The architecture of the NiFe-hydrogenase was expected to be similar to that of standard NiFe-hydrogenases, but the structures of the heterodisulfide reductase and the overall architecture of the complex were unknown before their study.

The complex consists of two hydrogenases and two heterodisulfide reductases; a total of 28 iron-sulfur clusters in the complex link the different ends of the electron transfer chains. Most eagerly awaited was the structure of the active-site Fe/S clusters in the heterodisulfide reductase. These active-site Fe/S clusters are mechanistically unique as they mediate reduction of a heterodisulfide in two single-electron steps. The characteristic binding sequence motif that serves as a marker for this cluster is found in more than 2000 protein sequences, indicating that these Fe/S clusters are widespread among anaerobic microorganisms.

Wagner *et al.* show that these active-site Fe/S clusters have an, until now, unobserved structure and function (*3*). [4Fe-4S] clusters are common to proteins with various physiological functions, from electron transfer to dehydrations and iron-sensing, and typically form a cubane shape, in which each iron is tetrahedrally coordinated by three inorganic sulfurs and one cysteine thiolate (*8*). Such cubane-type [4Fe-4S] clusters are also predominant in the HdrABC-MvhAGD structure, where they mediate electron transfer. By contrast, each of the two [4Fe-4S] clusters in the active site of heterodisulfide reductase resembles a cube from which one side has been opened, pulling one iron and one sulfur out of the cube (see the figure).

The authors also reveal why the noncubane [4Fe-4S] clusters come in pairs. When they soaked the HdrABC-MvhAGD crystals with CoM-S-S-CoB, they captured different reaction states in their structures. In one state, CoM-S-S-CoB is split and both fragments bind to the clusters, revealing how the two Fe/S clusters act in synchrony to split a disulfide bond.

The HdrABC-MvhAGD structure also starts to reveal some of the secrets of electron bifurcation. The challenge of bifurcation is connecting the upward and downward motion of the marbles (electrons). That is, the enzyme has to gate the electrons such that not only the spontaneous downward rolling occurs but also the energy-demanding upward pull. Thus, it has to make the easy pathway at times slower or less favorable than the energetically more demanding reduction of the ferredoxin. The long distances that Wagner *et al.* observed between the clusters interrupt the electron transfer flow and are likely part of the regulatory process, as they require conformational changes to connect the electron transfer chain. Future work should explore how these conformational changes control the coupled processes. ■

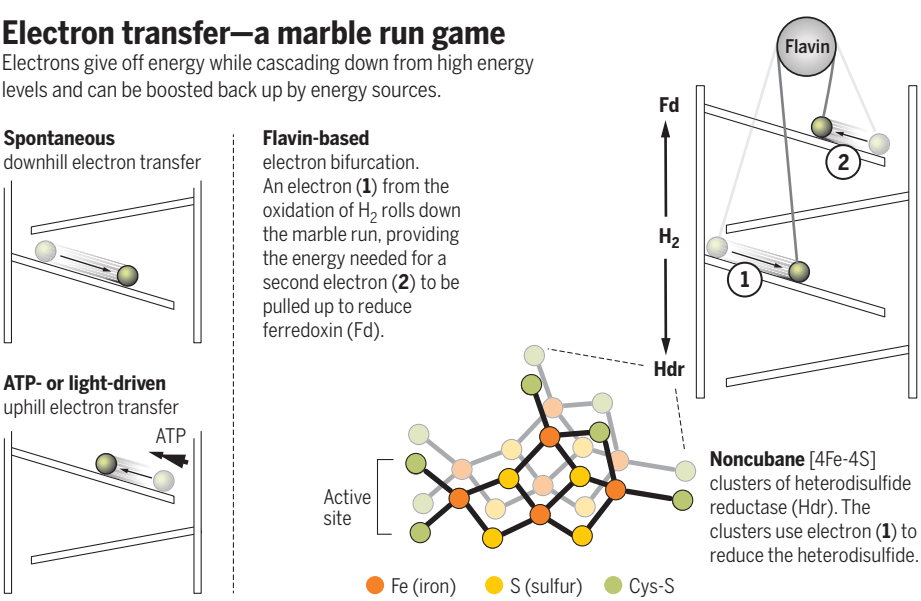
REFERENCES

1. R. K. Thauer, A. K. Kaster, H. Seedorf, W. Buckel, R. Hedderich, *Nat. Rev. Microbiol.* **6**, 579 (2008).
2. R. Conrad, *Environ. Microbiol. Rep.* **1**, 285 (2009).
3. T. Wagner, J. Koch, U. Ermler, S. Shima, *Science* **357**, 699 (2017).
4. A. Szent-Györgyi, *Introduction to a Submolecular Biology* (Academic Press, New York, 1960).
5. W. Buckel, R. K. Thauer, *Biochim. Biophys. Acta* **1827**, 94 (2013).
6. J. W. Peters, A. F. Miller, A. K. Jones, P. W. King, M. W. Adams, *Curr. Opin. Chem. Biol.* **31**, 146 (2016).
7. A. K. Kaster, J. Moll, K. Parey, R. K. Thauer, *Proc. Natl. Acad. Sci. U.S.A.* **108**, 2981 (2011).
8. D. C. Rees, J. B. Howard, *Science* **300**, 929 (2003).

