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Piezo1 Places a Brake on Megakaryocyte Maturation and Platelet Biogenesis

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About the Study

Years after the discovery of Piezo1/2 cation channels by Ardem Patapoutian and colleagues [1], investigations have continued, unfolding intriguing properties of these channels, the name of which means squeeze/press in Greek. Piezo1 and Piezo 2 are expressed in various cell types, with varying responses to mechanical forces projected by the extracellular matrix. The role of Piezo1 protein in maintenance of red blood cells shape and function has been reported in context of human mutations affecting this channel. A recent paper by Abbonante, et al. [2] described new roles for Piezo1 in affecting the development of a relatively rare hematopoietic cell, the Megakaryocyte (MK), as well as the level of its progeny, blood platelets, in health and disease.

Piezo1 senses mechanical forces acting on the plasma membrane, resulting in mobilization of calcium into the cells, thereby affecting processes, such as cellular adhesion, development and function, as well as overall tissue homeostasis [3,4]. Although relatively rare, Piezo1 mutations of gain-of-function or loss-of-function were identified and well described. Loss-of-function mutations manifest in lymphatic malformation, while gain-of-function mutations are associated with a syndrome characterized by hemolytic anemia. Accordingly, mechanical activation of Piezo1 was found to control erythrocyte hydration [5]. In the hematopoietic cell system, erythrocytes and MKs arise from an early common progenitor. Thus, it is not surprising that Piezo1 is also expressed in MKs, where it plays a role in controlling MK development, as well as platelet level. MK specific knockout of Piezo1/2 increased platelet level in mice. Pharmacological activation of Piezo1/2 in cell cultures resulted in shifting mouse or human MKs to low ploidy, while a selective Piezo1 inhibitor increased MK maturation and proplatelet production in human or mouse cultured cells.

Primary Myelofibrosis (PMF) is hallmarked by an increased number of MKs and a fibrotic and rigid bone marrow niche [6,7]. Interestingly, Piezo1 level is upregulated in MKs derived from a mouse model of PMF bearing a JAK2 hyperactivating mutation (Jak2V617F), and in MKs derived from PMF patients. Under these conditions too, Piezo1 places a brake on MK maturation and platelet formation [2], as manifested by reduced or increased proplatelet biogenesis upon Piezo1 activation or inhibition, respectively.

This study, while unraveling new roles for Piezo1 in the hematopoietic system, also raises intriguing inquiries that might be addressed in extended studies. Piezo1 expression has been reported to be induced by inflammatory cytokines or a rigid matrix [8-10]. Findings reported by Abbonante, et al. [2] raise the possibility of inducibility of Piezo1 gene expression under other bone marrow disease conditions associated with augmented inflammatory profile. Considering the expression of this ion channel in hematopoietic cells, it would be interesting to investigate the level of expression and possible function of Piezo1 and Piezo2 in early hematopoietic stem cells. Within MKs and other hematopoietic cells, Piezo proteins are likely to trigger different signaling pathways and affect properties such as cell adhesion or maturation, also depending on forces sensed by the extracellular matrix. Understanding better how Piezo1 affects specific cellular signaling pathways within MKs or other blood cells in health and disease could also enhance possible Piezo-based therapeutic applications.

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