UKE Paper of the Month Juli 2023

Adhesion to laminin-1 and collagen IV induces the formation of Ca^{2+} microdomains that increase T cell sensitivity

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ABSTRACT:

During an immune response, T cells migrate from blood vessel walls into inflamed tissues by migrating across the endothelium and through extracellular matrix (ECM). Integrins facilitate T cell binding to endothelial cells and ECM proteins. Here, we report that Ca^{2+} microdomains observed in the absence of T cell receptor (TCR)/CD3 stimulation are initial signaling events triggered by adhesion to ECM proteins that increase the sensitivity of primary murine T cells to activation. Adhesion to the ECM proteins collagen IV and laminin-1 increased the number of Ca^{2+} microdomains in a manner dependent on the kinase FAK, phospholipase C (PLC), and all three inositol 1,4,5-trisphosphate receptor (IP_3R) subtypes and promoted the nuclear translocation of the transcription factor NFAT-1. Mathematical modeling predicted that the formation of adhesion-dependent Ca^{2+} microdomains required the concerted activity of two to six IP_3Rs and ORAI1 channels to achieve the increase in the Ca^{2+} concentration in the ER-plasma membrane junction that was observed experimentally and that required SOCE. Further, adhesion-dependent Ca^{2+} microdomains were important for the magnitude of the TCR-induced activation of T cells on collagen IV as assessed by the global Ca^{2+} response and NFAT-1 nuclear translocation. Thus, adhesion to collagen IV and laminin-1 sensitizes T cells through a mechanism involving the formation of Ca^{2+} microdomains, and blocking this low-level sensitization decreases T cell activation upon TCR engagement.

STATEMENT:

In this interdisciplinary work, we were able to visualize and characterize for the first-time adhesion-dependent Ca^{2+} microdomains evoked by integrins, independent of T cell receptor stimulation. In response to adhesion to ECM proteins, these Ca^{2+} microdomains sensitize T cells for activation during the migration to a site of inflammation. Pharmacological blocking of these adhesion-dependent Ca^{2+} microdomains, might be a potential target for therapeutical intervention.This paper should be considered the paper of the month because it was supported by the UKE's Förderfonds Medizin (NWF 22/07), almost all co-authors belong to the UKE (15 out of 17) and furthermore Science Signalling decided to put our story on the cover!

BACKGROUND:

This work was mainly performed in the Ca^{2+} Signalling Group, Department of Biochemistry and Molecular Cell Biology by Mariella Weiß and supervised by PD Björn-Philipp Diercks. This work was supported by Förderfonds Medizin of the University Medical Center Hamburg-Eppendorf (grant NWF 22/07) and by the DFG SFB1328 “Adenine Nucleotides in Immunity and Inflammation” project A01, A02, A03 (project-number 335447717).