Concept Clearance

Branch: Genes Environment and Health Branch

Council Period: 202310

Concept Title: EPitranscriptomics CrOsstalks and Toxicants (EPCOT)

Introduction

The cell is a dynamic environment that utilizes a flow of genetic information from DNA to RNA to protein as depicted by the central dogma. However, the central dogma is no longer considered as such a linear or straightforward process. The epitranscriptome directs post-transcriptional modifications of both coding and non-coding RNAs that serve as an additional layer of gene expression regulation. In 2018, NIEHS began a concerted effort to support research that interrogates the impact of environmental exposures on epitranscriptomic processes and adverse health outcomes. The portfolio currently supports research on how exposures impact disease development through altering the landscape of epigenomic marks, e.g., m6A, m1A, pseudouridine as well as if the epitranscriptomic marks can be used as biomarkers of exposure/disease. Exciting new information is emerging about regulatory roles of epitranscriptomics in cellular regulation and epitranscriptomics crosstalks is one particularly fertile area which recently has been identified independently by three NIEHS-supported laboratories. Epitranscriptomics crosstalks is an emerging concept and is at the nexus of novel directions in multi-omics research and moreover encompasses objectives both in precision environmental health and exposomics.

Crosstalks can be defined as interactions between epitranscriptomic marks or RWEs (readers, writers, erasers) and epigenomic marks, genomic structures, and other epitranscriptomics marks. The literature cites examples of m6A regulating histone modifications in 2018 (Crystal Zhao - Nature Neuroscience); METTL14 (epitranscriptomic writer) coordination with H3K36me3 regulation of m6A deposition (Jianjun Chen – Nature 2019); and m6A modifications on carRNAs and mRNAs regulates chromatin state and transcription (Chuan He – Science 2020). In an unpublished Nature Cell Biology manuscript currently under revision, Yinsheng Wang and colleagues demonstrate how METTL3 (epitranscriptomic writer) promotes H3K9 acetylation through recruitment of HAT1 to chromatin. Epitranscriptomic crosstalks are potent means of regulating gene expression but there is little data on how exposures can impact these crosstalks or generate new crosstalks. Recent work from Victor Corces (PNAS 2022) sets precedent in demonstrating an endocrine disrupting chemical (EDC) can create new crosstalks that appear to be mechanistically associated with transgenerational inheritance of metabolic disorders. In utero exposures to bisphenol A (BPA) can cause obesity in the F2-F6 generations due to alterations between cis-regulatory elements (CREs) and CTCF binding sites in the *Fto* gene that dysregulate genes associated with appetite-controlling neurons in the hypothalamus. BPA exposures induce demethylation of a CTCF binding site in an enhancer of the Fto gene which then forms a novel crosstalk with the promoters of Irx3/Irx5 genes. Epigenetic modification of an epitranscriptomic m6A eraser (the RNA demethylase *Fto*) can lead to phenotypes that persist for up to six generations.

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 investigators employing environmental exposures and multi-omics approaches for discovery of novel epitranscriptomics crosstalk-mediated mechanisms and markers associated with perturbed functions/pathways and disease outcomes; encourage toxicologists to embrace this approach in mechanistic studies of exposure-induced disease; as well as stimulate research on multi-generational inheritance mediated by crosstalks. Potential longer-term impacts of crafting and supporting this solicitation potentially include: the development of emerging and cutting-edge science focused on exposure-induced impacts on interactions between mediators of epitranscriptomic processes and mediators of epigenomics with an exposure and disease context; catalytic stimulation of unsolicited applications in subsequent Council rounds; the development of software, databases, and analytical tools among other enabling technologies that address the contributions of exposures; and substantive efforts to conduct integrative multi-omics analyses in support of NIEHS priorities in Precision Environmental Health to assume and sustain a leadership role in the support of EHS relevant research in the field of dynamic nucleic acid 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.