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Role of Ubiquitin in combating against antibiotic resistant Bacteria

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ABSTRACT

Antibiotic resistance poses a significant global health threat, necessitating the exploration of novel therapeutic strategies. This review examines the intricate interplay between the host ubiquitin-proteasome system (UPS) and bacterial pathogens, emphasizing its potential as a target for host-directed therapies. The UPS plays a pivotal role in modulating immune responses and regulating cellular processes critical for pathogen clearance. Bacterial pathogens have evolved sophisticated mechanisms to subvert UPS functions, thereby enhancing their survival and virulence. Targeting specific components of the UPS, such as deubiquitinating enzymes and ubiquitin-like systems, offers promising avenues for therapeutic intervention. Additionally, leveraging targeted protein degradation technologies may provide novel strategies to disrupt bacterial resistance mechanisms. While challenges related to specificity and off-target effects remain, the modulation of the UPS presents a multifaceted approach to combating antibiotic-resistant infections. Continued interdisciplinary research is essential to elucidate the underlying molecular mechanisms and translate these insights into effective clinical interventions.

INTRODUCTION:

Antimicrobial resistance (AMR) is a global issue affecting countries at all income levels, driven by misuse and overuse of antibiotics in human medicine, agriculture, and animal farming.[1] This leads to the emergence of resistant bacteria, fungi, and viruses, reducing treatment effectiveness and resulting in longer hospital stays, increased medical costs, and higher mortality rates.[2] The rapid spread of resistant bacteria worldwide threatens to undermine significant medical advances achieved over the past century.[3] The history of antibiotic discovery and the emergence of resistance reveals a concerning trend, with resistance often following relatively quickly as new antibiotics are introduced.[4]

The ubiquitin-proteasome system (UPS) is a crucial regulatory pathway in eukaryotic cells, controlling protein degradation and maintaining cellular homeostasis.[5] It involves a sequential enzymatic cascade to tag target proteins with ubiquitin, marking them for degradation by the 26S proteasome.[6] The UPS regulates various cellular functions, including epigenetics, gene expression, cell cycle progression, and signal transduction.[7] Dysregulation of the UPS has been implicated in diseases like cancer, neurodegenerative disorders, autoimmune diseases, and cardiovascular diseases.[8] Therapeutic strategies targeting the UPS to treat diseases are essential

Ubiquitin signalling is crucial in the interaction between bacterial pathogens and their hosts, influencing the immune response and infection outcomes. The host ubiquitin system is essential for detecting and clearing bacteria, activating innate immune responses, and regulating DNA damage response during viral infections. [9] Bacterial pathogens

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manipulate the host ubiquitin system to promote their survival and dissemination by encoding E3 ligases and deubiquitinases, targeting host signalling pathways, modulating autophagy, and reversing lipopolysaccharide ubiquitylation. These strategies aim to manipulate the host ubiquitin system and disrupt immune responses.The aim of this review article is investigate the role of the ubiquitin in the combat against antibiotic resistant bacteria.[10]

The Ubiquitin-Proteasome System (UPS)

The ubiquitin-proteasome system (UPS) is a crucial mechanism for regulated protein degradation in eukaryotic cells, essential for maintaining cellular homeostasis and eliminating old, damaged, misfolded, or regulatory proteins.[11] The UPS machinery consists of several key components, including the Ubiquitin Activating Enzyme (E1), Ubiquitin-Conjugating Enzymes (E2), Ubiquitin Ligases (E3), the 26S Proteasome, and Deubiquitinating Enzymes (DUBs).[12] E1 activates ubiquitin through an ATP-dependent reaction, forming a high-energy thioester bond between E1 and ubiquitin. E2 enzymes accept ubiquitin from E1 and hold it in a thioester-linked form. E3 ligases recognize specific protein substrates and facilitate the transfer of ubiquitin from E2 to lysine residues on the substrate protein.[13] The 26S proteasome is a large, multi-subunit complex responsible for degrading poly-ubiquitinated proteins.[14] Deubiquitinating Enzymes (DUBs) reverse ubiquitination by removing ubiquitin chains from target proteins and recycling ubiquitin molecules for reuse.[15,16] The ubiquitination process involves a cascade of enzymatic reactions, including ubiquitin activation, ubiquitin conjugation, substrate recognition and ligation, and multiple rounds of ubiquitination.[15]

