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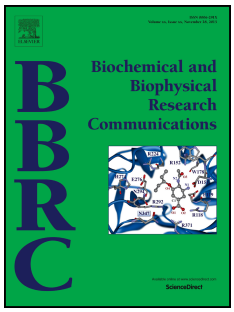

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The self-association and activity regulation of LRSAM1 E3 ligase

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Abstract

LRSAM1, a RING-type E3 ubiquitin ligase, is essential for regulating cargo sorting, signaling pathways, cell adhesion and anti-bacterial autophagy. It is important to elucidate the mechanism that underlies the regulation of LRSAM1 E3 ligase activity. Here, we reported that LRSAM1 exhibited self-association in vitro and in vivo. We found the self-association of LRSAM1 promotes intermolecular ubiquitination and proved a potential N-terminal ubiquitination. The E3 activity of LRSAM1 is amplified when the RING domain is present in tandem with its N-terminal domain(s). Furthermore, we found that the CC2-SAM domain had a strong inhibitory effect on the E3 activity of LRSAM1 in vitro and blocked ubiquitination of TSG101 in vivo; the tandem CC1 domain, but not the individual CC1 domain, could counteract this inhibition. Collectively, our data characterized the self-association of LRSAM1 and showed how its domains may contribute to its overall activity.