Nominated research accomplishment

'Discovery of Piezo1 channels as crucial sensors of mechanical cues in the context of activation and chemotaxis of human T lymphocytes'

The research pertains to discovery of a novel mechanosensory module in human T cells, driven by the professional mechanosensor Piezo1, which is critical for T cell activation and chemotactic migration of T cells. [*eLife, 2023; J Immunol (Cutting Edge), 2018; Crit Rev Immunol, 2019*].

a) **Crucial role of Piezo1 in human T cell activation (this is also the first report of a role of Piezo1 mechanosensory channels in the immune system)**
TCRs recognize peptides on MHC molecules and induce downstream signaling, leading to activation and clonal expansion. In addition to the strength of the interaction of TCRs with peptides on MHC molecules, mechanical forces contribute to optimal T cell activation, as reflected by the superior efficiency of immobilized TCR-cross-linking Abs compared with soluble Abs in TCR triggering, although a dedicated mechanotransduction module is not identified. We found that the professional mechanosensor protein Piezo1 is critically involved in human T cell activation. Although a deficiency in Piezo1 attenuates downstream events on ex vivo TCR triggering, a Piezo1 agonist can obviate the need to immobilize TCR-cross-linking Abs. Piezo1-driven Ca2+ influx, leading to calpain activation and organization of cortical actin scaffold, links this mechanosensor to optimal TCR signaling.

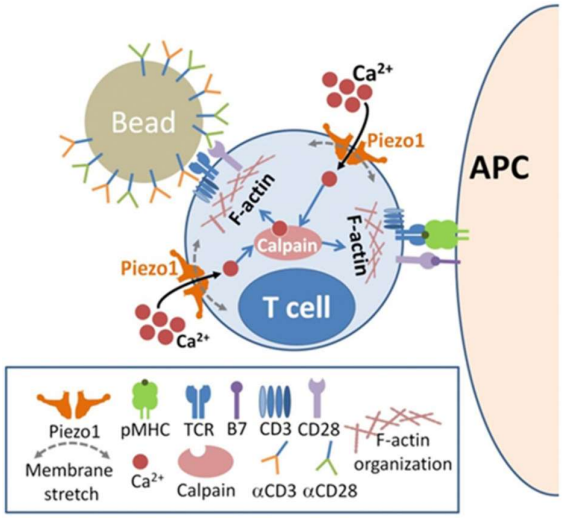

Figure 1: Proposed model for the role of Piezo1 in human T cell activation. Our data suggest that membrane stretch during immune synapse formation triggers Piezo1 activation and Ca2+ influx, which, in turn, activate calpain. Calpain activation helps in the organization of the cortical actin scaffold, thereby optimizing human T cell activation.

Reference (attached): Liu CSC, Raychaudhuri D, Paul B, Chakrabarty Y, Ghosh AR, Rahaman O, Talukdar A, Ganguly D*. Cutting Edge: Piezo1 mechanosensors optimize human T cell activation. Journal of Immunology, 2018 Feb 15;200(4):1255-1260.
Citations: 104

b) **Crucial role of Piezo1 in chemotactic migration of human T cells**
T cells are crucial for efficient antigen-specific immune responses and thus their migration within the body, to inflamed tissues from circulating blood or to secondary lymphoid organs, play a very critical role. A migrating T cell is expected to sense diverse external and membrane-

intrinsic mechano-physical cues, but molecular mechanisms of such mechanosensing in cell migration are not established. We found that deficiency of Piezo1 in human T cells interfered with integrin-dependent cellular motility on ICAM-1-coated surface. Piezo1 recruitment at the leading edge of moving T cells is dependent on and follows focal adhesion formation at the leading edge and local increase in membrane tension on chemokine receptor activation. Piezo1 recruitment and activation, followed by calcium influx and calpain activation, in turn are crucial for the integrin LFA-1 recruitment at the leading edge of the chemotactic human T cells. Thus we found that Piezo1 activation in response to local mechanical cues constitutes a membrane-intrinsic component of the 'outside-in' signaling in human T cells, migrating in response to chemokines, that mediates integrin recruitment to the leading edge.

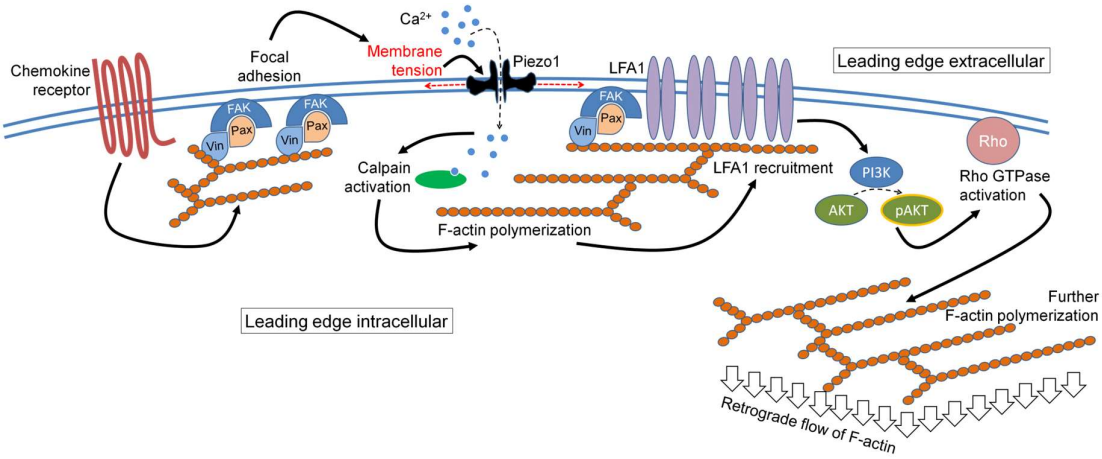

Figure 2: The mechanistic model depicting involvement of Piezo1 mechanosensing in leading edge events in a migrating T cell. Proposed model based on our data suggests chemokine receptor activation in human T cells lead to focal adhesion kinase activation and focal adhesion formation. Focal adhesions lead to localized increase in membrane tension at the leading edge plasma membrane which leads to Piezo1 recruitment and activation. Piezo1 activation leads to calpain activation which potentially drives further cytoskeletal consolidation to recruit integrin LFA1. LFA1 recruitment and activation lead to phosphorylation of AKT and downstream signaling eventually driving the retrograde actin flow in migrating human T cells.

Reference (attached): Liu CSC, Mandal T, Biswas P, Hoque MA, Bandopadhyay P, Sinha BP, Sarif J, D'Rozario R, Sinha DK, Sinha B, Ganguly D*. Piezo1 mechanosensing regulates integrin-dependent chemotactic migration in human T cell. eLife, 2023, in production, doi: https://doi.org/10.1101/2022.08.16.504114v2
Citations: 0 (in production)

Signature of the candidate:

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