The 26S proteasome is a large, multi-subunit protease complex essential for regulated protein degradation in eukaryotic cells. It plays a crucial role in various cellular processes, including protein homeostasis, stress response, cell division, and signal transduction. The 26S proteasome is the primary component of the ubiquitin-proteasome system (UPS), responsible for degrading proteins tagged with ubiquitin.[17] The proteasome consists of two main subcomplexes: the 20S core particle (CP) and the 19S regulatory particle (RP). The CP contains the proteolytic active sites, while the 19S RP recognizes and prepares ubiquitinated proteins for degradation. The 20S proteasome can degrade oxidized proteins even without the 19S RP. The 19S RP recognizes polyubiquitinated proteins, unfolds them, and translocates them into the 20S core particle. The proteasome's primary function is to degrade ubiquitinated proteins in a regulated manner. The proteasome's structure is barrel-shaped and consists of 33 different subunits.[18]

The Unfolded Protein Response (UPR) is a crucial quality control mechanism in cells, removing old, damaged, misfolded, or regulatory proteins to prevent cellular toxicity and aggregation diseases. It oversees the assembly of protein complexes and induces the degradation of defective complexes.[19] The UPS identifies misfolded proteins and targets them for degradation, ensuring proper composition and architecture of multimeric protein complexes. It also regulates mitochondrial function and efficiency, ensuring proper cell division.[20] The UPS regulates signal transduction pathways by modulating key regulatory proteins, fine-tuning cellular responses to stimuli. It also regulates hormone-responsive gene expression profiles, regulating immune signalling, and cell cycle control.[21] The UPS plays a crucial role in both innate and adaptive immune responses, affecting antigen presentation, T cell activation, and B cell activation. It also regulates inflammatory responses by targeting key signalling proteins. [22, 23] The UPS and autophagy are interconnected quality control systems that work together to maintain cellular homeostasis. [24] When the UPS is impaired, autophagy can step in to degrade ubiquitinated proteins and maintain cellular health.

Ubiquitin Signalling in Host Defense Against Bacterial Infections

The ubiquitin system is a crucial mechanism for host cells to recognize and respond to bacterial pathogens. It activates inflammation and degrades bacterial effectors, providing protection. The process is complex, involving various steps from pathogen recognition to cellular responses. Ubiquitination activates innate immunity, targets pathogen-containing vacuoles, facilitates autophagy, and regulates protein function. However, pathogens can manipulate the ubiquitin system to promote their survival. They can escape host responses, exploit the host ubiquitin system, interfere with ubiquitin-like pathways, and reverse ubiquitylation, blocking host immunity. Examples of ubiquitin-related interactions include Salmonella Typhimurium, Legionella pneumophila, and Mycobacterium tuberculosis. [25]

Ubiquitination is a regulatory mechanism in innate immunity, influencing pathogen recognition, immune signalling pathways, and autophagy. It is involved in the recognition of bacterial PAMPs, which induce inflammatory responses to ensure host defense. PRRs like Toll-like receptors (TLRs) and NOD-like receptors (NLRs) recognize these PAMPs, triggering intracellular signalling cascades that lead to the expression of inflammatory cytokines and interferons. [26] Ubiquitination directly regulates PRR activation and signalling, such as the recruitment of E3 ubiquitin ligases PUB12 and PUB13 to the FLS2 receptor complex upon flagellin detection in Arabidopsis.[27] Ubiquitination also regulates various immune

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signalling pathways, such as the linear ubiquitin chain assembly complex (LUBAC) and E3 ubiquitin ligases like RNF128, which promote innate antiviral immunity through K63-linked ubiquitination of TBK1. [28] Deubiquitinating enzymes (DUBs) play a critical role in regulating innate antiviral immunity. Pathogens can manipulate the host's ubiquitination system to evade immune responses, such as Herpesviruses. Understanding these complex interactions is vital for developing new therapeutic strategies against infectious diseases. [29]

