National Institute of Environmental Health Sciences

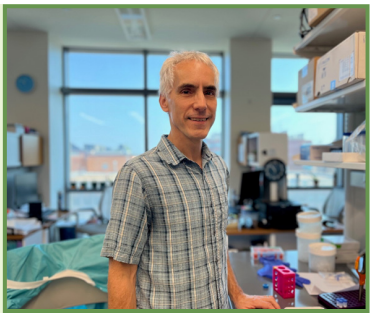
Addressing Environmental Exposures and Autism

NIEHS-funded research is untangling the complex interplay between genetics and environmental exposures to better understand their combined impact on autism spectrum disorders.

The National Institute of Environmental Health Sciences (NIEHS) supports research exploring how early-life environmental exposures may interact with genetic factors to influence brain development and contribute to autism spectrum disorder (ASD). ASD is a neurodevelopmental condition that affects communication, learning, behavior, and social interactions.

Mark Zylka, Ph.D., a professor at the University of North Carolina at Chapel Hill (UNC), works to identify environmental factors — particularly chemicals — that may contribute to ASD development. Early in his career, Zylka received funding from an NIH Director's Pioneer Award and then later an NIEHS Revolutionizing Innovative, Visionary Environmental Health Research (RIVER) award to explore how chemicals disrupt neurodevelopment. Building on this early support, he is designing methods to screen chemicals and the genes they target, which may also inform strategies to prevent those exposures.

Zylka and his team are studying the UBE3A gene's role in neurodevelopment and autism spectrum disorder (ASD). This gene codes for an enzyme that tags damaged or unnecessary proteins for breakdown, helping maintain cell function. UBE3A is essential for brain cell and nervous system function. People inherit two copies of UBE3A, one from each parent, but only the maternal copy is active in brain cells. If both copies are active or if mutations alter it's activity, it can affect brain development and neural circuits involved in cognition and behavior. Chemical exposures can also impact UBE3A, contributing to ASD characteristics.



"The Pioneer and RIVER awards gave me the flexibility to explore new reserach directions I hadn't preveously pursued, allowing me to follow the science and make discoveries that couldn't have been anticipated when the original awards were granted," Zylka said.

Impacts

Impacts of Untangling Gene-Environment Interactions

Pinpointing the problem:

- Discovered that substances that block enzymes necessary for cell division — such as cancer treatment drugs and certain environmental exposures — can turn on UBE3A and turn off other genes in people with ASD.[1,2]
- Reported a genetic mutation that increases the activity of UBE3A, which can influence the development of ASD.[3]
- Identified signaling pathways that contain several dysregulated (abnormal or impaired) genes linked to ASD.[5]

Understanding exposures:

- Developed a new, cost-effective, and rapid method to screen hundreds of chemicals for potential impacts on ASD.[4,6]
- Revealed that a new group of fungicides, called strobilurins, cause gene expression changes similar to those observed in individuals with ASD and other neurodegenerative conditions.[4]
- Found high levels of strobilurins in household dust and in urine samples collected from children and started investigating potential sources of exposure.[7,13]
- Observed that some strobilurins can cross the placenta and enter the brain of the developing embryo.[10]

Then and Now

- **Then:** Researchers believed that the paternal copy of the UBE3A gene remained turned off in offspring.
- **Now:** Zylka and team revealed that certain substances can turn on the paternal copy of UBE3A in neural tissue.[1] This finding led to new research applications, including potential therapeutics for Angelman syndrome, a neurodevelopmental disorder characterized by dysregulated expression of UBE3A.[14,15]
- **Then:** ASD researchers believed that only maternally inherited UBE3A mutations cause neurodevelopmental disorders.
- **Now:** Research in mice revealed that inheriting a mutated UBE3A gene, either paternally or maternally, can alter gene expression and result in developmental and behavioral characteristics linked to ASD.[11]
- **Then:** Most ASD research examined genetic changes in the brains of mice after death. However, since genes no longer function postmortem, the effects of a chemical exposure on gene function are largely not detectable, which results in researchers missing the links between genetic variation and gene expression.
- **Now:** Using special cells, researchers can identify groups of genetic changes and differences in expression linked to neurodevelopmental disorders, such as ASD.[12]

Timeline for Connecting Genetics and Environmental Exposures in Autism Risk

Fundamental Questions | Application and Synthesis | Implementation and Adjustment | Policy and Practice | Impact

2011

Fundamental Questions

First to discover that topoisomerase inhibitors, commonly used to treat cancer, turn on the paternal copy of the UBE3A gene and increase risk for ASD.[1]

2014

Fundamental Questions

Found that topoisomerase inhibitors reduce the expression of many long neuronal genes that are mutated in people with ASD.[2]

2015

Fundamental Questions

Revealed protein kinase A as the underlying mechanism by which mutation of UBE3A drives abnormal brain development.[3]

