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Review

Role of the E3 Ubiquitin Ligase RNF213 in Pathogen Control

Sumit Kumar Matta [1,*] and L. David Sibley [2]

[1] Faculty of Life Sciences and Biotechnology, South Asian University, New Delhi 110068, India
[2] Department of Molecular Microbiology, Washington University School of Medicine, St. Louis, MO 63110, USA
* Correspondence: sumitflsb@sau.int

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Abstract: Ubiquitination is an evolutionarily conserved post-translational modification in eukaryotes that regulates many cellular processes, including proteasomal protein degradation, DNA repair, protein/vesicular trafficking, and the cell cycle. It is also associated with the recognition and restriction of numerous intracellular infections in mammalian cells. Host cells decorate the diverse cytosolic niches of pathogens with mono- or polyubiquitin, a process that correlates with their restriction and clearance in certain cell types. RNF213 is a 591 kDa E3 ubiquitin ligase that has recently been shown to directly ubiquitinate various intracellular pathogens in human cells. Here, we review recent progress regarding the role of RNF213 in pathogen-associated ubiquitination and its downstream effector functions linked to other cell-autonomous innate immunity processes.

Keywords: ubiquitin, RNF213; cell-autonomous immunity; interferons

1. Introduction

Diverse intracellular pathogens of eukaryotic, prokaryotic or viral nature infect host cells primarily to acquire basic biomolecules as a source of nutrition or resources to fuel their replication and proliferation. The interactions between pathogens and host cells form the basis of the field known as host–pathogen interactions, which has gained increasing interest in recent years. At the cellular level, these interactions are complex and can influence the overall relationship between the host and the pathogen. At the organismal level, this can lead to different types of relationships such as mutualism, commensalism, or parasitism [1].

Host cells express inherent cellular defense against intracellular infections through a process called cell-autonomous innate immunity, which restricts pathogenic proliferation and supports host survival. Cell-autonomous innate immunity in mammalian cells counter cytosolic or vacuolar pathogens via different responses including compartmentalizing invading pathogen into non-proliferative environments or vesicles, shunting off their nutritional assimilation, directly damaging their components, and signaling their presence to other immune cells for their eventual clearance by humoral (B-cells) and cell-mediated (T-cell) immunity. In contrast, systemic innate immunity act on the whole organismal level that acts as first line of defense against infections. It primarily relies on inherent recognition of pathogen associate patterns and produces responses such as immune cell recruitment to site of infection, inflammatory signaling and cytokine production to limit expansion of pathogen in the acute infection phase.

2. RING Finger Protein 213

RING (Really Interesting New Gene) [2] Finger Protein 213 or RNF213 is a 591 kDa E3 ubiquitin ligase in humans that was originally identified as a susceptibility gene for moyamoya disease—a rare cerebrovascular condition affecting brain arteries and causing stroke [3]. Molecular mechanism linking RNF213 to cerebrovascular diseases remains poorly defined, apart from some genetic studies associating specific mutations with distinct

pathologies in humans. R4810K variant has a high co-relation with arterial stenosis and strokes within the East Asian population [4], whereas R2438C and A2826T variants co-relate with aneurysms in French-Canadian population [5]. RNF213 knockout in immortalized human cerebral microvascular endothelial cells disrupt their endothelial function and show increased blood-brain barrier permeability, highlighting its role in maintaining cerebrovascular endothelial integrity [6]. However, the precise cellular function and target substrates of this large E3 ubiquitin ligase remain incompletely defined, although its involvement in diverse cellular processes has been characterized since its identification as a major susceptibility factor for a rare genetic disorder of moyamoya disease. Mechanistically, RNF213 was first identified to be involved in removal of adipose triglyceride lipase (ATGL) from lipid bodies (LDs) via its AAA+ domain ATPase activity and RING domain ubiquitin ligase function [7]. Later, a genome-wide shRNA screen has also identified its role in mediating cellular lipotoxicity, in which RNF213 knockdown prevented palmitate-induced cell death in certain human cell types [8]. Interestingly the same study also identified that RNF213 knockdown co-related with decreased ubiquitinylation of NF-kB pathway proteins under lipotoxic stress [8]. All these studies highlight RNF213 as a multifunctional regulator whose cellular function extend beyond its role as a major determinant of a genetic cerebrovascular condition. Increasing evidence reviewed below now points to a central role for RNF213 in cell-autonomous innate immune defense against diverse intracellular pathogens, particularly through its ability of their cytosolic recognition and ubiquitination.