Autophagy and xenophagy are essential cellular processes that rely on ubiquitin-dependent pathways to target and degrade intracellular components and bacteria. [30] Ubiquitination is a post-translational modification where ubiquitin is attached to target proteins, facilitating the degradation of proteins. Selective autophagy receptors (SARs) recognize ubiquitinated cargo and facilitate their engulfment by autophagosomes.[31] Xenophagy targets intracellular bacteria for degradation, which is critical for host defense against bacterial infections. Ubiquitination also regulates the autophagy machinery itself, controlling the stability and activity of autophagy-related proteins (ATGs) [32] Viral modification of autophagy can be manipulated by viruses, with some expressing proteins that inhibit autophagy or exploit autophagy for replication and transmission. [33] Understanding these pathways is crucial for developing therapeutic strategies to target diseases like neurodegenerative disorders, cancer, and infectious diseases.[34]

Exploiting the UPS to Combat Antibiotic Resistance

The ubiquitin-proteasome system (UPS) is a critical cellular mechanism that regulates protein degradation and maintains cellular homeostasis. Recent studies have highlighted the potential of exploiting the UPS to combat antibiotic resistance by targeting bacterial factors and modulating host pathways.[35] Manipulating the UPS can enhance host defense, degrade resistance-conferring bacterial proteins, and leverage small molecules or antibodies to disrupt resistance mechanisms.[36]

Host-targeted therapies (HTTs) that inhibit deubiquitinating enzymes (DUBs) such as USP25, USP46, and Otud7b have shown promise in enhancing bacterial clearance. For instance, the DUB inhibitor AZ-1 has been demonstrated to reduce intracellular loads of multidrug-resistant bacteria and improve outcomes in infection models, particularly when combined with antibiotics. These findings suggest that modulating host UPS components can bolster the host's immune response, thereby aiding in the elimination of resistant pathogens.[37, 38]

Conversely, some bacteria employ effectors that mimic UPS components, such as E3 ligases and F-box domains, to degrade host resistance proteins, thereby subverting immune defenses and promoting infection. This molecular mimicry underscores the dynamic interplay between pathogens and the host UPS, highlighting the need for therapeutic strategies that can disrupt these interactions.[39] Additionally, advancements in targeted protein degradation (TPD) technologies, such as PROTACs, offer the potential to direct bacterial resistance proteins for ubiquitination and degradation, further expanding the arsenal against antibiotic resistance.[40]

In conclusion, targeting the UPS represents a multifaceted approach to overcoming antibiotic resistance. By inhibiting host DUBs, directing bacterial resistance proteins for degradation, and developing small molecules that manipulate ubiquitin signaling, these strategies can enhance host defense and may be combined with traditional antibiotics for improved efficacy against resistant pathogens. [41] Continued research and development in this area hold promise for novel therapeutic interventions in the fight against antibiotic-resistant infections.

Bacterial Evasion Strategies

Bacterial pathogens, including antibiotic-resistant strains, have evolved sophisticated mechanisms to subvert the host's immune defenses, often by targeting the ubiquitin-proteasome system (UPS). The UPS plays a pivotal role in regulating immune responses by mediating the degradation of key signaling proteins. By manipulating this system, bacteria can evade immune detection, persist within the host, and resist clearance, thereby complicating treatment strategies and the development of effective therapeutics.[42,43]

One prevalent strategy employed by bacteria involves the secretion of effector proteins that mimic host UPS components, such as E3 ligases or deubiquitinases. [44] These effectors can directly interfere with the host's ubiquitination machinery, disrupting the normal tagging and degradation of proteins involved in immune defense. For instance, Yersinia species produce YopJ, a deubiquitinating protease that removes K48- and K63-linked ubiquitin chains from key signaling intermediates, thereby inhibiting NF-κB and MAPK pathways essential for inflammatory responses.[45] Similarly, Shigella flexneri secretes OspI, which deamidates Ubc13, impairing its ability to form K63-linked polyubiquitin chains and dampening immune signalling.[46]

The manipulation of the UPS by antibiotic-resistant bacteria further underscores the complexity of host-pathogen interactions. For example, Staphylococcus aureus, a major antibiotic-resistant pathogen, employs

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a variety of immune evasion proteins that target neutrophil-mediated killing, a process that can involve UPS components. [47] Understanding these bacterial strategies is crucial for developing UPS-based therapeutics aimed at restoring or enhancing host immune function. Such interventions could potentially improve the clearance of resistant pathogens and mitigate the challenges posed by antibiotic resistance.

