News Release

LIMCH1-enriched extracellular vesicles promote vascular permeability in early-onset preeclampsia

Key Points

- By integrating serum extracellular vesicle (EV) proteomic analysis and placental tissue transcriptomic analysis, we identified LIMCH1 as an EV-associated protein related to the pathophysiology of early-onset preeclampsia (Eo-PE).
- LIMCH1-carrying EVs increase vascular endothelial permeability, thereby revealing a previously unrecognized mechanism underlying endothelial dysfunction in Eo-PE.
- These findings suggest the potential for developing biomarkers to predict Eo-PE severity and for establishing novel therapeutic strategies.

Summary

A research group led by Seiko Matsuo, MD, PhD (Assistant Professor), Akira Yokoi, MD, PhD (Lecturer; also affiliated with the Institute for Advanced Research), Hiroaki Kajiyama, MD, PhD (Professor), and Tomomi Kotani, MD, PhD (Hospital Professor; currently Professor at Hamamatsu University School of Medicine) from the Department of Obstetrics and Gynecology, Nagoya University Hospital, has elucidated a novel mechanism of vascular endothelial injury in early-onset preeclampsia (Eo-PE). The study demonstrates that extracellular vesicles (EVs) carrying LIMCH1 increase vascular permeability, thereby contributing to endothelial dysfunction in Eo-PE.

Eo-PE is a severe pregnancy complication with potentially life-threatening consequences for both the mother and the fetus. In affected women, the condition is characterized not only by hypertension but also by systemic vascular endothelial injury, which can progress to life-threatening complications such as pulmonary edema. Despite its clinical importance, the detailed mechanisms underlying Eo-PE remain incompletely understood, and delivery is currently the only definitive treatment. EVs, which are present in all human body fluids, have recently attracted attention as key mediators of intercellular communication. Based on the hypothesis that placental EVs contribute to maternal endothelial injury, the research team conducted this study.

By integrating serum EV proteomic analysis with placental RNA sequencing, the researchers newly identified LIMCH1 as an EV-associated protein related to

Eo-PE. LIMCH1 was highly expressed in Eo-PE placentas, particularly in syncytiotrophoblasts, which actively release EVs into the maternal circulation. The study further demonstrated that placental EVs carrying LIMCH1 were increased in the serum of women with Eo-PE. Functional analyses revealed that LIMCH1-carrying EVs reduced the expression of the tight junction protein ZO-1 in vascular endothelial cells, resulting in increased vascular permeability, as demonstrated through both in vitro and in vivo experiments.

These findings provide new mechanistic insights into the development of severe complications observed in Eo-PE, such as systemic edema and pulmonary edema. Moreover, the results suggest the potential for developing novel biomarkers to predict disease severity and for establishing innovative therapeutic strategies targeting EVs. This study is expected to contribute to future advances in perinatal medicine.

The results of this research were published online in *Science Advances* on January 28, 2026(January 29, 2026 JST).

Research Background

Preeclampsia (PE) is a pregnancy-specific disorder characterized by the new onset of hypertension during pregnancy and is one of the most serious pregnancy complications, exerting profound effects on both maternal and fetal health. In particular, Eo-PE, which develops before 34 weeks of gestation, is more likely to progress to severe disease and is associated with a high risk of preterm birth, fetal growth restriction, and maternal complications, including multiorgan dysfunction and death. Globally, PE remains a leading cause of maternal mortality, and overcoming this condition is a major challenge in perinatal medicine.

In Eo-PE, systemic vascular endothelial injury, in addition to hypertension and proteinuria, is considered a central feature of the disease pathophysiology. As endothelial dysfunction progresses, vascular permeability increases, leading to severe complications such as generalized edema, pulmonary edema, and cerebral edema. However, the molecular mechanisms underlying this endothelial injury remain incompletely understood. Currently, there is no definitive treatment for Eo-PE, and when maternal or fetal conditions deteriorate, delivery must be undertaken regardless of gestational age, posing a significant clinical challenge.

