological and disease functions in mammals. Moreover, recent studies have identified thousands of sites in human mRNAs for chemical modification, especially for N6-methyladenosine (m6A) suggesting that such modifications may play a role in the regulation of the mRNA processing and function including alternative splicing and gene expression. While RNA modification is emerging as an important area of research, the impacts of the environment on chemical modifications of RNA molecules (the epitranscriptome) in the development of adverse human health outcomes are relatively unexplored.

Technology advances in recent years have accelerated the detection of RNA modifications and The RNA Modification Database currently lists approximately 140 RNA modifications identified in prokaryotic and eukaryotic cells. This database also reveals transfer and ribosomal RNA are heavily modified, and many of these same modifications occur in messenger RNA and non-coding RNAs (including long non-coding (lncRNA) and microRNAs). The function of most of the modifications found in messenger and non-coding RNAs remains a mystery, despite their potential to influence RNA properties and functions, including RNA stability, trafficking, localization, activity (enzymatic, sensing, or regulatory), and interactions with other molecules.

The underlying importance of this emerging area for environmental health science research is rooted in RNA modifications serving as key regulatory components of multiple biological processes such as: differentiation and cell lineage determination/stem cell fate; mRNA stability, translation, splicing, transport; RNA structure; tRNA stress responses; post-transcriptional regulatory functions; and paternal inheritance. There are >60 known RNA post-transcriptional modifications in eukaryotes. The most prevalent RNA modification in mammals is m6A (N6-methyladenosine), followed by m5C (5-methylcytosine). Recent studies now report m1A (N1-methyladenosine) is emerging as a novel mark. In addition, multiple classes of RNAs (lncRNAs, microRNAs) are proving to be major regulators of cellular functional activities, and dynamic epitranscriptomic processes regulate the actions of these regulatory RNAs. RNA methylation is dynamically controlled; for example, the m6A methyltransferase complex co-transcriptionally adds (writes) methyl marks, while m6A can be removed passively through degradation of modified RNA or via active demethylation by m6A demethylases. These mechanisms can be rapidly deployed in response to stress challenges and importantly alter downstream protein profiles. RNA post-transcriptional modifications control the basic protein synthesis and thereby regulate a wide range of fundamental cellular processes. These RNA regulatory processes are likely targets for environmental challenges and associated with disease development and so there is an enormous potential for discovery of novel mechanisms as well as identifying new exposure responsive and/or therapeutic targets. RNA modifications also could be potentially valuable as biomarkers or signatures for toxicant exposure and/or disease progression. NIEHS can take advantage of the new tools developed with support from other NIH ICs as well leveraging the information garnered from workshops and webinars convened by other ICs, the trans-NIH E4 Working Group, and the RNA Institute at Albany to move the field.

Research Goals and Scope

The goal of this program is to support research that interrogates how environmental exposures impact this layer of cellular regulation. Soliciting applications in this emerging field via an RFA is intended to: engage leaders in the study of dynamic RNA modifications to use environmental exposures for discovery of novel RNA modification-mediated mechanisms and markers associated with perturbed functions/pathways and disease outcomes; encourage toxicologists to embrace this approach in mechanistic study of exposure-induced disease; as well as stimulate research on multi-generational inheritance mediated by RNA modifications. The longer-term impacts of crafting and supporting this solicitation potentially includes: the development of emerging and cutting-edge science focused on functional RNA modifications with an exposure and disease context; serving as a catalyst to stimulate unsolicited applications in subsequent Council rounds; support the development of software, databases, and analytical tools among other enabling technologies that address the contributions of exposures; and allow NIEHS to assume and sustain a leadership role in the support of EHS relevant research in the field of dynamic RNA modifications.

Mechanism and Justification
The purpose of this initiative is to build a foundation for committed research efforts in this emerging and understudied area of cellular regulation. The R01 mechanism will be used as it allows for adequate budget levels to support proteomics and next generation sequencing approaches as well as robust data analyses and technology refinements over a period of five years. The R01 mechanism will allow investigators to generate and test multiple hypotheses, leading to data generation and publications that will stimulate unsolicited R01 applications to progressively move the field forward.
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