The Bacterial Ubiquitin-like System

Bacterial lineages have independently evolved protein modification systems, termed ubiquitin-like (Ubl) systems, which exhibit mechanistic parallels to the eukaryotic ubiquitin-proteasome system (UPS).[48] These Ubl systems, while not universally distributed across the bacterial domain, participate in fundamental aspects of bacterial physiology and defense against environmental stressors, including bacteriophage infection. Emerging evidence further suggests a potential involvement of these regulatory pathways in modulating bacterial virulence and the development of antibiotic resistance, highlighting their significance in bacterial adaptation and survival.[49]

The molecular machinery of bacterial Ubl systems often comprises operons encoding homologs of the eukaryotic E1 ubiquitin-activating enzyme, E2 ubiquitin-conjugating enzyme, and the Ubl protein itself. These enzymatic components facilitate the conjugation of Ubls to lysine residues on target proteins, mirroring the ubiquitination process observed in eukaryotes.[50] Notably, bacteria also possess ancestral homologs of E1 and Ubl proteins primarily implicated in sulfur metabolism; however, their capacity for bona fide protein conjugation has only recently been elucidated. The association of identified bacterial Ubl systems with phage defense islands underscores their role in protecting bacteria from viral predation.[51]

Given the distinct structural and functional attributes of bacterial Ubl systems compared to the eukaryotic UPS, these pathways represent promising targets for the development of novel antimicrobial therapeutics.[52] Pharmacological inhibition of these bacterial-specific modification systems could disrupt crucial bacterial processes, such as defense mechanisms and adaptive responses potentially linked to virulence and antibiotic resistance, without significant off-target effects on host cells. Consequently, targeting bacterial Ubl systems offers a unique and potentially complementary strategy to combat the growing challenge of antibiotic-resistant infections.[53]

Table 1: Bacterial UBI systems

Feature	Eukaryotic UPS	Bacterial Ubl System
Core Components	E1, E2, E3, ubiquitin	E1, E2, Ubl (no canonical E3)
Function	Protein degradation, signalling	Antiviral defense, protein regulation
Prevalence	Universal in eukaryotes	Found in some bacteria
Mechanistic Parallels	Yes (conjugation cascade)	Yes (structural and mechanistic)

Challenges and Future Directions

The intricate relationship between ubiquitin signalling pathways and the multifaceted phenomenon of antibiotic resistance remains a subject of ongoing scientific inquiry. While contemporary investigations have established the involvement of deubiquitinating enzymes (DUBs) and the broader ubiquitin-proteasome system (UPS) in modulating host-pathogen interactions and shaping immune responses, the precise molecular mechanisms underpinning their influence on antibiotic resistance phenotypes necessitate further rigorous examination. For instance, pathogen-induced alterations in DUB expression have been observed to impact immunomodulatory pathways, such as the secretion of tumour necrosis factor-alpha (TNF-α); however, a comprehensive understanding of the scope and implications of these effects concerning resistance acquisition and maintenance requires in-depth mechanistic elucidation.[54, 55]

A salient imperative exists for expanded research endeavours aimed at the identification of specific UPS targets and the subsequent development of highly selective pharmacological modulators. Although certain small-molecule inhibitors, exemplified by AZ-1, have demonstrated preliminary efficacy in augmenting bacterial clearance and attenuating disease severity in preclinical models, their incomplete therapeutic potency and the consequent requirement for synergistic administration with conventional antibiotics underscore the critical need for the design and synthesis of more precise and efficacious modulatory agents.[56] The limited repertoire of regulatory agency-approved therapeutics targeting components of the UPS further highlights the inherent challenges associated with translating fundamental scientific discoveries into clinically viable antimicrobial interventions.[57]

