Calcium-Redox feedback loop in immune cells: New players and regulatory mechanisms (SFB1027 C4)

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Ca^{2+} release-activated Ca2+ (CRAC) channels were originally identified as store-operated highly selective Ca2+ channels in primary rat mast cells and Jurkat T cells (Hoth & Penner, 1992; Zweifach & Lewis, 1993), but have since been found in virtually all cell types. While STIM1 and Orai1 constitute the main subunits of CRAC channels in lymphocytes, other cell types contain different combinations/ratios of Orai1, Orai2 or Orai3 and STIM1 or STIM2. We are interested in physiological and pathophysiological regulation of CRAC channels by environmental factors such as oxidation, as well as by posttranslational alterations. During inflammation, immune and surrounding cells encounter environments rich in reactive oxygen species (ROS), generated by phagocytes such as monocyte-derived cells. We have shown in the past that Orai3 is critical in controlling the ROS sensitivity of store-operated Ca^{2+} entry (SOCE) and using MD simulations solved the mechanism of ROS induced inhibition of Orai1 (Alansary et al. 2016). The physiological role of Orai2, however, remains enigmatic. In T cells Orai2 can act as a negative regulator of SOCE but its role in other cell types with predominant Orai2 expression is unclear. In addition, the molecular differences governing STIM-Orai2 interfaces and thereby controlling Ca2+ are unclear. Data concerning novel regulatory mechanism will be presented.

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