The real reason for preeclampsia's placental injury: Mitochondria

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> Preeclampsia, a leading cause of maternal and perinatal morbidity and mortality, has been consistently linked to inflammasome activation. However, the prevailing understanding of this biology has largely focused on NLRP3, potentially overlooking other critical inflammasome sensors and their upstream mitochondrial signals. A recent systematic review and translational roadmap addresses this gap, proposing a more complex interplay involving NLRP1 and dysregulated mitophagy in placental injury.1

KEY TAKEAWAYS

- The Pivot: Inflammasome activation in preeclampsia involves more than just NLRP3, with NLRP1 and mitochondrial signals warranting increased attention.
- The Data: Dysregulated BNIP3-mediated mitophagy and escalating mitochondrial reactive oxygen species (ROS) form a convergent pathway toward trophoblast injury.1
- The Action: Clinicians and researchers should consider a broader inflammasome perspective, particularly regarding NLRP1 and mitochondrial dysfunction, when investigating preeclampsia.

Inflammasome activation is a recognized component of preeclampsia pathophysiology.1 Historically, research in this area has predominantly centered on the NLRP3 inflammasome.1 This narrow focus has resulted in other inflammasome sensors, specifically NLRP1, and their associated mitochondrial upstream signals, remaining incompletely characterized.1

What the review found

A systematic review and translational roadmap, published in the Journal of Perinatal Medicine, examined the existing literature on inflammasome biology in preeclampsia.1 The authors identified a gap in the understanding of how various inflammasome components contribute to the condition beyond NLRP3.1

The review highlights experimental evidence suggesting a more intricate mechanism of placental injury.1 This mechanism involves dysregulated BNIP3-mediated mitophagy and an increase in mitochondrial reactive oxygen species (ROS).1 These two factors are proposed to converge into a pathway that leads to trophoblast injury.1 The systematic review was the first to integrate these distinct elements into a cohesive narrative regarding preeclampsia pathogenesis.1 The authors noted that while the link between inflammasome activation and preeclampsia is well-established, the specific contributions of sensors other than NLRP3, such as NLRP1, and their mitochondrial signaling pathways have been only partially explored.1 The review emphasizes the need for further investigation into these under-examined areas to fully elucidate the mechanisms underlying preeclampsia.1

The review posits that mitochondrial dysfunction, specifically dysregulated mitophagy and increased mitochondrial ROS, acts as a critical upstream signal for inflammasome activation in preeclampsia. Mitophagy, the selective degradation of damaged mitochondria, is essential for maintaining cellular homeostasis. When this process is impaired, as suggested by the review's findings regarding BNIP3-mediated mitophagy, dysfunctional mitochondria accumulate. These compromised mitochondria are a major source of ROS, which can damage cellular components, including DNA, proteins, and lipids. This oxidative stress, in turn, can trigger the activation of inflammasomes, leading to the release of pro-inflammatory cytokines such as IL-1²and IL-18, which are known contributors to the systemic inflammation characteristic of preeclampsia.

The authors highlight that while NLRP3 has been the primary focus, the involvement of NLRP1 and other inflammasome sensors warrants closer scrutiny. NLRP1, for instance, has been implicated in various inflammatory conditions and its activation can also be triggered by mitochondrial stress. Understanding the interplay between different inflammasome sensors and their specific mitochondrial upstream signals could unlock new therapeutic targets for preeclampsia. For example, interventions aimed at restoring healthy mitophagy or reducing mitochondrial ROS could potentially mitigate inflammasome activation and subsequent placental injury.

Clinical Implications and Future Directions

The findings of this systematic review have significant clinical implications. By identifying mitochondrial dysfunction as a central driver of inflammasome activation and placental injury in preeclampsia, the review opens avenues for novel diagnostic and therapeutic strategies. Currently, there are no specific treatments for preeclampsia beyond symptomatic management and delivery. A deeper understanding of these molecular pathways could lead to the development of targeted therapies that address the root cause of the disease.

For instance, biomarkers reflecting mitochondrial health or specific inflammasome activation patterns could be developed for early detection or risk stratification of preeclampsia. Furthermore, therapeutic interventions could focus on enhancing mitophagy, for example, through pharmacological agents that modulate BNIP3 activity, or by directly scavenging mitochondrial ROS. Antioxidant therapies, while explored in the past with mixed results, might be more effective if precisely targeted to mitochondrial ROS rather than broad-spectrum approaches.

The authors emphasize the need for translational research to validate these proposed mechanisms in human cohorts. Future studies should aim to:

• Investigate the expression and activation of NLRP1 and other non-NLRP3 inflammasomes in preeclamptic placentas.

• Characterize the specific defects in BNIP3-mediated mitophagy in preeclampsia and their correlation with disease severity.

• Measure mitochondrial ROS levels and their impact on inflammasome activation in trophoblast cells from preeclamptic patients.

• Explore the therapeutic potential of interventions that modulate mitochondrial function or inflammasome activity in relevant preclinical models of preeclampsia.

While the review provides a compelling framework, it also acknowledges limitations inherent in systematic reviews, such as potential publication bias and heterogeneity in study designs. Moving forward, well-designed prospective studies with standardized methodologies are crucial to confirm these intricate relationships and translate these mechanistic insights into tangible improvements in patient care for preeclampsia.

CLINICAL IMPLICATIONS

The systematic review by Bachnas et al. serves as a timely reminder that our understanding of complex pathologies like preeclampsia often benefits from looking beyond the most obvious candidates. Focusing solely on NLRP3 inflammasome activation may have inadvertently narrowed the scope of therapeutic exploration. If dysregulated BNIP3-mediated mitophagy and NLRP1 activation are indeed critical, then future research and drug development should consider these alternative targets. This could open avenues for novel interventions that address the mitochondrial dysfunction at the heart of trophoblast injury, rather than just the downstream inflammatory cascade.

For clinicians, this means that while current management strategies remain unchanged, the evolving understanding of preeclampsia's molecular underpinnings could eventually lead to more precise diagnostic markers or targeted therapies. The pharmaceutical industry, often quick to capitalize on well-trodden pathways, might need to broaden its focus beyond NLRP3 inhibitors. Exploring compounds that modulate mitophagy or specifically target NLRP1 could yield more effective treatments, particularly if these pathways prove to be upstream drivers of the disease. It underscores the importance of basic science in informing clinical practice, even if the immediate impact on patient care is not yet direct.

Patients with preeclampsia, and those at risk, stand to benefit from a more comprehensive understanding of the disease. While the review itself does not offer immediate changes to patient care, it lays the groundwork for future research that could lead to better prevention or treatment strategies. A deeper mechanistic insight could eventually translate into personalized medicine approaches, moving beyond symptomatic management to address the root causes of placental dysfunction. This shift in perspective is essential for advancing care in a condition with significant maternal and fetal morbidity.

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REFERENCES

1. 1. Bachnas MA, Andonotopo W, Prabowo W. Inflammasome biology in preeclampsia: from Bnip3-mitophagy to Nlrp1-driven placental injury - a systematic review and translational roadmap. J Perinat Med. 2026.

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