3. Pathogen-Associated Ubiquitination (PAU)

Ubiquitination is a post-translational modification of proteins executed by a hierarchical covalent modification system consisting of three levels of ubiquitin conjugation—Activating E1 enzymes, Conjugating E2 enzymes, and terminal E3 ligases. E1 enzymes (2–4 in number) transfer ubiquitin to E2 enzymes (20–30 in number) and finally to E3 ubiquitin ligases. Eventually, E3 ubiquitin ligases (>600 in number) covalently tag diverse proteins with ubiquitin primarily on their lysine residues. E3 ubiquitin ligases are further classified into different groups—RING finger containing ligases, HECT [2] (Homologous to the E6AP Carboxyl Terminus) - type ligases and RING between RING (RBR) ligases. After conjugating to protein substrates, ubiquitin can also be conjugated to lysine residues of ubiquitin itself forming polyubiquitin chains. Depending on iterative ubiquitin tagging of unique residues (M1, K6, K11, K27, K29, K48 and/or K63), the substrate proteins are marked for different cellular processes and regulated cellular pathways like proteasomal degradation (K48, K11), cellular signaling (K63, M1) [9] etc.

Upon infection of mammalian cells, many intracellular pathogens get decorated by mono- and polyubiquitin molecules that mediate restriction of their intracellular proliferation and survival. Ubiquitination has long been measured using mouse monoclonal antibody FK2 in immunofluorescence assays that primarily recognizes mono- and polyubiquitin structures on the pathogen or its vacuolar niche [10,11]. Additionally, fluorescent reporters of ubiquitination have been made in mammalian cell lines [12], however study of real time ubiquitination of intracellular pathogens or their niches is still lacking.

Host E3 ubiquitin ligases play critical role in regulation of many aspects of innate and cell-autonomous immunity including pattern recognition receptor signaling (Toll like receptors, TLRs), cytosolic pathogen recognition (DNA sensor cGAS—cyclic GMP-AMP synthase; RNA sensor RIG-I—Retinoic acid-inducible gene I), and downstream responsive cellular signaling (Nuclear factor kappa B or NF-kB). Additionally, direct targeting of intracellular pathogens by E3 ubiquitin ligases has been an emerging field of investigation in cell biology and immunology. Ubiquitination as a host recognition response was first identified in *Salmonella* infection that highlighted its role in cell-autonomous defense [13]. Global proteomic analysis of human and *Salmonella* proteins during infection have identified many ubiquitinated membrane bound effector proteins of *Salmonella*, although the majority of observed changes occur in the human ubiquitome [14].

Ubiquitination is often correlated with proteasomal degradation of proteins. Ubiquitination of *Salmonella* in host cells is also associated with proteasomal staining [13]. Pathogen associated ubiquitination is often a mix of different kinds of poly-ubiquitin chains that primarily include M1, K48, and K63 modifications that are critical in restriction of pathogens like *Toxoplasma gondii* [15]. Recent findings show different intracellular ubiquitinated bacteria (*Streptococcus pneumoniae* and *Salmonella enterica*) associated with host AAA-ATPase VCP/p97 leading to their clearance via mechanical lysis by removal of their membrane proteins [16].

4. Emergence of Human RNF213 as Defense Factor against Diverse Pathogens

Despite reports of cytosolic pathogens being labelled by ubiquitin, only recently have studies defined the specific E3 ligases involved. Analysis of co-immunoprecipitated proteins with ubiquitinated LPS from *Salmonella* identified a ~600 kDa cognate E3 ubiquitin ligase RNF213 that was responsible for labeling [17]. Thereafter, there

