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Editorial

Editorial: **Mast cell degranulation and calcium entry—the Fyn-calcium store connection**

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Mast cells play a central role in adaptive and innate immune responses. IgE antigen stimulation of the high-affinity IgE receptor (FcεRI) results in rapid secretion of various granule-stored mediators responsible for allergies and other inflammatory diseases [1]. This degranulation process depends on an increase in intracellular Ca^{+2} concentration. Calcium needed for degranulation comes from intracellular stores and from Ca^{+2} influx from the extracellular medium through plasma membrane channels. The release of Ca^{+2} from the ER is mediated by the PLCγ signaling pathway.

The molecular sensor for the calcium store emptying on the ER membrane has been identified recently as the STIM1, and the associated plasma-membrane calcium channel has been identified as ORAI1 (reviewed in ref. [2]). The STIM-ORAI channels are the molecular mechanism underlying SOCE, which is the rapid Ca^{+2} influx from the ECM, following the emptying of intracellular Ca^{+2} stores from the ER (reviewed in ref. [3]). This highly selective, nonvoltage-dependent calcium influx is termed calcium release-activated calcium current.

Abbreviations: Ca^{+2}=calcium ion, CB=cord blood, ECM=extracellular matrix, PB=peripheral blood, siRNA=small interfering RNA, SOCE=store-operated calcium entry, STIM1=stromal interaction molecule 1, TRPC=transient potential receptor Ca^{+2} channel

However, recent evidence indicates that an initial nonstore-operated calcium influx is needed for full mast cell activation [4]. The canonical TRPC family has been involved in capacitive and noncapacitive Ca^{+2} entry in mast cells. TRPC channels range from cationic, nonselective to highly selective calcium channels.

Fyn kinase has been found recently to be an essential element for the positive control of FcεRI-induced degranulation, as BMMCs produced from Fyn−/− mice are unable to fully degranulate after FcεRI cross-linking [5]. It was found that full degranulation of Fyn−/− BMMCs can be obtained with a combination of a calcium ionophore (A23187) and an activator of PKC (phorbolmyristateacetate). However, the molecular mechanism involved was not deciphered.

The current work of Suzuki et al. [6] as well as a recent work by Sanchez-Miranda et al. [4] suggest that the defect in Fyn null mast cells is a result of the functional loss of a nonselective Ca^{+2} current rather than the loss of the STIM-ORAI-selective Ca^{+2}current described previously.

What is responsible for this nonselective Ca^{+2} current?

Sanchez-Miranda et al. [4] suggested recently that canonical TRPCs might be responsible for this Ca^{+2} current. In the current issue of *JLB*, Suzuki et al. [6] now demonstrate that the nonselective cation channel TRPC1 is involved in this Ca^{+2} response of mast cells and show that such channels contribute to mast cell degranulation. They show that Fyn null mast cells express reduced levels of TRPC1 and have normal depletion of intracellular calcium stores but an impaired calcium influx and that these mast cells fail to depolymerize cortical F-actin, a key step for granule-plasma membrane fusion. Furthermore, RNA interference silencing of TRPC1 expression in WT mast cells mimics the Fyn null defect in calcium influx, cortical F-actin depolymerization, and mast cell degranulation. Ectopic expression of Fyn or TRPC1 in Fyn null mast cells restores calcium responses and cortical F-actin depolymerization and increases mast cell degranulation.

In a recent work, Barbu et al. [7] found that decreased expression of Fyn has little if any effect on FcεRI-mediated mast cell activation. siRNA directed against Fyn had only a minor, nonsignificant effect on mast cell degranulation, cytokine release, and signaling events such as Akt phosphorylation. This is in striking contrast to the findings of Sanchez-Mirnada et al. [4] and Suzuki et al. [6]. This might be a result of the different genetic background of the mice lines used or a different population of mast cells, as Sanchez-Miranda et al. [4] and Suzuki et al. [6] used FcεRI-

