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POSTER ABSTRACTS

101.RED CELLS AND ERYTHROPOIESIS, EXCLUDING IRON

PIEZO1-TMEM16F Interplay in Hereditary Xerocytosis

Pengfei Liang, PhD[1], *Yang Zhang*[1], *Yui Chun Serena Wan*[1], *Shang Ma*[2], *Ping Dong*[1], *Augustus Lowry*[3], *Samuel Francis, MD*[1], *Sanjay Khandelwal, PhD*[4], *Martha Delahunty, PhD*[5], *Marilyn J. Telen, MD*[6], *John J Strouse, MD PhD*[7], *Gowthami Arepally, MD*[1], *Huanghe Yang, PhD*[3]

[1] Duke University, Durham
[2] UT Southwestern Medical Center, Dallas, TX
[3] Duke University School of Medicine, Durham, NC
[4] Duke Medical Center, Durham, NC
[5] Duke Comprehensive Sickle Cell Center, Duke Univ. School of Medicine, Durham, NC
[6] Duke Univ. Med. Ctr., Durham, NC
[7] Department of Medicine, Division of Hematology, Duke University School of Medicine, Durham, NC

Cell surface exposure of phosphatidylserine (PS), an anionic phospholipid that is usually confined to the inner leaflet of the plasma membrane, triggers a plethora of cellular responses. PS exposure in RBCs contributes to blood coagulation, promotes RBC aggregation and adhesion to endothelial cells, and accelerates the removal of aging RBCs from circulation. The existence of CaPLSase, a passive phospholipid transporter that catalyzes rapid PS exposure in response to intracellular Ca^{2+} elevation, was first observed in RBCs in the 1990s. However, the molecular identity of RBC CaPLSase, its activation mechanism and its role in red cell disorders remain elusive. Here we demonstrate that TMEM16F, the long-sought-after RBC CaPLSase, is activated by calcium influx through the mechanosensitive channel PIEZO1 in RBCs. PIEZO1-TMEM16F functional coupling is enhanced in RBCs from individuals with hereditary xerocytosis (HX), a RBC disorder caused by PIEZO1 gain-of-function (GOF) channelopathy. Enhanced PIEZO1-TMEM16F coupling leads to an increased propensity to expose PS, which may contribute to HX clinical manifestations including anemia, splenomegaly and post-splenectomy thrombosis. Pharmacological inhibition of PIEZO1 prevents calcium-induced dehydration, hemolysis and PS exposure in HX RBCs. Our study reveals an activation mechanism of TMEM16F and its pathophysiological function in HX, providing insights into potential treatment.

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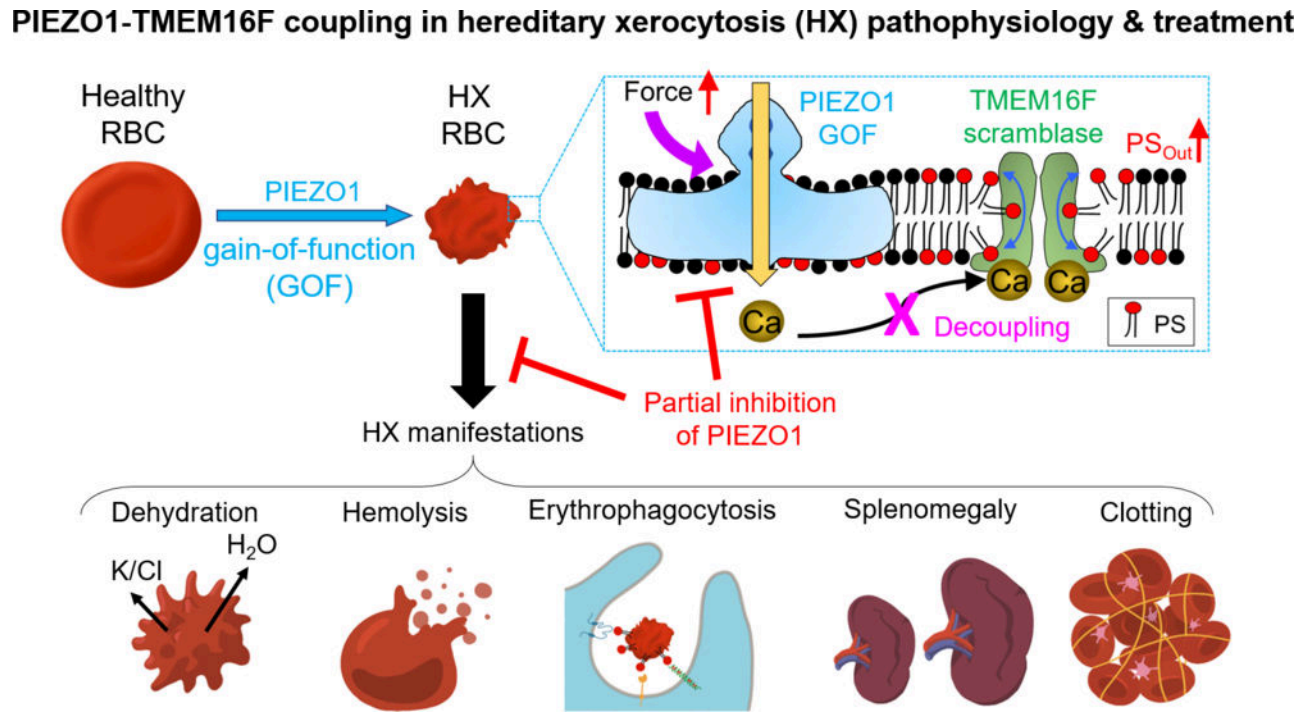

Figure 1

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