have been emerging reports of involvement of RNF213 in ubiquitination of varied intracellular pathogens including *Listeria* [18], *Chlamydia* [19], *Toxoplasma* [20,21], and *Shigella* [22]. Apart from involvement in controlling prokaryotic and eukaryotic intracellular infections, RNF213 has also been involved in controlling different viral infections like herpes simplex virus 1 (HSV-1), human respiratory syncytial virus (RSV), coxsackievirus B3 [18] and vesicular stomatitis virus [21]. Shorter RNF213 isoform (Isoform 2) was recently shown to restrict Zika virus infection by directly targeting viral proteins for degradation [23]. During Influenza A virus infection, the antiviral activity of RNF213 operates through amplification of interferon production, mediated by its interaction with melanoma-differentiation-associated gene 5 (MDA5) and its subsequent K63-linked polyubiquitination [24]. The same study also shows that RNF213 directly targets the influenza nucleoprotein (NP) for proteasomal degradation via K48-linked polyubiquitination [24]. RNF213 recruitment kinetics to the pathogenic vacuole (*Toxoplasma*) occurs in a rate limited cooperative manner [25], which also suggests presence of a tightly regulated process of recognition of host-pathogen interface. Recruitment to such diverse pathogens and their distinct cytosolic niches suggests a broad-spectrum role for RNF213 in regulating common downstream host processes and/or targeting multiple pathogen derived cytosolic exposed substrates. RNF213 role in removal of lipase from lipid droplets [7] also suggests its direct involvement in regulating the cytosolic expansion of pathogen containing compartments, which may contribute to their proliferation and growth.

RNF213 is constitutively expressed but is also an interferon stimulated gene (ISG), expressed downstream of both type I and II interferons (IFNs) in human cells. Induction of RNF213 is involved in control of *Toxoplasma gondii* infection downstream of both IFNs in human macrophages [21]. Critical residues in the ATPase domain and C-terminal ubiquitinylating domain are also involved in recruitment to and ubiquitination of intracellular pathogens [17,21]. Recent findings show that cellular ATP levels directly co-relate with RNF213 activity against pathogens via linking of its AAA+ ATPase activity with its E3 ubiquitin ligase function [26].

Different bacterial virulence effectors have also been identified that counteract RNF213 mediated restriction of pathogens -like IpaH1.4 of *Shigella* target RNF213 for proteasomal degradation thereby preventing its E3 ligase activity on LPS [22]. Similarly, esterase TssM of *Burkholderia* remove RNF213 mediated LPS ubiquitination [27]. GarD of *Chlamydia* prevent recruitment of RNF213 to its resident inclusion bodies by a yet unknown mechanism [19]. Like ubiquitin, ISG15 or Interferon-Stimulated Gene 15 is also a protein that gets covalently linked to different proteins as a post-translational modification to regulate their function. Although, there is still no clear elucidated role of ISG15 under intracellular infections, RNF213 has been observed to interact with ISGylated proteins [18]. RNF213 interaction with ISGylated proteins promotes its ISGylation and oligomerization on lipid droplets downstream of interferon stimulation, a process that correlates with its antimicrobial activity against *Listeria monocytogenes*, herpes simplex virus 1, human respiratory syncytial virus, and coxsackievirus B3 [18].

RNF213 restricts a range of viral infections, although it remains unclear whether it exerts this anti-viral function via modulation of the host vesicular structures or interaction with of any viral macromolecular structure. For prokaryotic and eukaryotic infections, both cytosol exposed and intravacuolar pathogens get decorated with RNF213 and polyubiquitin chains. In *Salmonella*, LPS on the bacterial surface is an established target of RNF213 E3 ubiquitin ligase activity [17]. On the contrary, in eukaryotic *Toxoplasma* infection, there is still no evidence that RNF213 or its E3 ligase activity crosses the parasitophorous vacuolar membrane (PVM) to the parasite. This is in contrast to action of guanylate binding proteins (GBPs), which get recruited to *Toxoplasma* membrane after rupturing the PVM in murine cells [28].

5. PAU Linked Cell-Autonomous Defense Processes

Ubiquitination of intracellular pathogens also leads to recruitment of other cellular factors like autophagy adaptors, signaling transducers, cytosolic sensors etc. [29]. Recruitment of RNF213 to diverse pathogens correlates with its ability to ubiquitinylate their cytosolic niches, leading to pathogen restriction. Despite similarities in RNF213 recruitment, the downstream mechanisms of restriction vary among pathogens. For example, the restriction of *Salmonella* involves direct ubiquitination of its outer membrane proteins [14] and activation of host autophagy [30]. RNF213 has also been shown to interact with and regulate the nuclear translocation of Forkhead Box Protein O1 (FOXO1) transcription factor that leads to expression of metabolic and cell cycle genes [31]. Direct RNF213 mediated proteasomal degradation of Replication and Transcription Activator (RTA) of Kaposi's sarcoma-associated herpesvirus (KSHV) and murine gammaherpesvirus 68 (MHV-68) via K48 linked ubiquitination restrict their infections [32].

