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The role and mechanism of ubiquitin system in innate immune regulation

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Abstract
Pattern- recognition receptors (PRRs) include the cell surface or endosomal membrane localized Toll-like receptors (TLRs) and the cytoplasmic PRRs such as RIG-I-like receptors (RLRs), NOD-like receptors (NLRs) and cytoplasmic DNA receptors (CDRs). Triggering of PRRs culminates in the transcriptional induction of pro-inflammatory cytokines and type I interferons (IFNs) that coordinate protection against pathogens but require tight control to avert inflammatory diseases. The mechanisms underlying this strict regulation are unclear.

Ubiquitiation is a reversible post-translational modification that controls nearly all cellular processes including the immune system. We identified, H2A deubiquitinase myb-like SWIM and MPN domains 1 (MYSM1) a previously described as a key component of epigenetic signaling machinery as a key negative regulator of the innate immune system that guards against an overzealous self-destructive immune response. In response to microbial stimuli, MYSM1 accumulated in the cytoplasm where it interacted with and inactivated TRAF3 and TRAF6 complexes to terminate TLR, RLR and CDR pathways for pro-inflammatory and type I interferone responses. Consequently, MYSM1 deficiency in mice resulted in hyper-inflammation and enhanced viral clearance but also susceptibility to septic shock.

NOD2, belonging to the intracellular NLR family. A focal point of NOD2 signalling is RIP2, which upon polyubiquitination nucleates the NOD2:RIP2 complex, enabling signaling events leading to inflammation, yet the precise nature and the regulation of the polyubiquitins coordinating this process remains unclear. We show that NOD2 signaling involves conjugation of RIP2 with K63, K48 and M1 polyubiquitin chains as well as with non-canonical K27 chains. Furthermore, we identify MYSM1 as the proximal deubiquitinase that attenuates NOD2- RIP2 complex assembly by selectively removing the K63, M1 and K27 chains. Consequently, MYSM1 deficient mice have unrestrained NOD2- mediated peritonitis and liver injury. Henceforth, this study provide a complete description of the polyubiquitin modifications in the NOD2:RIP2 signalling and reveal MYSM1 as a central negative regulator that prevents excessive inflammation.

In order to overcome the host barrier to infection, some pathogens elude the immune defense by hijacking the ubiquitin system. Francisella tularensis is one of the most infectious bacteria. It employs several mechanisms to evade detection by the innate immune system, but how remains obscure. Here, we showed that Francisella triggers but concomitantly inhibits the TLRs, RLRs and CDRs pathway by inhibiting K63-linked polyubiquitination and assembly of TRAF6 and TRAF3 complexes that control the transcriptional responses of PRRs.

In summary, my work identify MYSM1 as a key negative regulator of the innate immune system. Although, mainly located in the nucleus MYSM1 rapidly amass in the cytoplasm, where it interacts with and inactivates the key PRR signalling complexes. Afterward, MYSM1 undergoes proteaosomal degradation to avert sustained immune suppression. Thus, MYSM1 is part of a highly versatile negative feedback regulatory mechanism, which in response to biological danger is swiftly activated in "on-and-off" manner to restore immune homeostasis. Furthermore, Francisella targets the ubiquitin system to inhibt multiple PRRs hence allowing this bacterium to invade and proliferate in the host without evoking a self- limiting innate immune response.

Keywords
The ubiquitin system, Deubiquitinase, MYSM1, Innate immune regulation Toll-like receptor, RIG-l like receptors, Cytoplasmic DNA receptors, NOD-like receptors, *Francisella tularensis,* Immune subversion

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