10.1126/science.aao2439

Electron transfer—a marble run game

Electrons give off energy while cascading down from high energy levels and can be boosted back up by energy sources.



GRAPHIC: K. SUTLIFF/*SCIENCE*

DEVELOPMENTAL BIOLOGY

Circulating peptide prevents preeclampsia

Mouse ELA has a critical role in placental development and function, with implications for human pregnancy

By **Robert C. Wirka** *and* **Thomas Quertermous**

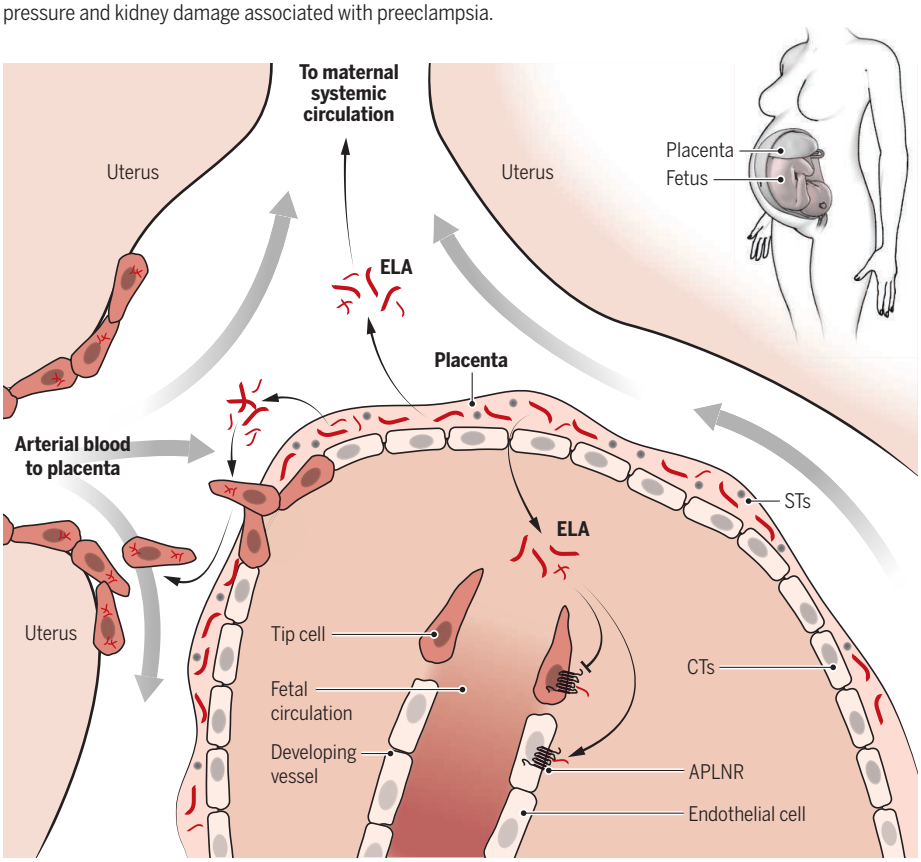
Preeclampsia (PE) is a devastating complication of pregnancy that puts both mother and child at risk for clinical complications. In severe cases, PE can progress to multiorgan dysfunction and death. Characterized by hypertension (high blood pressure) and proteinuria (protein in the urine), the syndrome occurs in up to 8% of pregnancies. Although it is widely accepted that the pathophysiology of PE involves disturbance of normal blood vessel function in the placenta and the development and function of the placenta, the exact mechanisms underlying PE have not been defined. Discovery of the causal mechanisms in PE is urgently needed so that early assessment of risk and therapeutic interventions can be developed. On page 707 of this issue, Ho *et al.* (*1*) report breakthrough insights into the mechanisms of PE. They reveal a central role for ELABELA (ELA), a recently discovered circulating peptide ligand, in placental vascular development and PE in mice.

ELA is a component of the ELA–apelin (APLN)–apelin receptor (APLNR) pathway. Both ELA and APLN peptides bind the G protein–coupled receptor APLNR, and APLN-APLNR have been shown to regulate fluid balance, cardiac contractility, local regulation of blood flow, and angiogenesis (the formation of blood vessels)—all processes that regulate delivery of blood to peripheral tissues (*2*). ELA was discovered as an early embryonic regulator of cellular movement with a critical role in migration and development of cardiac progenitor cells (*3*,

Division of Cardiovascular Medicine, Stanford University, Stanford, CA 94305, USA. Email: tomq1@stanford.edu

The maternal-fetal interface within the developing placenta

ELA is produced by syncytiotrophoblasts (STs), which form a barrier with cytotrophoblasts (CTs) that separate fetal and maternal blood but allow exchange of gases and nutrients. ELA regulates fetal angiogenesis, and possibly CT migration into maternal arteries. ELA in the maternal systemic circulation may mitigate high blood pressure and kidney damage associated with preeclampsia.



