**UKE Paper of the Month December 2015**

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**Frontrunners of T cell activation: Initial, localized Ca2+ signals mediated by NAADP and the type 1 ryanodine receptor**

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**ABSTRACT:**
The activation of T cells is the fundamental on switch for the adaptive immune system. Ca2+ signaling is essential for T cell activation and starts as initial, short-lived, localized Ca2+ signals. The second messenger nicotinic acid adenine dinucleotide phosphate (NAADP) forms rapidly upon T cell activation and stimulates early Ca2+ signaling. We developed a high-resolution imaging technique using multiple fluorescent Ca2+ indicator dyes to characterize these early signaling events and investigate the channels involved in NAADP-dependent Ca2+ signals. In the first seconds of activation of either primary murine T cells or human Jurkat cells with beads coated with an antibody against CD3, we detected Ca2+ signals with diameters close to the limit of detection and that were close to the activation site at the plasma membrane. In Jurkat cells in which the ryanodine receptor (RyR) was knocked down or in primary T cells from RyR1−/− mice, either these early Ca2+ signals were not detected or the number of signals was markedly reduced. Local Ca2+ signals observed within 20 ms upon microinjection of Jurkat cells with NAADP were also sensitive to RyR knockdown. In contrast, TRPM2 (transient receptor potential channel, subtype melastatin 2), a potential NAADP target channel, was not required for the formation of initial Ca2+ signals in primary T cells. Thus, through our high-resolution imaging method, we characterized early Ca2+ release events in T cells and obtained evidence for the involvement of RyR and NAADP in such signals

**STATEMENT:**
*In this interdisciplinary work we were able to image and characterize subcellular Ca2+ signals in none excitable T cells for the first time and this opens a completely new possibility to analyze initial activation of the adaptive immune system*.

**BACKGROUND:**
This work was performed at the Department of Biochemistry and Molecular Cell Biology in the group of Andreas H. Guse in cooperation with the Department of Computational Neuroscience and Department of Immunology at UKE and the Institute for Multiple Sclerosis Research, Department of Neuro-immunology, Gemeinnützige Hertie-Stiftung and University Medical Center Göttingen and the Max-Planck-Institute for Experimental Medicine, Göttingen. It was part of the PhD thesis of M.Sc. Björn-Philipp Diercks. This study was supported by the Deutsche Forschungsgemeinschaft (grants GU 360/15-1 and 360/16-1 to A.H.G., and grants FL 377/2-1 and TRR-SFB43-TP B11 to A.F.), the Forschungszentrum Medizintechnik Hamburg (to I.M.A.W. and R.W.), Förderfonds Medizin of the University Medical Center Hamburg-Eppendorf (grant NWF 15/13 to I.M.A.W.), the Hertie Foundation (grant P1130072 to A.F. and D.L.), and the Landesforschungsförderung of the City of Hamburg (Research Group ReAd Me to A.H.G., I.M.A.W., and H.-W.M).