Available at https://www.iasj.net/iasj
Iraqi Academic Scientific Journals
Journal homepage:
https://journals.uokerbala.edu.iq/index.php/UOKJ

Research Article

Bacterial Toxin-Mediated Immune Evasion and Disruption of Host Immunity

[1,]Doaa Faik Ali Alasady ,[2,]Hadeel amoori abd ali
[1,]College of Sciences, University of Kerbala, Iraq[2,] karbala Education Directorate, Iraq

Article Info
Article history:
Received 19 -12-2025
Received in revised form 16-2-2026
Accepted 5-4-2026
Available online 31 -3 -2026
Keywords: bacterial toxins, immune evasion, exotoxins, endotoxins, toxin–antitoxin systems, immune modulation

Abstract

Bacterial toxins are master manipulators of host immunity, serving as crucial virulence factors that enable pathogens to evade, dysregulate, and ultimately overcome host defenses. This article review aimed to explore how bacterial toxins, including exotoxins and endotoxins, change immunological activities and cause diseases. Exotoxins, which include super antigens, membrane-living toxins, and A-B type toxins, disrupt the communication between immune cells, increase cytokine production, leading to cell lysis or immunological paralysis. Endotoxins, especially lipopolysaccharide from Gram-negative bacteria, activate macrophage and causes systemic immune reaction, leading to septic shock. Moreover, TA systems, which regulate bacterial persistence and biofilm formation, thereby promoting chronic infections that evade immune clearance and antibiotic treatment, biofilm, and multidrug resistance, allowing them to stay alive, even under stress conditions. Finally, cyto-lethal distending toxins or CDTs, act as genotoxin and damage host's DNA, modulate the cellular cycle, and suppress adaptive immunity, for example, by inhibiting T and B cell proliferation. Recently, progress in the development of a cell-coated or CMN nanoparticles represents a novel approach to toxin neutralization, which anchors bacterial toxins away from their physiological receptors by mimicking host cells. Therefore, a comprehensive understanding of how toxins, TA systems, and CDTs subvert immunity is crucial for developing targeted anti-virulence strategies and novel therapeutics to counteract antibiotic-resistant infections

Corresponding Author E-mail: doaa.f@uokerbala.edu.iq
Peer review under responsibility of Iraqi Academic Scientific Journal and University of Kerbala.

Introduction

How Bacteria Destroy the Immune System: When infected by bacterial pathogens, the body launches an innate and adaptive immune response aimed at destroying the invaders and restoring internal balance. However, occasionally the body's reaction runs wild. Excessive response would facilitate tissue injury; insufficient response or transient one would fail to clear the pathogens. A wide variety of bacterially derived toxins during infection may have profound effects on the immune response. For instance, bacterial toxins may help bacteria to escape immune surveillance, access the protective environment available for them within eukaryotic cells or either dampen or enhance pro-inflammatory reactions. Moreover, it has become evident in the past several years that bacterial toxins can induce other cellular responses besides their direct noxious effects. For instance, pore-forming toxins have the ability not only to stimulate cell lysis but also autophagy, pyro ptosis or MAPK signaling and so on. This results on host immune response that get used to the infection and modifies local and systemic inflammatory responses (1). Exotoxins may be in the form of single peptides or heterologous protein complexes trimmed at different sites of the cell. At the level of the cell membrane, they may enter the plasma membrane and induce damage, bind to receptors for internalization, or alter relationships with different cell populations. For exotoxins to exert their intracellular effects they need to penetrate the eukaryotic cell membrane. (2). Bacteria can induce disease by two mechanisms of, invasion and inflammation and toxin (1). Bacterial toxins are poisons can also cause pathogenic effect in some other microorganism. Depending on the nature and dose of the toxin as well as the targeted cells, effects include intracellular and extracellular cell damage, tissue or organ failure, regulation of innate and adaptive immune responses, and neurotransmission dysfunction. Virulence is the genetically controlled bacteria's ability to generate toxic substances that cause harmful effects called toxigenicity and play a role in causing diseases.. "Toxinoses."

Exotoxins are classified into three types, based on their structures and functions:

i) super antigens
ii) membrane disrupting toxins
iii) A-B toxins

Super antigens (Type I Toxins)

Super antigens are classified as class I toxins because they cannot enter cells. This triggers immune responses, such as lipopolysaccharide (LPS) or lipoteichoic acid (LTA)-induced shock. However, bacterial protein toxins that cause shock syndrome are called toxic shock syndrome toxins (TSSTs), which are different from LPS or LTAs. TSSTs induce aberrant interactions between macrophages and T cells, resulting in cytokine release and causing super antigen-mediated shock. Super antigens have a synergistic action with LPS as the HELSA do on constraining their cytokine secretions. The action of these toxins is dependent on their interaction with major histocompatibility complex class II (MHC II) and macrophage receptors in the helper T cells. Antigen-presenting cells including macrophages, educate their antigen into peptides and show them, along with MHC II on the cell surface as part of an MHC-peptide complex. It is only a minority of immune-responding cells (TH cells) which have receptors with the capacity to identify this complex. Nonspecific binding of the bacterial toxins (super antigens and MHC II molecules) to macrophages results in greater pairing between TH cells and macrophages. When these TH cells are activated by macrophages, they secrete immune-related cytokines such as interleukin-2 (IL-2), which results in a high IL-2 content in the blood. Levels this high can result in symptoms of nausea, vomiting,

diarrhea, hypocalcaemia and even shock and death.(3).

