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The inheritance of nongenetic information—supplemental information beyond genomic sequences—has the potential to explain still-mysterious aspects of phenotypic variability, disease risks, and evolutionary trajectories. Using the nematode *Caenorhabditis elegans*, the Wahba lab seeks to understand the regulation and consequences of nongenetic inheritance.

The successful acquisition and transmission of biological information is a universal property of living systems. While hardwired genetic material underlies the vast majority of information transfer, a large body of evidence indicates that organisms also transmit a more malleable set of nongenetic information within and across generations. Faithful inheritance of this additional information—in the form of RNAs, proteins, epigenetic chromatin marks, and other biomolecules—is essential for development and short-term adaptation. But is it also important for more long-term, transgenerational adaptation? And do changes in nongenetic information persist sufficiently to contribute to organisms' phenotypic and evolutionary trajectories? The answers to these questions remain fragmentary, stemming in part from a limited understanding of how nongenetic inheritance is achieved and regulated.

The Wahba lab seeks to understand the role of nongenetic inheritance mechanisms in disease and evolutionary processes by dissecting the processes and parameters influencing it, the biological functions impacted, and their physiological relevance. Research in the lab builds on Wahba's previous findings about the role of small RNAs and their protein partners, Argonautes, in the transgenerational maintenance of the germline's immortal character. In most metazoans, Argonaute/sRNA systems are central to the transgenerational inheritance of gene regulation programs, but a full mechanistic understanding of initiation and inheritance determinants remains under investigation.

Using the free-living nematode *C. elegans* as a model system, Wahba's work has found that some heritable sRNAs propagate through self-perpetuating amplification cycles, a strategy that allows for the indefinite spread of silencing signals across generations but risks overamplifying them. To limit the potentially dire consequences of sRNA overamplification, Wahba identified the piRNA pathway (involving a second type of Argonaute/sRNA ribonucleoprotein) as an essential negative modulator of it. In the absence of piRNAs, worms progressively lose fertility over multiple generations until they become completely sterile, the result of genes targeted by endogenous Argonautes/sRNAs succumbing to perpetual and inappropriate transgenerational silencing.

The roles Argonautes/sRNAs play in maintaining germline mortality highlight the potent nature of nongenetic inheritance, and the existence of molecular machineries dedicated to its active limitation and regulation. By delineating the mechanistic principles underlying acquisition and inheritance of nongenetic information, the Wahba lab's ultimate hope is to address a fundamental question facing researchers across many biological fields: whether it is time to revamp the framework for inheritance to incorporate transmission of molecular factors that transcend DNA sequences.

EDUCATION

B.S. in biology and math, 2006
College of William and Mary

Ph.D. in biology, 2013
Johns Hopkins University

POSTDOC

Stanford University, 2014–2022

POSITIONS

Assistant Professor, 2023–
The Rockefeller University

AWARDS

Helen Hay Whitney Foundation Fellow, 2014

Irma T. Hirschl and Monique Weill-Caulier Trust Research Award, 2023

SELECTED PUBLICATIONS

Wahba, L., et al. An essential role for the piRNA pathway in regulating the ribosomal RNA pool in *C. elegans. Dev Cell* 56, 2295–2312 (2021).

Wahba, L., et al. S1-DRIP-seq identifies high expression and polyA tracts as major contributors to R-loop formation. *Genes Dev.* 30, 1327–1338 (2016).

Wahba, L., et al. The homologous recombination machinery mediates RNA-DNA hybrid formation and associated chromosome instability. *Elife* 2:e00505 (2013).

Wahba, L., et al. RNase H and multiple RNA biogenesis factors cooperate to prevent RNA:DNA hybrids from generating genome instability. *Mol Cell* 44, 978–988 (2011).