Other E3 ligases such as RNF166 also play a critical role in pathogen associated ubiquitination by promoting the recruitment of autophagy adaptors like p62 and NDP52 to intracellular bacteria like *Salmonella*, *Listeria* and *Shigella*, showing how ubiquitination acts upstream of adaptor assembly and cargo recognition [33].

Ubiquitination of intracellular bacteria act as "eat-me signals" that trigger their selective cytosolic engulfment or autophagy called as "Xenophagy". Ubiquitination is recognized by different host proteins like p62, NDP52/CALCOCO2, and optineurin, which link ubiquitinated pathogens to LC3-positive membranes and drive their autophagic clearance. Host TBK1 is a critical adaptor that primarily promote autophagic mediated anti-microbial cell-autonomous defense [34]. Importantly, ubiquitin chains of different linkages like K48 and K63 can independently recruit critical regulators such as TBK1 [30], leading to amplification of antibacterial signaling and restriction of pathogenic growth and survival. This redundancy in ubiquitin mediated recognition and downstream signaling maintains robustness across different host defense even when pathogens attempt to evade individual pathways.

6. Pathogenic Ubiquitination in Immune Signaling

In contrast to direct damage or degradation of proteins at the host-pathogen interface, the role of ubiquitination in cytosolic immunity is primarily due to downstream responses upon pathogen recognition receptor (PRRs) signaling. Signal transduction from PRRs occurs through adaptor proteins and involves extensive regulation by ubiquitination. In TLR signaling, MyD88-dependent pathways recruit IRAK kinases (Interleukin-1 receptor-associated kinases; IRAK4, IRAK1, IRAK2), leading to activation of TRAF6 (TNF receptor associated factor 6), which is an E3 ubiquitin ligase that mediates K63 linked polyubiquitination, a modification essential for downstream signaling [35].

This ubiquitination event serves as a scaffold for the recruitment and activation of the kinase TAK1 (Transforming growth factor-β-activated kinase 1), which activates the IKK (IkappaB kinase) complex and MAP (Mitogen Activated Protein) kinase pathways (c-Jun N-terminal kinase or JNK, p38), ultimately inducing NF-kB and AP-1 (Activator Protein 1) dependent proinflammatory gene expression [35]. TRIF (Tor/interleukin receptor or TIR domain containing adapter inducing interferon-b) dependent pathway that is downstream of TLR3 and TLR4 activation, in which RIP1 (Receptor Interacting Protein 1) undergoes K63 linked polyubiquitination leading to inflammatory signaling via recruitment of TAK1 and IKK complexes [36]. Similarly, in NLR (Nucleotide binding domain and Leucine rich repeat containing) signaling, NOD1 (Nucleotide binding oligomerization domain containing 1) and NOD2 adaptor RIP2 (Receptor Interacting Protein 2) is also ubiquitinated via K63 linked polyubiquitin chains, that in turn leads to activation of NF-kB and MAPKs [37]. RLR (RIG-1 like receptors) signaling pathways also involve ubiquitin-regulated mechanisms. Although MAVS (Mitochondrial Antiviral-Signaling protein) serves as the primary adaptor, TRAF family proteins (notably TRAF3, TRAF2, TRAF5, and TRAF6) participate in signaling, and many of these proteins function as E3 ubiquitin ligases or are themselves ubiquitinated during activation, contributing to interferon induction and inflammatory responses [38].

Overall, in PRRs signaling, ubiquitin modifications of host factors are not degradative but instead function as signaling platforms that amplify innate immune responses, linking PRR activation to downstream kinase cascades and cytokine production.

7. Conclusions and Future Perspectives

Prokaryotic, eukaryotic and viral pathogens infect host cells for their growth and proliferation, triggering host cell-autonomous immunity programs that act to limit and restrict infection. Pathogen associated ubiquitination acts as a central regulator of cell autonomous immunity, integrating multiple antimicrobial defense processes within the cell. It enables the marking of intracellular pathogens for restriction, promotes the recruitment of host adaptor proteins, and activates immune and inflammatory signaling pathways. Together, these events ensure efficient recognition and clearance of invading pathogens (Figure 1).

