MAST CELLS (MCs) are a component of the immune system, which mediate inflammatory responses and allergic immune reactions. MCs are involved in a variety of allergic diseases such as anaphylaxis, allergic rhinitis, and asthma (2, 3). The MCs can be activated via the attachment of IgE to high-affinity IgE receptors (FcεRI) on the MC membrane, as well as by other physical or chemical stimuli. Upon activation, MCs release a variety of immune mediators from their cytoplasmic granules, a cellular process called degranulation. The machinery of degranulation involves an increase in intracellular Ca²⁺ and actin cytoskeleton disassembly that enables the secretory vesicles to move to the plasma membrane. Thus, regulation of Ca²⁺-dependent actin cytoskeleton dynamics is a crucial step in the eventual degranulation of MCs. Previously, it has been shown that serum- and glucocorticoid-inducible kinase (SGK1) is a powerful regulator of Ca²⁺ entry and exocytosis of granules in MCs (7). However, a missing link in this picture has been the role of SGK1 in actin depolymerization that leads to degranulation. Now this picture has been more completely mapped by the work of Shumilina and coworkers (5).

In this issue of American Journal of Physiology-Cell Physiology, Shumilina and coworkers establish, for the first time, the role of SGK1 in promoting F-actin disassembly upon MC stimulation via FcεRI receptor activation. Using bone marrow cells derived from sgk1+/+ and sgk1−/− mice, the authors measured the changes in intracellular Ca²⁺ upon stimulation and showed that the increase in cell Ca²⁺ was attenuated in sgk1−/− cells in comparison to sgk1+/+ cells. Then they proceeded to demonstrate that sgk1-dependent Ca²⁺ entry provokes depolymerization of F-actin and leads to degranulation. Furthermore, they have identified that the SGK1-stimulated Ca²⁺ influx is mediated via Ca²⁺ release-activated Ca²⁺ (CRAC) channels, a key Ca²⁺ pathway for stress activated Ca²⁺ entry. These findings establish a novel SGK1-dependent signaling pathway, viz., SGK1-stimulated Ca²⁺ increase causes F-actin reorganization, leading to degranulation in MCs. As background, SGK1 is known to regulate a variety of ion channels, including epithelial sodium channels, voltage-gated K⁺ channels, Ca²⁺-permeable transient receptor potential channels (TRPV4, TRPV5, and TRPV6), and store-operated Ca²⁺ channels (4). SGK1 is also known to play a regulatory role in many cell functions, including cell volume regulation, cell proliferation, and migration (4). Recent studies have provided evidence that SGK1 promotes the interaction between ion channel proteins and F-actin. For instance, SGK1 directly phosphorylates TRPV4 leading to enhanced interaction between TRPV4 and F-actin (6). Since processes such as cell migration and growth involve F-actin assembly/disassembly, logic dictates that SGK1 may have a more direct role in F-actin polymerization. The findings of Shumilina and coworkers lay out a clear pathway of SGK1 stimulation in MCs, showing that SGK1-activated Ca²⁺ uptake via CRAC causes actin depolymerization and subsequent MC degranulation. The significance of these results is that they reveal a new function of SGK1 in cells.

While these findings provide clear evidence that SGK1-dependent Ca²⁺ entry can regulate actin cytoskeleton in MCs, other parallel mechanisms may exist. It has been reported that p21-activated kinase Pak1-deficient MCs exhibit a reduction in the FcεRI-induced Ca²⁺ response as well as diminished cytoskeleton disassembly, suggesting small RhoGTPases may also be involved in regulation of cytoskeleton reorganization and degranulation (1). The current findings spur the need to further investigate whether or not Pak1 plays a direct role in actin polymerization. In addition, other Ca²⁺-dependent pathways might also affect actin cytoskeleton structure. For example, intracellular Ca²⁺ is involved in myosin-II-based contractility that triggers the reorganization of actin cytoskeleton. There is evidence that myosin II-based contractility is required for the cortical F-actin disassembly in MCs (8). This suggests another pathway: Ca²⁺ → CaM → myosin light chain kinase (MLCK) → myosin-II activation → contraction → disassembly. However, the results of Sullivan et al. (8) suggest that myosin plays a modulatory rather than an essential role in the process of degranulation. In light of the present findings, further investigations into the mechanisms linking cytosolic Ca²⁺ and actin cytoskeleton disassembly in MCs become imperative.

These findings also raise many intriguing new questions and open avenues to map the complete machinery of mast cell function. For example, the expression of SGK1 itself is sensitive to cell volume; conversely, SGK1 regulates cell volume via its effect on a variety of Ca²⁺-permeable ion channels and other transport activities. This suggests the possibility of a feedback loop: SGK1 regulates actin cytoskeleton via its activation of Ca²⁺ uptake, while the expression of SGK1 or the Ca²⁺ influx may be modulated by cytoskeleton.

The role of SGK1 in Ca²⁺ signaling and Ca²⁺-dependent actin cytoskeleton reorganization is also of broad interest to many ongoing areas of research. The current findings not only provide insight into the molecular mechanism of MCs degranulation process, but the results may also be broadly applicable to other SGK1-dependent cell functions, such as cell migration, attachment and growth under physiologic and pathophysiologic conditions. The discovery of the direct link between SGK1...
to actin cytoskeleton reassembly opens new avenues for many such investigations.

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AUTHOR CONTRIBUTIONS
S.Z.H. drafted the manuscript.

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