Josh Baxt
February 24, 2022

New Insights into Preeclampsia Could Lead to Better Care

Using a newly created model, Miller School researchers identify a gene associated with the disease and test a possible treatment

University of Miami Miller School researchers, led by Shathiyah Kulandavelu, Ph.D., and Joshua Hare, M.D., have shown that mutations in a single gene, called GSNOR, can cause many of the complications associated with preeclampsia, a life-threatening condition affecting pregnant women. These findings could lead to new diagnostics and treatments, as well as sparking continuing research. The study, titled "S-Nitrosoglutathione Reductase Deficiency Causes Aberrant Palcental S-Nitrosylation and Preeclampsia," was published on February 22, in the *Journal of the American Heart Association* as part of the *Go Red for Women* issue.

A single gene mutation may cause preeclampsia.

"Medicine has made little to no progress in understanding and treating preeclampsia, and that is reflected in high mortality and complication rates among mothers and newborns," said Dr. Hare, principal investigator on the study and director of the Miller School's Interdisciplinary Stem Cell Institute. "Now, we have discovered an animal model for the syndrome, which is already providing new information into how we might treat it."

Preeclampsia causes high blood pressure in mothers, typically in their third trimester, and in some cases generates organ damage, driving higher mortality in mothers and babies, as well as premature births. In addition, while some women fully recover, others face elevated cardiovascular risks for years after their pregnancies.

Though preeclampsia is a complex disease, the study found that at least one potential cause is quite simple – a problem in the GSNOR gene.

The Role of Nitrosylation

Many enzymes undergo a process called nitrosylation, during which a nitric oxide (NO) molecule is attached to the enzyme, increasing its activity. GSNOR removes NO molecules from these enzymes, returning them to a less-active state.

GSNOR performs this function on many enzymes, giving it a major impact on cell biology. As a result, when defects in the gene impair GSNOR function, or eliminate the protein entirely, widespread increases in nitrosylation can drive high blood pressure and other preeclampsia-associated effects. Using a GSNOR-deficient mouse model has given the researchers tremendous opportunities to investigate the disease, identify biomarkers and test possible treatments.

“With their groundbreaking research, Drs. Kulandavelu and Hare and colleagues have provided a huge leap forward in understanding the pathophysiology of preeclampsia and provided us with a credible animal model to study this enigmatic disorder,” said Michael Paidas, M.D., who chairs the Department of Obstetrics, Gynecology and Reproductive Sciences. “Their research paves the way for more clinical

trials, which are urgently needed to prevent and treat this common and dangerous pregnancy-related disorder."

To help validate the GSNOR link, the team collected human placentas from preeclampsia patients at Jackson Memorial Hospital. Further analysis showed these women also experienced GSNOR loss, confirming the mechanism is important in human disease. The team is continuing to study these placentas to identify biomarkers that could inform treatment and delineate the mechanisms that may be driving increased mortality in Black and other communities.

Unanswered Questions Remain

"Hispanic and African American populations have increased incidence of preeclampsia," said Dr. Kulandavelu, assistant research professor in the Department of Pediatrics and first author on the paper. "This has been well-established, but we don't really know why. Our goal now is to analyze some of the placentas we've collected and find markers that could identify women who may be predisposed to preeclampsia and start early treatment."

In addition to identifying GSNOR's role in preeclampsia, the researchers also tested a possible treatment, showing that large doses of vitamin C alleviated the symptoms in their models. However, the authors caution that this approach may not be effective in human patients. In fact, vitamin C has failed to treat preeclampsia in clinical trials.

"When we look at preeclampsia, we're finding there are many different subtypes," Dr. Kulandavelu said. "So there could be women with a variety of causes, including increased inflammation, oxidative stress or a genetic disorder, as well

as problems with nitrosylation.”

While a defective GSNOR gene may be one of several potential mechanisms causing preeclampsia, identifying this issue and developing the first robust animal model for the disease is an important step toward better care.

“In one fell swoop, we took away two or three layers of the onion and provided major insights into preeclampsia’s causes, as well as a potential treatment,” Dr. Hare said. “That doesn't mean it’s the only thing going wrong, but it does provide critical information for a pathway that is playing a major role in at least some women.”

Content Type article