RNF213 is a large RING-type E3 ligase that was first identified as a susceptibility factor to cerebrovascular pathologies in moyamoya disease. However, its role has since been characterized in various cellular processes like lipid metabolism, lipotoxic stress, and regulation of NF-kB signaling. More remarkably, RNF213 has been found to be recruited to a wide range of intracellular pathogens, where it mediates ubiquitination either directly on pathogen associated molecules or on host derived membranes at the host-pathogen interface. Its role in cell-autonomous innate immunity became evident when it was co-immunoprecipitated with ubiquitinated LPS from *Salmonella*. Thereafter, its broad-spectrum ability to modify diverse intracellular pathogens including *Listeria*, *Chlamydia*, *Toxoplasma*, *Shigella*, and several viruses have strongly established its role as cell-autonomous innate immunity factor in humans. RNF213 activity significantly depends on its AAA+ ATPase and C-terminal ubiquitin ligase domains and is tightly regulated by cellular ATP levels and interferon signaling. In response to this host defense pathway, pathogens secrete different effectors that degrade, deubiquitinate, or inhibit RNF213 mediated degradation of their proteins to evade restriction.

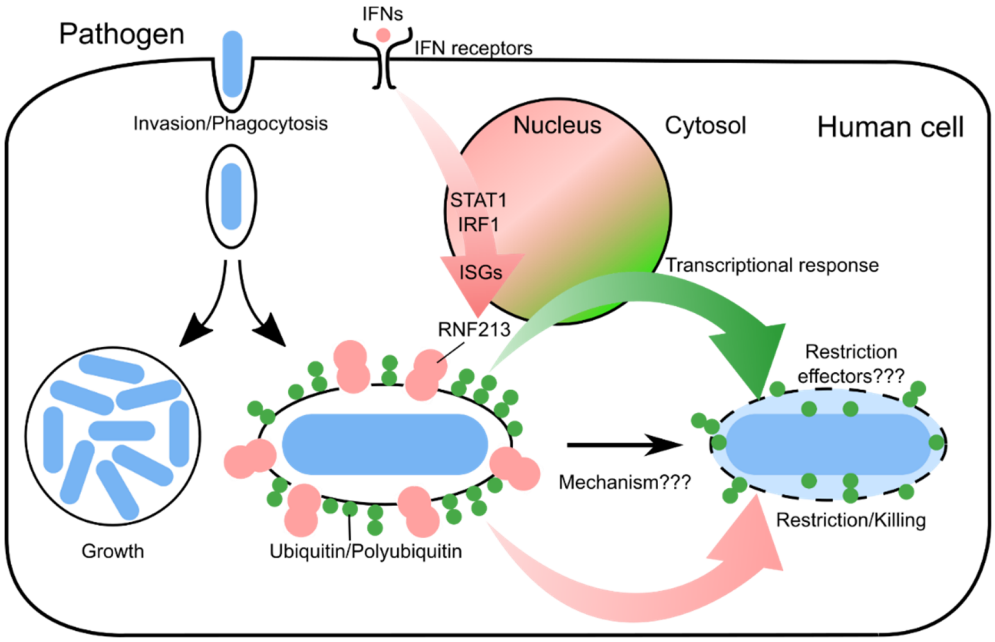

Figure 1. RNF213 mediated pathogen associated ubiquitination and control of intracellular pathogens. RNF213 is an Interferon Stimulated Gene (ISG) downstream of both type I and II IFNs. Like other ISGs, RNF213 expression is driven by nuclear localization and activity of STAT1 and IRF1 transcription factors. RNF213 gets recruited to the cytosolic niche of intracellular pathogens- either to their exposed surfaces or associated vesicular membranes, mediating their mono/poly-ubiquitination resulting in their restriction.

Ubiquitination of prokaryotic and eukaryotic pathogens can occur on the membranes of their vacuolar niches (PVM in *Toxoplasma*), or directly to their surfaces in case of cytosolic exposure (LPS on *Salmonella*). This versatility suggests that RNF213 functions as an upstream regulator of a conserved defense response across phylogenetically diverse pathogens, enabling human cells to sense and recruit on to the intracellular pathogens irrespective of their cytosolic exposure. Such spatially restricted activity reflects a tightly controlled cellular process rather than nonspecific protein modification.

