Dendritic cell maturation and chemotaxis is regulated by TRPM2-mediated lysosomal Ca^{2+} release

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ABSTRACT **Chemokines induce calcium (Ca^{2+}) signaling and chemotaxis in dendritic cells (DCs), but the molecular players involved in shaping intracellular Ca^{2+} changes remain to be characterized. Using siRNA and knockout mice, we show that in addition to inositol 1,4,5-trisphosphate (IP_3)-mediated Ca^{2+} release and store-operated Ca^{2+} entry (SOCE), the transient receptor potential melastatin 2 (TRPM2) channel contributes to Ca^{2+}release but not Ca^{2+} influx in mouse DCs. Consistent with these findings, TRPM2 expression in DCs is restricted to endolysosomal vesicles, whereas in neutrophils, the channel localizes to the plasma membrane. TRPM2-deficient DCs show impaired maturation and severely compromised chemokine-activated directional migration as well as bacterial-induced DC trafficking to the draining lymph nodes. Defective DC chemotaxis is due to perturbed chemokine-receptor-initiated Ca^{2+} signaling mechanisms, which include suppression of TRPM2-mediated Ca^{2+} release and secondary modification of SOCE. DCs deficient in both TRPM2 and IP_3 receptor signaling lose their ability to perform chemotaxis entirely. These results highlight TRPM2 as a key player regulating DC chemotaxis through its function as Ca^{2+} release channel and confirm ADP-ribose as a novel second messenger for intracellular Ca^{2+} mobilization.—Sumoza-Toledo, A., Lange, I., Cortado, H., Bhagat, H., Mori, Y., Fleig, A., Penner, R., Partida-Sánchez, S. Dendritic cell maturation and chemotaxis is regulated by TRPM2-mediated lysosomal Ca^{2+} release. *FASEB J.* 25, 3529–3542 (2011). www.fasebj.org**

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MIGRATION OF DENDRITIC CELLS (DCs) and other phagocytic cells to sites of infection and inflammation is a critical step toward an effective defense against pathogens (1–3). Phagocytes migrate throughout the body by following chemical cues from small molecules that are produced either endogenously (chemokines) or exogenously [microbially derived chemoattractants; *e.g.*, N-formylmethionyl-leucyl-phenylalanine (fMLP)]. DCs sense chemotactic signals *via* G-protein-coupled receptors (GPCRs) expressed on their plasma membrane (1, 4, 5). Although chemokine receptor stimulation elicits increases in intracellular Ca^{2+} ($[Ca^{2+}]_i$) in DCs (6–9), the ion channels that regulate the Ca^{2+} signals associated with chemokine-dependent migration of DCs remain unidentified.

The transient receptor potential melastatin-2 (TRPM2) is a calcium-permeable nonselective cation channel (10, 11) containing a Nudix-like region that binds and hydrolyzes ADP-ribose (ADPR) to ribose 5-phosphate and adenosine monophosphate (AMP) (10). ADPR binding to the Nudix-like domain induces cation currents across the plasma membrane, allowing Na^+ and Ca^{2+} influx (10, 11). TRPM2 gating by ADPR is facilitated further by the presence of nicotinic acid adenine dinucleotide phosphate (NAADP), cyclic ADPR (cADPR), hydrogen peroxide (H_2O_2), and Ca^{2+} (12–16), whereas channel activity is regulated negatively by AMP and permeating protons (pH; refs. 10, 17, 18). In addition to its role as a cation channel in the plasma membrane, TRPM2 functions as a lysosomal calcium-release channel in the rat pancreatic cell line INS-1 (19).

TRPM2 is expressed in the plasma membrane of human and mouse polymorphonuclear neutrophils (PMNs), monocytes (19–22), and Jurkat T cells (23). A recent study indicates that TRPM2 represents a key inflammatory mediator in cells of myeloid origin and that TRPM2-deficient mice are more resistant to induced experimental colitis due to defective chemokine production by monocytes and reduction of PMN infil-

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