The manipulation of the host UPS engenders potential liabilities, notably the risk of off-target effects and associated toxicities. [58] Given the ubiquitous involvement of the UPS in a diverse array of fundamental cellular processes, encompassing cell cycle progression, apoptotic signaling, and immune regulation, broad or non-selective inhibition of this system can perturb normal cellular homeostasis, potentially leading to adverse physiological

consequences.[59] Clinical experience derived from the application of proteasome inhibitors in oncological therapeutics has revealed inherent limitations pertaining to undesirable side effects and the emergence of drug resistance, thereby emphasizing the paramount importance of developing highly selective and context-dependent UPS modulators to mitigate these risks and enhance therapeutic translatability.[60]

Addressing the extant limitations in our understanding and the challenges in therapeutic development necessitates the implementation of interdisciplinary research strategies that synergistically integrate the expertise of microbiology, immunology, and pharmaceutical sciences.[61] The convergence of knowledge from these disparate yet complementary fieldsholdsthe potential to accelerate the identification of critical UPS components that govern host defence mechanisms, delineate their specific roles in the context of antibiotic resistance, and ultimately facilitate the rational design of targeted therapeutic interventions. Such integrated approaches are poised to yield innovative host-directed therapies that can effectively complement traditional antimicrobial agents in combating the escalating global threat of antibiotic-resistant bacteria.[62] Future perspectives on the successful clinical translation of UPS-based strategies hinge on continued progress in elucidating the nuanced regulation of immune responses by the UPS, the development of next-generation modulators exhibiting enhanced specificity and efficacy, and the exploration of synergistic therapeutic regimens incorporating existing antibiotics.[63]

CONCLUSION:

This review underscores the pivotal role of the host ubiquitin-proteasome system (UPS) in modulating immune responses to bacterial pathogens and highlights the sophisticated strategies employed by bacteria to subvert this system. The intricate interplay between ubiquitin signalling pathways and the mechanisms underlying antibiotic resistance presents a promising avenue for therapeutic intervention. Targeting specific components of the UPS, such as deubiquitinating enzymes, or leveraging targeted protein degradation approaches against bacterial resistance factors, offers novel strategies to complement traditional antibiotics.

The potential of harnessing ubiquitin signalling as a novel strategy to combat the escalating challenge of antibiotic resistance is substantial. Modulating the host UPS to enhance pathogen clearance, disrupting bacterial mimicry of UPS components, and targeting unique bacterial ubiquitin-like systems provide multifaceted approaches to overcome resistance mechanisms. The development of selective modulators and the exploration of synergistic combinations with existing antibiotics hold the key to translating these insights into effective clinical applications.

In conclusion, continued and intensified research at the intersection of ubiquitin signalling and antibiotic resistance is of paramount importance. Interdisciplinary efforts integrating microbiology, immunology, and drug discovery are crucial to fully elucidate the underlying molecular mechanisms and to identify and validate novel therapeutic targets. Overcoming current limitations in specificity and efficacy will pave the way for innovative strategies that can effectively address the growing threat posed by antibiotic-resistant bacteria.

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REFERENCES

1. Tang KWK, Millar BC, Moore JE. Antimicrobial Resistance (AMR). Br J Biomed Sci. 2023 ; 28;80:11387.
2. Pieri A, Aschbacher R, Fasani G, Mariella J, Brusetti L, Pagani E, et al. Country Income Is Only One of the Tiles: The Global Journey of Antimicrobial Resistance among Humans, Animals, and Environment. Antibiotics. 2020;1;9(8):473.
3. Dadgostar P. Antimicrobial Resistance: Implications and Costs. Infect Drug Resist. 2019; 12:3903–10.
4. Cook MA, Wright GD. The past, present, and future of antibiotics. Sci Transl Med. 2022; 10;14(657):eabo7793.
5. Li Y, Li S, Wu H. Ubiquitination-Proteasome System (UPS) and Autophagy Two Main Protein Degradation Machineries in Response to Cell Stress. Cells. 2022;11(5):851.
6. Qu J, Zou T, Lin Z. The Roles of the Ubiquitin–Proteasome System in the Endoplasmic Reticulum Stress Pathway. Int J Mol Sci. 2021;22(4):1526.
7. Çetin G, Klafack S, Studencka-Turski M, Krüger E, Ebstein F. The Ubiquitin–Proteasome System in Immune Cells. Biomolecules. 2021;11(1):60.
8. Vozandychova V, Stojkova P, Hercik K, Rehulka P, Stulik J. The Ubiquitination System within Bacterial Host–Pathogen Interactions. Microorganisms. 2021;9(3):638.
9. Mukherjee R, Dikic I. Regulation of Host-Pathogen Interactions via the Ubiquitin System. Annu Rev Microbiol. 2022;76(1):211–33.
10. Qiu M, Chen J, Li X, Zhuang J. Intersection of the Ubiquitin–Proteasome System with Oxidative Stress in Cardiovascular Disease. Int J Mol Sci. 2022;23(20):12197.
11. Franić D, Zubčić K, Boban M. Nuclear Ubiquitin-Proteasome Pathways in Proteostasis Maintenance. Biomolecules. 2021;11(1):54.
12. Fhu CW, Ali A. Dysregulation of the Ubiquitin Proteasome System in Human Malignancies: A Window for Therapeutic Intervention. Cancers. 202;13(7):1513.
13. Yadav D, Lee JY, Puranik N, Chauhan PS, Chavda V, Jin JO, et al. Modulating the Ubiquitin–Proteasome System: A Therapeutic Strategy for Autoimmune Diseases. Cells. 2022;11(7):1093.
14. Yang Q, Zhao J, Chen D, Wang Y. E3 ubiquitin ligases: styles,