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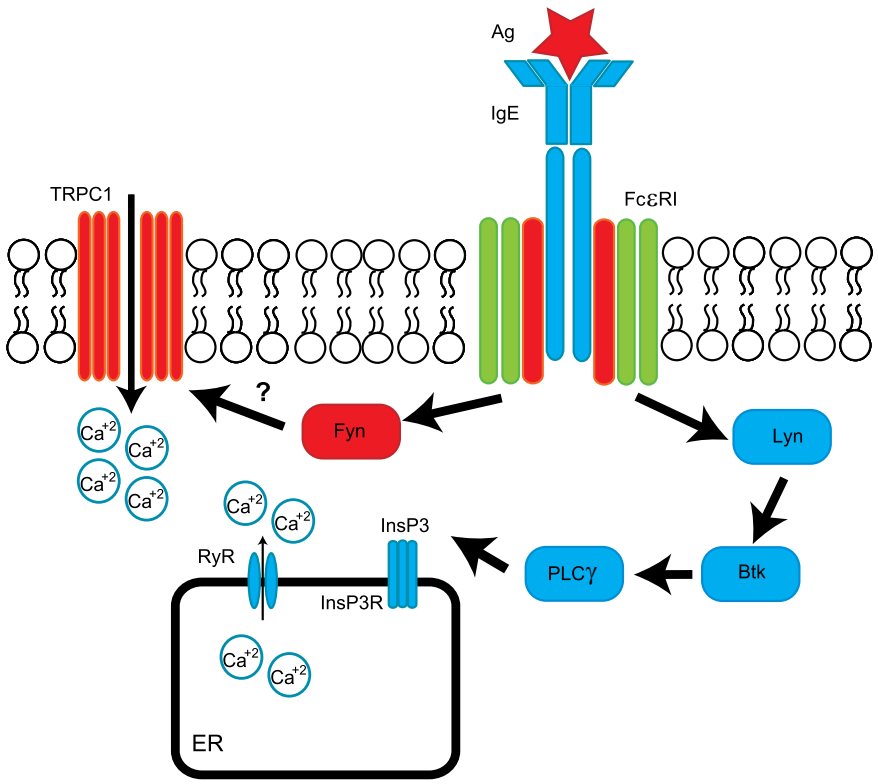

Figure 1. Schematic representation of calcium response during FcεRI-mediated mast cell activation. IgE-antigen complexes bind the high-affinity FcεRI receptors, activating the Lyn-Btk-PLCγ cascade. Inositol triphosphate (InsP3) is synthesized, binds the InsP3R, and causes the release of Ca^{+2} from the ER through ryanodine receptors (RyR), followed by SOCE mediated by STIM-ORAI channels (not depicted in this representation). The recent works by Suzuki et al. and Sanchez-Miranda et al. [4] suggest a new signaling pathway involving the Fyn kinase and TRPC1 channel, resulting in Ca^{+2} influx through the plasma membrane.

positive cells, and Barbu et al. [7] did not characterize the mast cells used in their experiment. Furthermore, although Barbu et al. [7] knocked down Fyn expression in C57Bl/6 female-derived BMMC using siRNA against Fyn, Sanchez-Miranda et al. [4] and Suzuki et al. [6] used BMMC derived, respectively, from 129Sv and 129SvXC57/BL6 mice.

This controversy may be another example of the differential gene expression across mast cell phenotypes, raising the question of the general applicability of findings in mast cell research. For example, Inomata et al. [8] compared the differential gene expression profile of progenitor-derived CB mast cells, progenitor-derived adult PB mast cells, and lung-derived mast cells. Among the most markedly up-regulated transcripts in CB-derived mast cells, Inomata et al. [8] focused on TLR2. CB-derived mast cells expressed functional TLR2, and PB-derived mast cells, under the same culture condition, did not.

TRPC1 channels are expressed in vascular endothelial cells and in T and B lymphocytes and are important in vascular tone and immune responses (reviewed in ref. [9]). Drugs targeting TRPC1 could prove to be beneficial in controlling endothelial cell permeability during chronic inflammation and following coronary artery bypass grafting.

What is the importance of the current finding? TRPC1 is expressed in human skin mast cells but not in CB-derived mast cells or in human lung mast cells [10], opening an opportunity to target skin mast cells without affecting other mast cell phenotypes. Furthermore, as the skin mast cell phenotype is different from other mast cell phenotypes, the identification of TRPC1 as an important mediator of mast cell degranulation creates new possibilities of therapeutic intervention, not only in skin diseases, such as atopic dermatitis, chronic urticaria, mastocytosis, and juvenile dermatomyositis, but also in wound healing. Recent evidence in animal models shows that by stabilizing mast cells at the early stages of wound healing, wound contraction is reduced (reviewed in ref. [11]). Further elucidation of the calcium response pathway during FcεRI-mediated mast cell activation (**Fig. 1**) might yield new therapeutic opportunities for skin diseases and wound healing.

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