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POSTER ABSTRACTS

301.VASCULATURE, ENDOTHELIUM, THROMBOSIS AND PLATELETS: BASIC AND TRANSLATIONAL

Transducing Force into Procoagulation: PIEZO1-TMEM16F Functional Coupling in Blood Lining Cells

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Thrombosis is a major global disease burden that accounts for 1 in 4 deaths worldwide. Hypertension and preeclampsia greatly increase thrombotic risks by imposing high blood pressure and abnormal hemodynamic shear stress on blood-lining cells, namely endothelial cells (ECs) and placental syncytiotrophoblasts (STBs) in pregnant women. Nonetheless, it remains elusive how abnormal mechanical forces under hypertensive conditions promote coagulation. PIEZO1 mechanosensitive ion channel is a major force sensor in a wide variety of cells, including red blood cells (RBCs) and endothelial cells (ECs), where it transduces mechanical forces into chemical signals through its ion permeability to calcium. On the other hand, TMEM16F is a calcium-activated lipid scramblase (CaPLSase) that translocates phosphatidylserine (PS), an important procoagulant factor, to the cell surfaces of blood cells and endothelial cells. We recently discovered that TMEM16F is the sole CaPLSase in placental trophoblasts and RBCs. Our preliminary results show that PIEZO1 and TMEM16F are functionally coupled in RBCs, and calcium entry through PIEZO1 activates TMEM16F, leading to PS exposure. Based on all these, we hypothesize that in the blood lining cells, PIEZO1-TMEM16F coupling is responsible for transducing mechanical forces into PS exposure, a critical procoagulant signal for blood coagulation.

By employing immunostaining, patch clamp electrophysiology, and a fluorescence microscopy-based scrambling assay, we show that PIEZO1 is functionally expressed in placental trophoblasts, including STBs. We further demonstrate that PIEZO1 activation, either stimulated by its agonist Yoda1 or by shear stress, induces PS exposure in BeWo human trophoblast cell line and human umbilical vein endothelial cell line (HUVEC) but not the TMEM16F deficient cell lines. In addition, using chromogenic tenase and prothrombinase, and fluorescence fibrin assays, we show that PIEZO1 activation by its agonist, Yoda1, triggered coagulation activities in a TMEM16F-dependent fashion in trophoblasts. Our study thus discovers the functional expression of the PIEZO1 mechanosensitive channel in placental trophoblasts and elucidates a novel force-induced procoagulant mechanism in blood-lining cells. In this mechanism, PIEZO1-TMEM16F coupling transduces mechanical forces into procoagulant PS exposure on the blood lining cells. Enhanced PIEZO1-TMEM16F coupling may contribute to hypercoagulable states in hypertension and preeclampsia, and breaking the coupling is therefore a potential therapeutic strategy to prevent thrombotic risks associated with these diseases.

Disclosures No relevant conflicts of interest to declare.

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