structures and functions. Mol Biomed. 2021;2(1):23.
15. Chanda S, Atla S, Sheng X, Nyalata S, Alugubelli YR, Coleman DD, et al. Ubiquitin Azapeptide Esters as Next-Generation Activity-Based Probes for Cysteine Enzymes in the Ubiquitin Signal Pathway. J Am Chem Soc. 2025;147(21):17817–28.
16. Liu F, Chen J, Li K, Li H, Zhu Y, Zhai Y, et al. Ubiquitination and deubiquitination in cancer: from mechanisms to novel therapeutic approaches. Mol Cancer. 2024;23(1):148.
17. Yang W, Wang S, Tong S, Zhang WD, Qin JJ. Expanding the ubiquitin code in pancreatic cancer. Biochim Biophys Acta BBA - Mol Basis Dis. 2024 Jan;1870(1):166884.
18. Li D, Ma Q. Ubiquitin-specific protease: an emerging key player in cardiomyopathy. Cell Commun Signal. 2025;23(1):143.
19. Zeng L, Zhang X, Huang Z, Song S, Li M, Wang T, et al. Ubiquitin proteasome system in cardiac fibrosis. J Adv Res. 2024;S2090123224005629.
20. Baker HA, Bernardini JP. It's not just a phase; ubiquitination in cytosolic protein quality control. Biochem Soc Trans. 2021;49(1):365–77.
21. Cilleros-Holgado P, Gómez-Fernández D, Piñero-Pérez R, Romero-Domínguez JM, Reche-López D, López-Cabrera A, et al. Mitochondrial Quality Control via Mitochondrial Unfolded Protein Response (mtUPR) in Ageing and Neurodegenerative Diseases. Biomolecules. 2023;13(12):1789.
22. Roy S, Ghosh MK. Ubiquitin proteasome system (UPS): a crucial determinant of the epigenetic landscape in cancer. Epigenomics. 2025;17(9):625–44.
23. Langin G, González-Fuente M, Üstün S. The Plant Ubiquitin–Proteasome System as a Target for Microbial Manipulation. Annu Rev Phytopathol. 2023;61(1):351–75.
24. Al Hasan MA, Sultana S, Bin Islam S, Mondal M, Al Mamun A. Protein Degradation Through Ubiquitination: Insights into the Ubiquitin-Proteasome System Across Biology and Disease [Internet]. 2025 [cited 2025 Jun 6]. Available from: https://www.preprints.org/manuscript/202504.2585/v1
25. Shariq M, Quadir N, Alam A, Zarin S, Sheikh JA, Sharma N, et al. The exploitation of host autophagy and ubiquitin machinery by Mycobacterium tuberculosis in shaping immune responses and host defense during infection. Autophagy. 2023;19(1):3–23.
26. Tripathi-Giesgen I, Behrends C, Alpi AF. The ubiquitin ligation machinery in the defense against bacterial pathogens. EMBO Rep. 202 ;22(11):e52864.
27. Franklin TG, Pruneda JN. Bacteria make surgical strikes on host ubiquitin signaling. Leong JM, editor. PLOS Pathog. 2021 Mar 18;17(3):e1009341.
28. Apte S, Bhutda S, Ghosh S, Sharma K, Barton TE, Dibyachintan S, et al. An innate pathogen sensing strategy involving ubiquitination of bacterial surface proteins. Sci Adv. 2023;9(12):eade1851.
29. Deng C, Chen D, Yang L, Zhang Y, Jin C, Li Y, et al. The role of cGAS-STING pathway ubiquitination in innate immunity and multiple diseases. Front Immunol. 2025;16:1522200.
30. Qin C, Lu Y, Bai L, Wang K. The molecular regulation of autophagy in antimicrobial immunity. Su B, editor. J Mol Cell Biol. 2022;14(4):mjac015.
31. Mello-Vieira J, Bopp T, Dikic I. Ubiquitination and cell-autonomous immunity. Curr Opin Immunol. 2023;84:102368.
32. Garcia-Sanchez JA, Ewbank JJ, Visvikis O. Ubiquitin-related processes and innate immunity in C. elegans. Cell Mol Life Sci. 2021;78(9):4305–33.
33. Martín-Vicente M, Resino S, Martínez I. Early innate immune response triggered by the human respiratory syncytial virus and its regulation by ubiquitination/deubiquitination processes. J Biomed Sci. 2022;29(1):11.
34. Huang S, Cheng A, Wang M, Yin Z, Huang J, Jia R. Viruses utilize ubiquitination systems to escape TLR/RLR-mediated innate immunity. Front Immunol. 2022;13:1065211.
35. Abbas R, Larisch S. Killing by Degradation: Regulation of Apoptosis by the Ubiquitin-Proteasome-System. Cells. 2021;10(12):3465.