Despite these advances, the molecular mechanisms underlying RNF213 function remain poorly defined. In particular, its direct substrates during infection are not well characterized. It is unclear whether RNF213 primarily targets pathogen derived components, host factors, or a combination of both. Resolving this question will be essential to understand how ubiquitination at the host–pathogen interface drives downstream antimicrobial phenotypes.

Another critical area of investigation is the regulation of RNF213 activity. It is likely subject to multiple upstream signals that control its recruitment and function, potentially involving pathogen sensing pathways, metabolic states, and post translational modifications. In addition, its interplay with other ubiquitin ligases remains largely unexplored, but may be important for generating specific ubiquitin chain architectures required for distinct defense pathways.

Given its involvement in diverse infections and disease contexts, RNF213 represents a promising target for therapeutic intervention, with potential to enhance host defense or its modulation at the cellular level.

Author Contributions

S.K.M. and L.D.S. conceptualized the content, reviewed the literature, analyzed the data, wrote, edited, and proofread the manuscript All authors have read and agreed to the published version of the manuscript.

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Conflicts of Interest

The authors declare no conflict of interests.

Use of AI and AI-Assisted Technologies

No AI tools were utilized for this paper.

References

1. Casadevall, A.; Pirofski, L. The Damage-Response Framework of Microbial Pathogenesis. *Nat. Rev. Microbiol.* **2003**, *1*, 17–24. https://doi.org/10.1038/nrmicro732.
2. Metzger, M.B.; Hristova, V.A.; Weissman, A.M. HECT and RING Finger Families of E3 Ubiquitin Ligases at a Glance. *J. Cell Sci.* **2012**, *125 Pt 3*, 531–537. https://doi.org/10.1242/jcs.091777.
3. Kamada, F.; Aoki, Y.; Narisawa, A.; et al. A Genome-Wide Association Study Identifies RNF213 as the First Moyamoya Disease Gene. *J. Hum. Genet.* **2011**, *56*, 34–40. https://doi.org/10.1038/jhg.2010.132.
4. Okazaki, S.; Morimoto, T.; Kamatani, Y.; et al. Moyamoya Disease Susceptibility Variant RNF213 p.R4810K Increases the Risk of Ischemic Stroke Attributable to Large-Artery Atherosclerosis. *Circulation* **2019**, *139*, 295–298. https://doi.org/10.1161/CIRCULATIONAHA.118.038439.
5. Zhou, S.; Ambalavanan, A.; Rochefort, D.; et al. RNF213 Is Associated with Intracranial Aneurysms in the French-Canadian Population. *Am. J. Hum. Genet.* **2016**, *99*, 1072–1085. https://doi.org/10.1016/j.ajhg.2016.09.001.
6. Roy, V.; Ross, J.P.; Pépin, R.; et al. Moyamoya Disease Susceptibility Gene RNF213 Regulates Endothelial Barrier Function. *Stroke* **2022**, *53*, 1263–1275. https://doi.org/10.1161/STROKEAHA.120.032691.
7. Sugihara, M.; Morito, D.; Ainuki, S.; et al. The AAA+ ATPase/Ubiquitin Ligase Mysterin Stabilizes Cytoplasmic Lipid Droplets. *J. Cell Biol.* **2019**, *218*, 949–960. https://doi.org/10.1083/jcb.201712120.
8. Piccolis, M.; Bond, L.M.; Kampmann, M.; et al. Probing the Global Cellular Responses to Lipotoxicity Caused by Saturated Fatty Acids. *Mol. Cell* **2019**, *74*, 32–44.e8. https://doi.org/10.1016/j.molcel.2019.01.036.