4). Importantly, ELA has also been shown in rodent models to delay development of systemic hypertension and preserve cellular architecture in the kidney, an organ that is often damaged in PE (*5*). Also, ELA improved high blood pressure and cardiac hypertrophy in the setting of pulmonary artery hypertension in rodents (*6*).

To investigate the developmental and adult physiological roles for ELA, the authors created and studied *Ela*-null mice. They noted cardiovascular developmental defects in many of the embryos studied, confirming earlier findings in developmental model systems (*3*, *4*). Loss of *Ela* was associated with fetal demise, especially in mothers devoid of all ELA expression. Interestingly, pregnant *Ela*-null mice exhibited elevated blood pressure and proteinuria, which were associated with changes in the placenta and kidney, clinical features that are strongly reminiscent of PE. Characterization of cellular patterns of expression of ELA and APLNR in the placenta, and identification of cellular and molecular defects in mice missing this peptide, provide compelling evidence for a central role of ELA in placental vascular development (see the figure).

Most interesting, from a clinical standpoint, are the observations related to circulating levels of ELA. The investigators measured circulating peptide amounts, which correlated with those of maternal proteinuria as well as other PE disease features in the placenta and kidney. These findings suggest that measurement of circulating ELA concentrations in pregnant women, either alone or in combination with other biomarkers that correlate with PE, such as the circulating vascular endothelial growth factor receptor called soluble fms-related tyrosine kinase 1 (sFLT1), might allow the identification of those women at risk for developing PE. Early and more definitive diagnosis of the syndrome could improve treatment.

Furthermore, the administration of recombinant ELA peptide to pregnant *Ela*-null mice with a PE-like phenotype was shown to prevent proteinuria and kidney pathology associated with PE, normalize maternal blood pressure, and prevent fetal weight loss without adverse effects on embryonic development. Although there are substantial differences between placental biology in humans versus mice, these data suggest the attractive possibility that ELA may be useful as a therapy for PE.

Another interesting finding in this study is that ELA and APLN, both ligands for the same receptor, APLNR, have very different and possibly opposing effects on placental angiogenesis and the development of PE. For instance, these two peptides produced opposite effects on placental gene expression. If ELA and APLN are both found in the circulation and activate the same receptor, what is the molecular basis for their different functional profiles? One possible explanation is that ELA can also activate a second receptor, independent of APLNR. A second possibility is that ELA and APLN differentially engage APLNR, in a manner that activates different downstream cellular signaling. Both hypotheses are consistent with the great divergence between the primary structures of the two peptides. Regardless of the molecular mechanism, these data suggest that it may be the balance of circulating ELA and APLN peptide concentrations in the setting of pregnancy that is important for the risk of PE.

The most obvious question is whether these findings apply to humans. The authors show that ELA is expressed by similar cell types in the human placenta and that treatment of a human trophoblast-like cell line (trophoblasts form the placenta) with ELA leads to increased invasiveness, a property that aids in placental blood supply. Intriguingly, ELA is detected in the plasma of men and nonpregnant women (*6*). Thus, there is a clear need to study the behavior of plasma ELA in humans and to determine the association of plasma ELA concentrations with both PE and its risk factors (such as obesity, hypertension, diabetes, and renal disease) in human patients. A causal role for ELA in PE in humans could be further studied through Mendelian randomization, in which genetic factors determining plasma ELA concentrations are tested for their association with PE. Finally, it will be important to integrate ELA into known molecular pathways in the placenta, for instance, the pathway including the angiogenesis-associated factor sFLT1. Such work will further guide the possible implementation of ELA in the clinic. ■

REFERENCES

1. L. Ho *et al.*, *Science* **357**, 707 (2017).
2. P. Yang *et al.*, *Trends Pharmacol. Sci.* **36**, 560 (2015).
3. S. C. Chng *et al.*, *Dev. Cell* **27**, 672 (2013).
4. A. Pauli *et al.*, *Science* **343**, 1248636 (2014).
5. C. A. Schreiber *et al.*, *Curr. Gene Ther.* **16**, 349 (2016).
6. P. Yang *et al.*, *Circulation* **135**, 1160 (2017).

10.1126/science.aao2642

GRAPHIC: C. BICKEL/*SCIENCE*

Circulating peptide prevents preeclampsia

Robert C. Wirka and Thomas Quertermous

Science **357** (6352), 643-644.
DOI: 10.1126/science.aao2642