36. Roy PK, Biswas A, K. D, Mandal M. An insight into the ubiquitin-proteasomal axis and related therapeutic approaches towards central nervous system malignancies. Biochim Biophys Acta BBA - Rev Cancer. 2022;1877(3):188734.
37. Santelices J, Schultz AC, Walker A, Adams N, Tirado D, Barker H, et al. Targeting deubiquitinating enzymes (DUBs) and ubiquitin pathway modulators to enhance host defense against bacterial infections [Internet]. 2025 [cited 2025 Jun 6]. Available from: http://biorxiv.org/lookup/doi/10.1101/2025.01.27.635188
38. Bialek W, Collawn JF, Bartoszewski R. Ubiquitin-Dependent and Independent Proteasomal Degradation in Host-Pathogen Interactions. Molecules. 2023;28(18):6740.
39. Yan Y, Wang H, Bi Y, Song F. Rice E3 ubiquitin ligases: From key modulators of host immunity to potential breeding applications. Plant Commun. 2024;5(12):101128.
40. Grishin A, Voth K, Gagarinova A, Cygler M. Structural biology of the invasion arsenal of Gram-negative bacterial pathogens. FEBS J. 2022;289(6):1385–427.
41. Atta-ur-Rahman, Chaudhary MI, editors. Frontiers in Anti-Infective Drug Discovery: Volume 9 [Internet]. BENTHAM SCIENCE PUBLISHERS; 2021 [cited 2025 Jun 6]. (Frontiers in Anti-Infective Drug Discovery; vol. 9). Available from: https://www.eurekaselect.com/193514/volume/9
42. Bhat SA, Vasi Z, Adhikari R, Gudur A, Ali A, Jiang L, et al. Ubiquitin proteasome system in immune regulation and therapeutics. Curr Opin Pharmacol. 2022;67:102310.
43. Hu X, Wang J, Chu M, Liu Y, Wang Z wei, Zhu X. Emerging Role of Ubiquitination in the Regulation of PD-1/PD-L1 in Cancer Immunotherapy. Mol Ther. 2021;29(3):908–19.
44. Bullones-Bolaños A, Bernal-Bayard J, Ramos-Morales F. The NEL Family of Bacterial E3 Ubiquitin Ligases. Int J Mol Sci. 2022 ;23(14):7725.
45. Roberts CG, Franklin TG, Pruneda JN. Ubiquitin-targeted bacterial effectors: rule breakers of the ubiquitin system. EMBO J. 2023;42(18):e114318.
46. Banerjee R. Synthetic Biology-Based Approaches to Investigate Host–Pathogen Interactions. SynBio. 2025;3(1):4.
47. Von Köckritz-Blickwede M, Winstel V. Molecular Prerequisites for Neutrophil Extracellular Trap Formation and Evasion Mechanisms of Staphylococcus aureus. Front Immunol. 2022;13:836278.
48. Meng C, Jiao F, Zhou G, Wang L, Wu S, Fan C, et al. Selective Autophagy Mediated by Protein Ubiquitination in Major Prevalent Zoonoses. Ren L, editor. Transbound Emerg Dis. 2025; (1):6238787.
49. Gu X, Nardone C, Kamitaki N, Mao A, Elledge SJ, Greenberg ME. The midnolin-proteasome pathway catches proteins for ubiquitination-independent degradation. Science. 2023; 381(6660):eadh5021.
50. Ebstein F, Küry S, Papendorf JJ, Krüger E. Neurodevelopmental Disorders (NDD) Caused by Genomic Alterations of the Ubiquitin-Proteasome System (UPS): the Possible Contribution of Immune Dysregulation to Disease Pathogenesis. Front Mol Neurosci. 2021;14:733012.
51. Kaminskaya AN, Evpak AS, Belogurov AA, Kudriaeva AA. Tracking of Ubiquitin Signaling through 3.5 Billion Years of Combinatorial Conjugation. Int J Mol Sci. 2024 ;25(16):8671.
52. Wanka V, Fottner M, Cigler M, Lang K. Genetic Code Expansion Approaches to Decipher the Ubiquitin Code. Chem Rev. 2024;124(20):11544–84.
53. Termathe M, Leidel SA. Urm1: A Non-Canonical UBL. Biomolecules. 2021; 11(2):139.
54. Chutani N, Singh AK, Kadumuri RV, Pakala SB, Chavali S. Structural and Functional Attributes of Microrchidia Family of Chromatin Remodelers. J Mol Biol. 2022;434(14):167664.
55. Snyder NA, Silva GM. Deubiquitinating enzymes (DUBs): Regulation, homeostasis, and oxidative stress response. J Biol Chem. 2021;297(3):101077.
56. Spano D, Catara G. Targeting the Ubiquitin–Proteasome System and Recent Advances in Cancer Therapy. Cells. 2023;13(1):29.
57. LaPlante G, Zhang W. Targeting the Ubiquitin-Proteasome System for Cancer Therapeutics by Small-Molecule