9. Akutsu, M.; Dikic, I.; Bremm, A. Ubiquitin Chain Diversity at a Glance. *J. Cell Sci.* **2016**, *129*, 875–880. https://doi.org/10.1242/jcs.183954.
10. Fujimuro, M.; Sawada, H.; Yokosawa, H. Production and Characterization of Monoclonal Antibodies Specific to Multi-Ubiquitin Chains of Polyubiquitinated Proteins. *FEBS Lett.* **1994**, *349*, 173–180. https://doi.org/10.1016/0014-5793(94)00647-4.
11. Haldar, A.K.; Foltz, C.; Finethy, R.; et al. Ubiquitin Systems Mark Pathogen-Containing Vacuoles as Targets for Host Defense by Guanylate Binding Proteins. *Proc. Natl. Acad. Sci. USA* **2015**, *112*, E5628–E5637. https://doi.org/10.1073/pnas.1515966112.
12. Dantuma, N.P.; Lindsten, K.; Glas, R.; et al. Short-Lived Green Fluorescent Proteins for Quantifying Ubiquitin/Proteasome-Dependent Proteolysis in Living Cells. *Nat. Biotechnol.* **2000**, *18*, 538–543. https://doi.org/10.1038/75406.
13. Perrin, A.J.; Jiang, X.; Birmingham, C.L.; et al. Recognition of Bacteria in the Cytosol of Mammalian Cells by the Ubiquitin System. *Curr. Biol.* **2004**, *14*, 806–811. https://doi.org/10.1016/j.cub.2004.04.033.
14. Fiskin, E.; Bionda, T.; Dikic, I.; et al. Global Analysis of Host and Bacterial Ubiquitinome in Response to Salmonella Typhimurium Infection. *Mol. Cell* **2016**, *62*, 967–981. https://doi.org/10.1016/j.molcel.2016.04.015.
15. Clough, B.; Wright, J.D.; Pereira, P.M.; et al. K63-Linked Ubiquitination Targets Toxoplasma Gondii for Endo-Lysosomal Destruction in IFNγ-Stimulated Human Cells. *PLoS Pathog.* **2016**, *12*, e1006027. https://doi.org/10.1371/journal.ppat.1006027.
16. Ghosh, S.; Roy, S.; Baid, N.; et al. Host AAA-ATPase VCP/P97 Lyses Ubiquitinated Intracellular Bacteria as an Innate Antimicrobial Defence. *Nat. Microbiol.* **2025**, *10*, 1099–1114. https://doi.org/10.1038/s41564-025-01984-y.
17. Otten, E.G.; Werner, E.; Crespillo-Casado, A.; et al. Ubiquitylation of Lipopolysaccharide by RNF213 during Bacterial Infection. *Nature* **2021**, *594*, 111–116. https://doi.org/10.1038/s41586-021-03566-4.
18. Thery, F.; Martina, L.; Asselman, C.; et al. Ring Finger Protein 213 Assembles into a Sensor for ISGylated Proteins with Antimicrobial Activity. *Nat. Commun.* **2021**, *12*, 5772. https://doi.org/10.1038/s41467-021-26061-w.
19. Walsh, S.C.; Reitano, J.R.; Dickinson, M.S.; et al. The Bacterial Effector GarD Shields Chlamydia Trachomatis Inclusions from RNF213-Mediated Ubiquitylation and Destruction. *Cell Host Microbe* **2022**, *30*, 1671–1684.e9. https://doi.org/10.1016/j.chom.2022.08.008.
20. Hernandez, D.; Walsh, S.; Saavedra Sanchez, L.; et al. Interferon-Inducible E3 Ligase RNF213 Facilitates Host-Protective Linear and K63-Linked Ubiquitylation of Toxoplasma Gondii Parasitophorous Vacuoles. *mBio* **2022**, *13*, e0188822. https://doi.org/10.1128/mbio.01888-22.
21. Matta, S.K.; Kohio, H.P.; Chandra, P.; et al. Genome-Wide and Targeted CRISPR Screens Identify RNF213 as a Mediator of Interferon Gamma-Dependent Pathogen Restriction in Human Cells. *Proc. Natl. Acad. Sci. USA* **2024**, *121*, e2315865120. https://doi.org/10.1073/pnas.2315865120.