In recent years, EVs have attracted increasing attention as key mediators of intercellular communication. EVs are membrane-bound nano-sized particles present in all human body fluids, including blood, urine, and amniotic fluid. They carry proteins and nucleic acids that reflect the physiological and pathological states of their cells of origin and have been implicated as disease biomarkers

and pathogenic mediators in a wide range of conditions, such as cancer and inflammatory diseases. In PE, it has been hypothesized that placental EVs are released into the maternal circulation and exert detrimental effects on vascular endothelial cells; however, which specific EV-associated molecules drive vascular injury and through what mechanisms has remained unclear.

In this study, based on this hypothesis, we integrated serum EV proteomic analysis with placental RNA sequencing analysis to newly identify LIMCH1 as an EV-associated protein related to Eo-PE. Furthermore, we demonstrated that EVs carrying LIMCH1 increase vascular permeability, providing new insight into the molecular mechanisms underlying endothelial dysfunction in Eo-PE (Fig. 1).

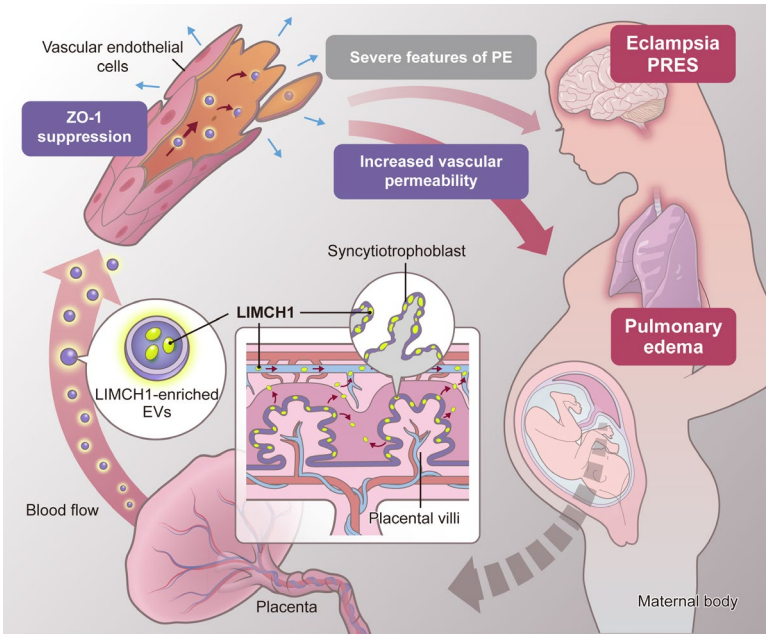

Fig. 1. Mechanism of increased vascular permeability mediated by LIMCH1-enriched EVs

Research Results

In this study, to elucidate the molecular basis of vascular endothelial injury in Eo-PE, we focused on EVs present in maternal serum. First, EVs were isolated from the serum of women with Eo-PE and those with normal pregnancies, followed by comprehensive EV proteomic analysis. The proteomic data were then integrated with placental RNA sequencing results to identify EV-associated proteins of placental origin that are specifically increased in Eo-PE.

Through this integrative analysis, LIMCH1 (LIM and calponin homology domain-containing protein 1) was newly identified as an EV-associated protein related to Eo-PE. LIMCH1 was highly expressed in Eo-PE placentas, with particularly strong expression in syncytiotrophoblasts, which actively release EVs into the maternal circulation (Fig. 2). Furthermore, analysis of serum EVs demonstrated that placental EVs carrying LIMCH1 were increased in the

circulation of women with Eo-PE.

