The dual role of STIM1 *O*-GlcNAcylation on SOCE activity

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O-GlcNAcylation of the stromal interaction molecule 1 (STIM1) is known to impair store-operated Ca^{2+} entry (SOCE). Because it has not been identified the *O*-GlcNAcylation sites of STIM1, we examined whether the Serine/Threonine (Ser/Thr) residues (Ser-575, Ser-608, Ser-621, and Thr-626) of STIM1 S/P-rich domain and the adjacent region were *O*-GlcNAcylated or not using co-immunoprecipitation. The result showed that Ser-621 and Thr -626 residues were *O*-GlcNAcylated. To examine the role of the *O*-GlcNAcylation on SOCE activity, we established the STIM1 knockout HEK293 cells by the CRISPR/Cas9 system, and then, transfected T626A (Thr-626 substituted to Ala) to the cells. Surprisingly, the SOCE activity was reduced via reduced phosphorylation at Ser-621 residue in T626A transfected cells. It was also shown that the SOCE activity was reduced with the treatment of *O*-GlcNAcase inhibitor Thiamet G via reduced phosphorylation at Ser-621 residue in STIM1 wild-type transfected cells. These data may indicate that both decreased *O*-GlcNAcylation of STIM1 at Thr-626 and/or increased STIM1 *O*-GlcNAcylation at Ser-621 results in impaired SOCE activity. This is the first report showing the dual role of *O*-GlcNAcylation in regulating the SOCE activity of STIM1.