22. Naydenova, K.; Boyle, K.B.; Pathe, C.; et al. Shigella Flexneri Evades LPS Ubiquitylation through IpaH1.4-Mediated Degradation of RNF213. *Nat. Struct. Mol. Biol.* **2025**, *32*, 1741–1751. https://doi.org/10.1038/s41594-025-01530-8.
23. Yang, X.; Chen, T.; Ren, B.; et al. RNF213 Isoform 2 Restricts Zika Virus through Antiviral Signaling and Viral Protein Degradation. *iScience* **2026**, *29*, 116284. https://doi.org/10.1016/j.isci.2026.116284.
24. Li, H.; Zhang, Y.; Wang, J.; et al. RNF213 Is an Interferon-Stimulated Gene That Targets Influenza A Virus NP and Activates MDA5 to Restrict Infection. *Adv. Sci.* **2026**, *13*, e11012. https://doi.org/10.1002/advs.202511012.
25. Crespillo-Casado, A.; Pothukuchi, P.; Naydenova, K.; et al. Recognition of Phylogenetically Diverse Pathogens through Enzymatically Amplified Recruitment of RNF213. *EMBO Rep.* **2024**, *25*, 4979–5005. https://doi.org/10.1038/s44319-024-00280-w.
26. Ahel, J.; Balci, A.; Faas, V.; et al. ATP Functions as a Pathogen-Associated Molecular Pattern to Activate the E3 Ubiquitin Ligase RNF213. *Nat. Commun.* **2025**, *16*, 4414. https://doi.org/10.1038/s41467-025-59444-4.
27. Szczesna, M.; Huang, Y.; Lacoursiere, R.E.; et al. Bacterial Esterases Reverse Lipopolysaccharide Ubiquitylation to Block Host Immunity. *Cell Host Microbe* **2024**, *32*, 913–924.e7. https://doi.org/10.1016/j.chom.2024.04.012.
28. Kravets, E.; Degrandi, D.; Ma, Q.; et al. Guanylate Binding Proteins Directly Attack Toxoplasma Gondii via Supramolecular Complexes. *eLife* **2016**, *5*, e11479. https://doi.org/10.7554/eLife.11479.
29. Manzanillo, P.S.; Ayres, J.S.; Watson, R.O.; et al. The Ubiquitin Ligase Parkin Mediates Resistance to Intracellular Pathogens. *Nature* **2013**, *501*, 512–516. https://doi.org/10.1038/nature12566.
30. Thurston, T.L.; Boyle, K.B.; Allen, M.; et al. Recruitment of TBK1 to Cytosol-Invading Salmonella Induces WIPI2-Dependent Antibacterial Autophagy. *EMBO J.* **2016**, *35*, 1779–1792. https://doi.org/10.15252/embj.201694491.
31. Yang, X.; Zhu, X.; Sheng, J.; et al. RNF213 Promotes Treg Cell Differentiation by Facilitating K63-Linked Ubiquitination and Nuclear Translocation of FOXO1. *Nat. Commun.* **2024**, *15*, 5961. https://doi.org/10.1038/s41467-024-50392-z.
32. Tian, H.; Yu, K.; He, L.; et al. RNF213 Modulates γ-Herpesvirus Infection and Reactivation via Targeting the Viral Replication and Transcription Activator. *Proc. Natl. Acad. Sci. USA* **2023**, *120*, e2218825120. https://doi.org/10.1073/pnas.2218825120.
33. Heath, R.J.; Goel, G.; Baxt, L.A.; et al. RNF166 Determines Recruitment of Adaptor Proteins during Antibacterial Autophagy. *Cell Rep.* **2016**, *17*, 2183–2194. https://doi.org/10.1016/j.celrep.2016.11.005.
34. Pilli, M.; Arko-Mensah, J.; Ponpuak, M.; et al. TBK-1 Promotes Autophagy-Mediated Antimicrobial Defense by Controlling Autophagosome Maturation. *Immunity* **2012**, *37*, 223–234. https://doi.org/10.1016/j.immuni.2012.04.015.
35. Cohen, P.; Strickson, S. The Role of Hybrid Ubiquitin Chains in the MyD88 and Other Innate Immune Signalling Pathways. *Cell Death Differ.* **2017**, *24*, 1153–1159. https://doi.org/10.1038/cdd.2017.17.
36. Cusson-Hermance, N.; Khurana, S.; Lee, T.H.; et al. Rip1 Mediates the Trif-Dependent Toll-like Receptor 3- and 4-Induced NF-κB Activation but Does Not Contribute to Interferon Regulatory Factor 3 Activation. *J. Biol. Chem.* **2005**, *280*, 36560–36566. https://doi.org/10.1074/jbc.M506831200.
37. Yang, Y.; Yin, C.; Pandey, A.; et al. NOD2 Pathway Activation by MDP or Mycobacterium Tuberculosis Infection Involves the Stable Polyubiquitination of Rip2. *J. Biol. Chem.* **2007**, *282*, 36223–36229. https://doi.org/10.1074/jbc.M703079200.
38. Liu, S.; Chen, J.; Cai, X.; et al. MAVS Recruits Multiple Ubiquitin E3 Ligases to Activate Antiviral Signaling Cascades. *eLife* **2013**, *2*, e00785. https://doi.org/10.7554/eLife.00785.