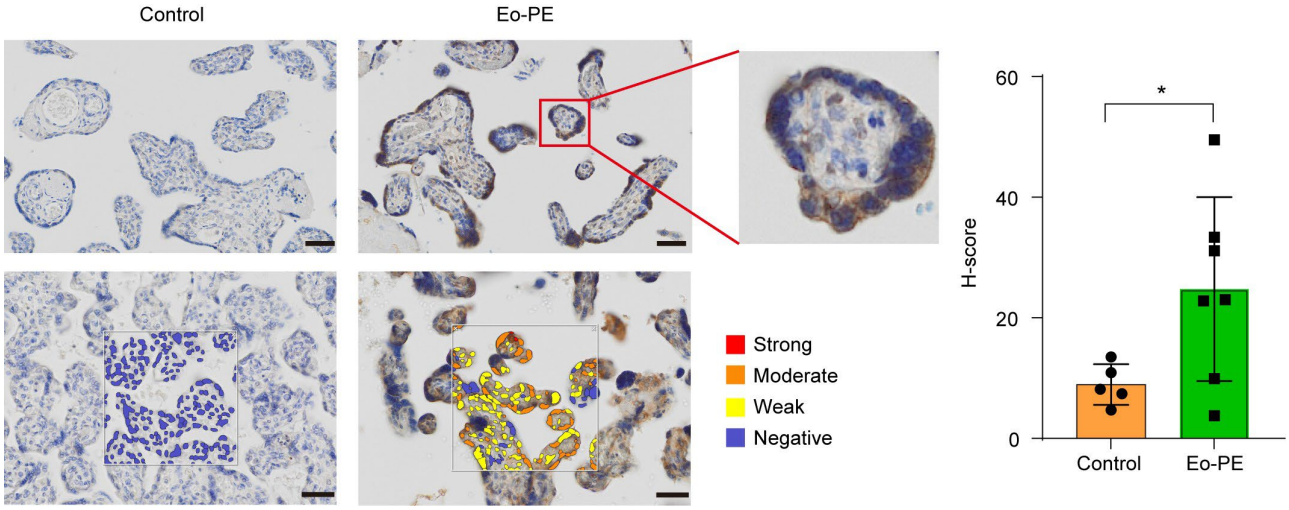

Fig. 2. High expression of LIMCH1 in Eo-PE placentas

Further functional analyses of LIMCH1-carrying EVs revealed that these EVs are taken up by vascular endothelial cells and reduce the expression of ZO-1, a tight junction protein essential for maintaining intercellular junction integrity. As a consequence, endothelial barrier function was disrupted, leading to increased vascular permeability. These effects were consistently confirmed through both in vitro experiments and in vivo studies using a mouse model (Fig. 3).