2016

Fundamental Questions

Developed a method to identify candidate chemical risks for ASD by screening and grouping substances that alter gene expression in the brain similar to what is seen in ASD.[4]

2016

Fundamental Questions

Found that a new class of fungicides, called strobilurins, can kill neurons and produce gene expression changes similar to those in people with ASD and other neurodegenerative conditions.[4]

2017

Fundamental Questions

Found that UBE3A can act via the Wnt signaling pathway, a pathway that is implicated in ASD risk.[5]

2019

Implementation and Adjustment

Adapted a method that uses 2D RNA sequencing to rapidly screen large chemical libraries and identify those that produce genetic changes linked to neurodevelopmental disorders.[5]

2019

Fundamental Questions

Detected high levels of strobilurins in household dust and suggested that mold-resistant wallboard was a potential source of exposure, but other sources of that fungicide in the homes were not ruled out.[7]

2022

Fundamental Questions

Found that the chemical diethanolamine — a common ingredient in shampoos and soaps — increased Wnt signaling in cells with a higher expression of the UBE3A gene.[8]

2022

Fundamental Questions

In mice, revealed that prenatal exposure to the pesticide pyrethroid can increase expression of the CHD8 gene, which has been linked to ASD risk.[9]

2022

Fundamental Questions

Detected the fungicide azoxystrobin in pregnant women and revealed it can be transferred across the placenta and enter the fetal brain. Observed high levels of cell damage in neurons of embryos.[10]

2023

Fundamental Questions

Discovered that inheriting a mutated UBE3A gene either maternally or paternally altered gene expression early in life and was linked to developmental and behavioral characteristics connected to ASD.[11]

2023

Fundamental Questions

Developed a new approach that activates the Wnt pathway in human neural progenitors — special cells that mimic cells in the early stages of neurodevelopment — to identify groups of genetic variants associated with ASD.[12]

2024

Fundamental Questions

Found the fungicides azoxystrobin and thiabendazole, commonly used in drywall, in urine samples from children.[13]

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NIEHS supported research for all the milestones highlighted above.

Linking Fungicides to Neurotoxicity

Zylka and his team were the first to reveal that strobilurin fungicides could be toxic to neurons. They exposed mouse neurons to about 300 chemicals and sequenced RNA to identify genes that were misregulated compared to untreated neurons. Using computer programs, they grouped chemicals by their effects on gene expression.[4]

Strobilurin fungicides altered many of the same genes affected in the brains of people with ASD. Specifically, these fungicides reduced the expression of genes crucial for neuron communication and increased the expression of genes associated with brain inflammation.

Strobilurin fungicides are commonly used in agriculture, exposing people via food consumption. However, Zylka and collaborators found that construction companies are also adding these fungicides to drywall to prevent mildew and mold and can be detected at high levels in household dust.[7]

In studies using human urine samples from pregnant mothers and their children, the team found high levels of azoxystrobin, a type of strobilurin fungicide, and thiabendazole, another type of fungicide also detected in drywall samples.[10, 13] Zylka suggests that co-exposure to these two chemicals could be used as a chemical fingerprint to indicate when drywall is the exposure source.

Fungicides are often used in construction materials to prevent mold, but whether or not they contribute to human exposures is understudied.

Research Challenges and Solutions

Challenge: Individuals are exposed to a variety of chemicals simultaneously and at diverse doses throughout their lives, complicating the link between exposure and effects.

Solution: Zylka and team developed an approach that can screen large chemical libraries rapidly to identify chemicals that cause genetic changes linked to ASD risk.

Challenge: Animal studies often focus on genetic models or controlled environments and don't fully capture the range of factors influencing ASD risk in humans.

Solution: Zylka partnered with experts from diverse research fields to assess environmental exposures, analyze biological samples from humans, and conduct studies using special human cells.

Multidisciplinary Collaborations

According to Zylka, making scientific progress is difficult if researchers are siloed. He attributes much of his success to the scientific collaborations he made along the way, including:

- A partnership with Heather Stapleton, Ph.D., of Duke University, who obtained samples and analyzed them for a variety of contaminants, including fungicides.
- Collaborative research with UNC's Stephanie Engel, Ph.D., and Kun Lu, Ph.D., to assess exposure to fungicides from urine samples from pregnant women and their children.

"By bringing in collaborators from different research fields, we were able to access a variety of samples, skills, and knowledge," said Zylka. "This allowed us to answer questions that we've long had but were not able to fully address with just animal models."

Training the Next Generation of Scientists

"I feel very proud that my former students are now incredibly successful in their own research, and some are even advancing the field of ASD research in their own labs," Zylka said.

For example, Brandon Pearson, Ph.D., a former student of Zylka, is now a professor at Columbia University, leading an NIEHS-funded project on the brain's response to pesticides and environmental exposures. He is also exploring how nonchemical factors, like parental stress, may amplify the risk of neurodevelopmental disorders.

Zylka and lab members.