Cell Calcium 80 (2019) 192–193

Contents lists available at ScienceDirect

Cell Calcium

journal homepage: www.elsevier.com/locate/ceca

Commentary

STIM1 holds a STING in its (N-terminal) tail

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A B S T R A C T

The Ca^{2+} sensor STIM1 is essential for adaptive immune responses, yet patients with hypomorphic *STIM1* mutations develop both immunodeficiency and autoimmunity, implying that STIM1 also restrains immune responses. This study by Srikanth et al demonstrates that STIM1 tethers STING, a major inducer of the interferon (IFN) response, to the endoplasmic reticulum (ER) to prevent constitutive STING activation.

The endoplasmic reticulum (ER) is a critical site for multiple physiologic processes that are central to induction of an inflammatory response. Amongst these are Ca^{2+} mobilization in response to various physiological agonists, which activates store-operated Ca^{2+} entry (SOCE). ER Ca^{2+} release triggers the ER-resident Ca^{2+} sensor Stromal Interaction Molecule 1 (STIM1) to cluster and translocate to ER-plasma membrane (PM) junctions. At the ER-PM junctions, STIM1 interacts with and activates the Ca^{2+} channel Orai1, allowing Ca^{2+} influx across the PM [2]. Both *ORAI1* and *STIM1* are critical for adaptive immunity, and hypomorphic mutations in either gene cause severe combined immunodeficiency (SCID) [3]. Many proteins essential for immune function also have roles in promoting central or peripheral tolerance; thus, several SCID-causing mutations also lead to autoimmunity or lymphoproliferation. Indeed, STIM1 deficiency causes autoimmune hemolytic anemia and thrombocytopenia, lymphadenopathy and hepatosplenomegaly. This prompted Srikanth et al to investigate the mechanisms by which, in addition to regulating the adaptive immune responses, STIM1 might repress innate immune responses [1].

To determine whether STIM1 might constitutively restrain immune function, Srikanth et al measured the expression of type I interferon (IFN), IL-6, and interferon- (IFN-) stimulated genes (ISGs) in cells derived from *Stim1*$^{-/-}$ mice. Unstimulated *Stim1*$^{-/-}$ murine embryonic fibroblasts and bone-marrow derived macrophages both showed increased expression of type I IFN, IL-6, and ISGs, as did human *STIM1*-/- THP1 cells. Notably, this was not observed upon Orai1 deletion, indicating that blockade of SOCE does not underlie this increased type I IFN response. Remarkably, a patient with a novel frameshift mutation in *STIM1* presented with mild immunodeficiency but also with enhanced cytokine production, expression of ISGs, and symptoms reminiscent of STING-associated vasculopathy in infancy (SAVI), which is caused by constitutively activating *TMEM173/STING* mutations [4].

STIM1 is found throughout the ER membrane in the resting state, prior to ER Ca^{2+} release, and ER stress is a potent inducer of the IFN response [5]. This observation led the authors to consider interactions between STIM1 and ER-resident proteins upstream of type I IFN production. STimulator of INterferon Genes (STING) is a major ER-resident adapter that activates the type I IFN response to cytoplasmic dsDNA, which is recognized and bound by the cytoplasmic DNA sensor cGAS (cyclic GMP-AMP synthase). DNA-bound cGAS produces a cyclic dinucleotide, 2′,3′-cGAMP (cGAMP) that acts as a STING ligand. cGAMP provokes STING translocation to the ER-Golgi compartment (ERGIC), recruiting TANK-binding kinase and activating interferon regulatory factor 3 (IRF3), which is an IFN-inducing transcription factor [6].

Because both STIM1 and STING localize to the ER during the resting state, the authors hypothesized that STIM1 might restrain interferon production via STING. Indeed, they found that STIM1-deficient cells exhibited enhanced STING activation in response to cGAMP. Accordingly, deletion of *TMEM173*, which codes for STING, prevented type I IFN activation in STIM1-deficient cells. STIM1 and STING physically interacted within the ER, primarily via their N-terminal domains, and STIM1 deletion allowed STING to traffic more efficiently to the ERGIC. STING proteins bearing SAVI-causing mutations bound less efficiently to STIM1 than wild-type STING, and transfection of HEK293 T cells with STIM1 partially reversed the constitutive ERGIC trafficking of STING SAVI mutants. STIM1-deficient human and mouse cells were resistant to viral infection, and resistance was dependent on JAK-STAT signaling, which is activated by type I IFN. Finally, deletion of Stim1, but not Orai1, from murine myeloid cells conferred resistance to herpes simplex virus 1 (HSV-1)-mediated viral encephalitis in vivo. This elegant series of experiments confirms that STIM1 restrains innate

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https://doi.org/10.1016/j.ceca.2019.03.003
Received 4 March 2019; Received in revised form 6 March 2019; Accepted 6 March 2019
Available online 07 March 2019
0143-4160/ Published by Elsevier Ltd.