Membrane Disrupting Toxins (Type II Toxins)

Plasma membrane of host cells are damaged by the pore-forming toxins, thus resulting in cell lysis. These toxins seem to operate by two specific ways to disrupt host cell plasma membrane. They may serve primarily to destroy host immune cells, including phagocytes. In some openers, bacteria escape from phagosomes into the cytoplasm through penetration of phagocytes and eventually give rise to phagolysosomes. There are two groups of pores-forming toxins which damage the membrane. The former generates protein channels in the plasma membrane. The osmotic pressure in the host cytoplasm is greater than that of the outside, resulting in membrane rupture and cell swelling. Since the cell membrane is unable to accommodate such an abrupt volume inrush, the cell lyses ultimately. (4)

The second type of toxins are enzymes that cleave the phospholipid component of the membrane. They are similar to phospholipases, cytolysis and hemolysis in breaking the cell membrane lipids as enzymes. The charged groups at the lipid bilayer heads, on the other hand, support and stabilize the host cell membrane. The disruption of these head groups by phospholipases renders the membrane structure unstable and results in lysis of host cells. Other phospholipases cleave at sites other than those described above and also render the host cell membrane ineffective. Hemolysis(from *staphylox* or *streptococus*) Because RBC also have the system of toxin and this type of toxins damage cell membranes. Since, however, these poisons are directed against the cell membrane, they can be effective against other cells and are known as cytolysis. Some toxins can kill phagocytic white blood cells by creating protein channels known as leucotoxins (chiefly from *Staphylococcus* and *Streptococcus*). Leukotoxins are also active on macrophages and phagocytes within tissues.. (3) .

A-B Toxins (Type III Toxins)

The first type of toxin studied were A-B toxins which contained two polypeptide chains. The A subunit is a virulent enzyme and the B subunit binds to receptors present on human cell membranes including those for diphtheria, tetanus, botulinum toxin, cholera toxin and E. coli enterotoxin.

The A subunit (the enzymatic portion) catalyzes the ribosylation of adenosine di phosphate (ADP), which translocate ADP-ribose to acceptor proteins in human cells. ADP-ribosylation may block or activate pathogenic proteins. Bacterial secretion systems secrete exotoxins into the extracellular space, however mammalian cells directly release exotoxins.

The direct entry of exotoxins into mammalian cells is very effective, since exposed to the environment (or components thereof) only for a short time and are little affected by the host immune system and/or by extracellular antibodies. Bacteria have six secretion system types, among which the type III (injectable systems) is the most widely associated with virulence.
.(2)

