Calcium Signaling in Serine ubiquitination and ER remodeling

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Ubiquitination of proteins regulates a number of key cellular processes including protein degradation, endocytosis, translation, innate immunity and DNA repair. Conventional ubiquitination involves the ATP-dependent formation of amide bonds between the ubiquitin C-terminus and primary amines in substrate proteins. Recently, we described an unconventional phosphoribosyl-dependent serine ubiquitination of host substrate by a family of SidE enzymes that act as effector protein of pathogenic Legionella pneumophila. SdeA acts as a catalytic platform that promotes conjugation of phophoribosyl-bridged ubiquitin on substrate serines (PR-ubiquitination). Modification of Ub by PR or ADPR impair the function of eukaryotic cells by inhibiting canonical ubiquitination including mitophagy, DNA repair, TNF signaling and proteasomal degradation. This activity is counteracted by the action of yet another Legionella effector SidJ that shares the genetic locus with the SidEs and opposes their toxicity in yeast and mammalian cells. SidJ is a glutamylase that modifies the catalytic glutamate in the mART domain of SidEs thus blocking their ubiquitin ligase activity. SidJ binding to calmodulin (CaM) and changes in calcium concentrations regulate the glutamylation activity of SidJ. ER-based fluxes of Calcium lead to inhibition of CaM binding to SidJ and thus blocking its glutamylase activity. We determined the cryo-EM structure of SidJ/human apo-CaM complex revealing the architecture of this unique glutamylase. In infected cells, glutamylation of SidEs is detected on the surface of Legionella-containing vacuoles (LCVs) in a SidJ-dependent manner. We have also demonstrated that serine ubiquitination of several ER-resident proteins including FAM134, Lunapark and Tex264 regulate in turn the remodeling and functions of ER. Taken together, calcium signaling may regulate SidE-mediated cellular functions and control protein glutamylation, an understudied protein modification during bacterial infection in eukaryotes.