UKE Paper of the Month März 2022

P2X4 and P2X7 are essential players in basal T cell activity and Ca^{2+} signaling milliseconds after T cell activation

Brock, Valerie J, Wolf, Insa M A, Er-lukowiak, Marco Lory, Niels, Stähler, Tobias, Woelk, Lena-Marie, Mittrücker, Hans-Willi, Müller, Christa E, Koch-Nolte, Friedrich, Rissiek, Björn, Werner, René, Guse, Andreas H, Diercks, Björn-Philipp

Science Advances 2022 Feb 04; 8 (5), eabl9770

ABSTRACT:
Initial T cell activation is triggered by the formation of highly dynamic, spatiotemporally restricted Ca^{2+} microdomains. Purinergic signaling is known to be involved in Ca^{2+} influx in T cells at later stages compared to the initial microdomain formation. Using a high-resolution Ca^{2+} live-cell imaging system, we show that the two purinergic cation channels P2X4 and P2X7 not only are involved in the global Ca^{2+} signals but also promote initial Ca^{2+} micro- domains tens of milliseconds after T cell stimulation. These Ca^{2+} microdomains were significantly decreased in T cells from $P2rx4^{-/-}$ and $P2rx7^{-/-}$ mice or by pharmacological inhibition or blocking. Furthermore, we show a pannexin-1– dependent activation of P2X4 in the absence of T cell receptor/CD3 stimulation. Subsequently, upon T cell receptor/CD3 stimulation, ATP release is increased and autocrine activation of both P2X4 and P2X7 then amplifies initial Ca^{2+} microdomains already in the first second of T cell activation.

STATEMENT:
Although, the ATP-gated channels P2X4 and P2X7 were shown to influence global Ca^{2+} signals and the immune response some years before, their role in the formation of initial Ca^{2+} signals in the first milliseconds after T cell activation was still unclear. In this publication, we show for the first time the role of P2X4 and P2X7 on the formation of Ca^{2+} microdomains before and after T cell stimulation. The infrequent, T cell receptor stimulation independent Ca^{2+} microdomains are promoted by P2X4 but not by P2X7. In contrast, only P2X7 influence the expression of NUR77 and the proliferation of the T cells. The results highlight the functional differences of P2X4 and P2X7 and opens up advanced possibilities for clinical interventions based on these differences.

BACKGROUND:
This work was mainly performed in the Ca^{2+} Signalling Group, Department of Biochemistry and Molecular Cell Biology, by the first authors Valerie J. Brock and supervised by Björn-Philipp Diercks.Importantly, the project was supported by the DFG SFB1328 “Adenine Nucleotides in Immunity and Inflammation” project A02, A03, A11 and Z02.