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DoI-10.004687/1000-9035.2025.223

Inhibitors. Cancers. 2021;13(12):3079.
58. Zhang J, Liu L, Wang Z, Hou M, Dong Z, Yu J, et al. Ubiquitin-proteasome system-based signature to predict the prognosis and drug sensitivity of hepatocellular carcinoma. Front Pharmacol. 2023;14:1172908.
59. Ma X, Zhang C, Kim DY, Huang Y, Chatt E, He P, et al. Ubiquitylome analysis reveals a central role for the ubiquitin-proteasome system in plant innate immunity. Plant Physiol. 2021;185(4):1943–65.
60. Rothweiler EM, Brennan PE, Huber KVM. Covalent fragment-based ligand screening approaches for identification of novel ubiquitin proteasome system modulators. Biol Chem. 2022;403(4):391–402.
61. Đorđević S, Gonzalez MM, Conejos-Sánchez I, Carreira B, Pozzi S, Acúrcio RC, et al. Current hurdles to the translation of nanomedicines from bench to the clinic. Drug Deliv Transl Res. 2022;12(3):500–25.
62. Aliabadi F, Sohrabi B, Mostafavi E, Pazoki-Toroudi H, Webster TJ. Ubiquitin–proteasome system and the role of its inhibitors in cancer therapy. Open Biol. 2021;11(4):200390.
63. Heo AJ, Ji CH, Kwon YT. The Cys/N-degron pathway in the ubiquitin–proteasome system and autophagy. Trends Cell Biol. 2023;33(3):247–59.