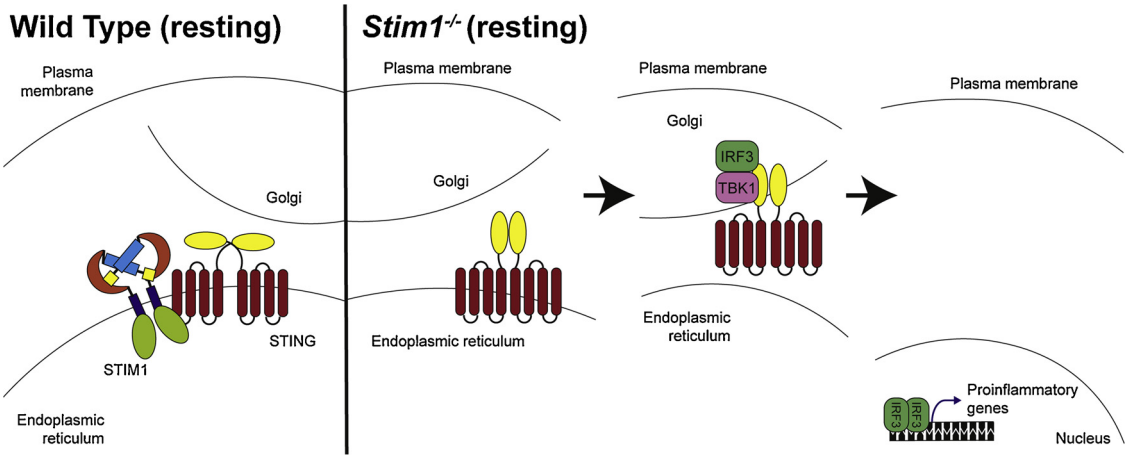

Fig. 1. In the resting state, STIM1 is bound to STING within the endoplasmic reticulum (ER). This interaction retains STING in the ER, preventing activation. In the absence of STIM1, STING constitutively trafficks to the ER-Golgi compartment (ERGIC), recruits TANK-binding kinase (TBK), and activates interferon regulatory factor 3 (IRF3). IRF3 dimerizes, translocates to the nucleus, and acts as an activating transcription factor for type I interferon and other proinflammatory genes.

immune responses via a mechanism that is independent of its well-established role in SOCE (Fig. 1).

These findings raise several important questions for future investigation. One important question is how STIM1 might regulate STING in various cell types to affect innate and adaptive immune responses. While the authors focused on myeloid cells due to the well-characterized actions of STING in these cell types, STING also induces type I IFN production and cell death in T cells [7]. Patients with hypomorphic *STIM1* mutations often develop autoimmune cytopenias, which are primarily mediated by adaptive cells. Moreover, many patients with *ORAI1* loss-of-function mutations also develop autoimmunity, which implicates SOCE-dependent mechanisms such as impaired peripheral tolerance due to defective regulatory T cell function [3]. Indeed, the considerable phenotypic heterogeneity of STIM1 deficiency seen by this and other groups raises the possibility that STIM1 restrains immune activation via both SOCE-dependent and -independent mechanisms [3].

The association between STIM1 and STING may also result in a reciprocal action, through which STING regulates STIM1 activity. The authors provide evidence that STING inhibits SOCE in HEK293 T cells, Jurkat cells, and mouse embryonic fibroblasts (MEFs), but not in THP1 cells. Nonetheless, the possibility that ER-resident STING may repress STIM1 is intriguing. If this mechanism depends upon STING ER residency, it could paradoxically cause STIM1 activation upon STING translocation to the ERGIC and may even contribute to the adaptive immune dysregulation that may be seen in SAVI [4].

Another question is whether STIM1 functions as an "ER retention factor" for other proteins involved in innate immunity or other physiologic processes. Moreover, because Ca^{2+} store depletion induces a conformational change in the N-terminal domain of STIM1, the effectiveness of STIM1 as an "ER retention factor" may be altered upon STIM1 activation. Indeed, the authors demonstrate reduced association of the two proteins when STIM1 was activated by Ca^{2+} depletion. It remains to be seen whether dynamic changes in STIM1 conformation during SOCE affect STIM1-mediated tethering of STING to the ER and downstream interferon production. Such mechanisms could also partially explain the observation that STING mediates the IFN response to ER stress caused by Ca^{2+} mobilization [5]. Finally, this study raises the possibility that other ER-resident proteins may also promote STING ER residency. Indeed, STIM1 deficiency only partially induces STING translocation to the ERGIC, and STIM1 does not completely rescue the phenotype of SAVI-mutant STING. Identifying these proteins and elucidating the mechanisms by which they tether STING to the ER could help to develop novel strategies for modulating STING-dependent type I IFN responses.

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