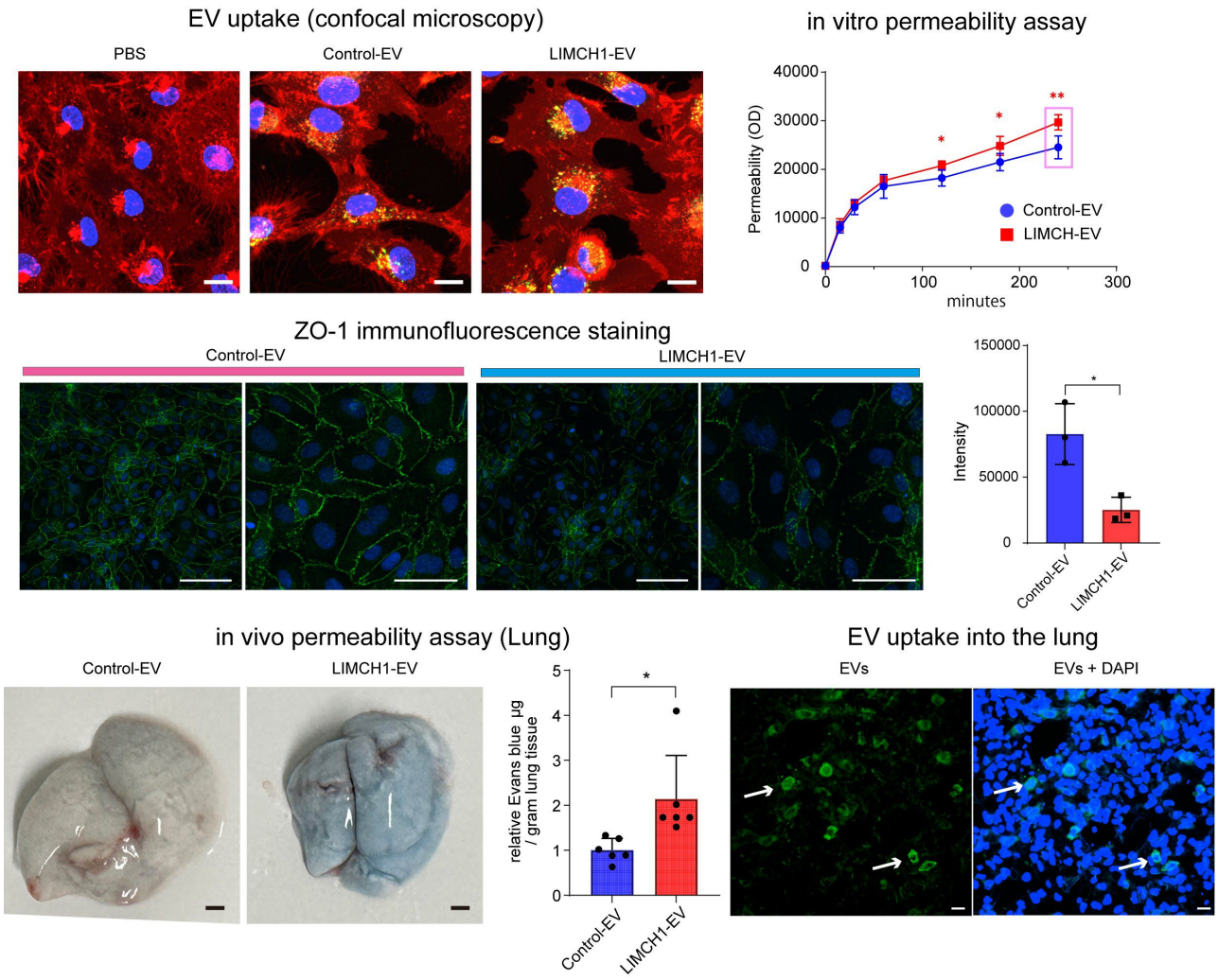

Fig. 3. Functional analysis of LIMCH1-carrying EVs

Collectively, these findings suggest that severe complications observed in Eo-PE, such as systemic edema and pulmonary edema, may arise through disruption of the vascular endothelial barrier mediated by LIMCH1-carrying EVs. This study thus presents a previously unrecognized molecular mechanism underlying vascular injury in Eo-PE.

Future Perspective

The findings of this study open new possibilities for predicting disease severity and developing therapeutic strategies for Eo-PE. First, EVs carrying LIMCH1 have the potential to serve as novel biomarkers reflecting the risk of disease progression in Eo-PE. If LIMCH1 levels in EVs can be assessed through blood tests during pregnancy, it may become possible to detect the extent of vascular injury earlier and more accurately than with conventional assessments such as blood pressure measurement and urine testing.

In addition, the development of therapeutic strategies targeting EVs

themselves or LIMCH1 represents a promising future direction. Approaches aimed at suppressing the production or pathological effects of disease-associated EVs, as well as the development of novel therapies to protect the vascular endothelial barrier, may offer new treatment options. Such strategies could provide alternatives to delivery, which is currently the only definitive intervention for Eo-PE.

Future studies will require validation in larger clinical cohorts and further analyses of the associations between LIMCH1-carrying EVs and clinical manifestations to establish robust evidence for clinical application. The insights gained from this study are expected to advance not only the understanding of Eo-PE but also broader mechanisms of vascular dysfunction during pregnancy, ultimately contributing to improved quality of perinatal care.

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