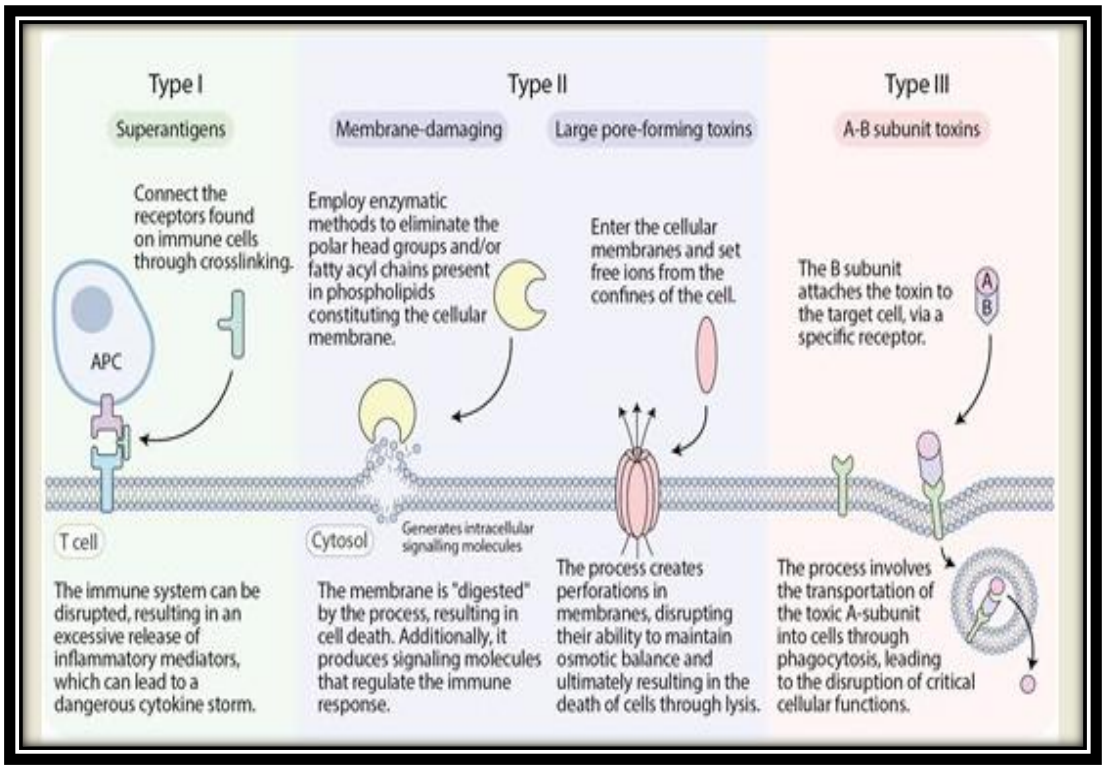

Image (1). Exotoxins are the main ways that bacteria cause disease, and they are classified into Type I (cause damage without entering host cells, stimulating the immune system), Type II (pore-forming or membrane-disrupting toxins allowing bacteria to penetrate cell membranes) and Types III A/B (two components; component B: receptors on host cells bind to this protein; component A: enzymatic activities involved in cellular injury) according to their mechanisms of action. This analogue presents a comprehensive illustration of varied classes of exotoxins and the corresponding interactions with host cells.(5)

Endotoxins Within Bacterial Cell, Released After Its Death

They are distributed on the cell wall of Gram negative bacteria. This outer membrane composed of lipopolysaccharide (LPS) and phospholipids surrounds The peptidoglycan layer constitutes the cell wall. Lipopolysaccharide (LPS) is a contaminant byproduct of which one of the components is lipid A. The majority of endotoxins belong to the lip- id and exotoxin (3). Endotoxins primarily act on macrophages. The killing of bacteria by macrophage results in the shedding of endotoxins (LPS) from the surface of gram negative bacteria. These endotoxins are small molecules that also associate with LPS-binding proteins located in the cytosol. Activation of the macrophages results in the release of interleukin-1 (IL), tumor necrosis factor (TNF), and nitric oxide. The symptoms with which septic shock most commonly presents are fever and hypotension, symptoms that are frequently underestimated. Patients with septic shock have clinical manifestations such as fever and hypotension) These are accompanied by tachycardia, tachypnea, and leukocytosis. Septic shock can be life-threatening and the mortality rate may range from 30% to 50%. Besides the endotoxins, septic shock also can be precipitated by some surface molecules of gram-positive bacteria. It is for instance, a pernicious ingredient, which made from

fatty acids including of β-hydroxymyristate. The fatty acid profile of other Gram-positive bacteria might be different. A polysaccharide core located close to the molecular mid-point and extending from the bacterial surface is present in most Gram-positive bacteria. The polysaccharide (O-antigen), which forms the surface of the bacterium, is one of the most important antigens in Gram-negative bacteria as they have an extensive degree of antigenic diversity. Fever can be induced by macrophages releasing IL-1 (endogenous pyrogen) and IL-6. Interleukins have effects in the hypothalamus' thermoregulatory center. Nitric oxide is a vasodilator; TNF causes capillary leak, and bradykinin is both a vasodilator and increases capillary permeability. Each of these can result in hypotension, shock, and decreased perfusion to vital organs. Activated coagulation pathways may be related to disseminated intravascular coagulation (DIC) and can cause thrombosis, tissue ischemia and other organ dysfunction. Endotoxin in samples of intravenous infusions from hospitals has been known to precipitate septic shock, one of the symptoms being fever.(4,6)

Types of toxin-antitoxin modules

Antitoxin mechanisms of action by which antitoxin inhibits the toxin activity to which it is bound were categorized into six types (7). In these different kinds of TA systems, toxins are usually proteins whereas antitoxins could be in various forms. cascades TA module types II, IV, V and VI are protein-based antitoxins; types I and III are sRNA based.(8).

Toxin-antitoxin and their role in bacterial pathogenesis

Bacteria contain numerous TA (toxin-antitoxin) families. Yamaguchi et al. (9) have determined that the genome of E. coli possesses 36 Chromosomally encoded TA modules while M. TB H37 Rv strain harbors more than 80 TA modules (10,11). A high number of TA modules in pathogens like M. tuberculosis is thought to be essential for various processes, including persistent bacterial infections and the development of multidrug resistance biofilm formation which increase the pathogenicity of bacteria (12). Pathogenicity TA modules can establish drug-resistant flora that cause chronic or recurrent infections. Some *Escherichia coli* strains, as well as *Shigella* and *Campylobacter* species, have been shown to produce cytotoxic, cytostrophic toxins (CDTs).(13).

Follow the discovery of CDT, numerous Gram-negative pathogens were identified that target and control eukaryotic cell cycle through DNA damage. Thus, CDT is a genotoxin (14). The *E. coli* CDT (Ec-CDT) was reported to induce the cell cycle arrest at G2/M, eventually intoxicating mammalian host cells (15). CDT is a tripartite toxin made of CDTA, CDTB and CDTC subunits encoded by three genes located on the same operon. Both their structure and function in inter-cellular interaction dictate the toxicity of EVs. CDT is an A-B2 type exotoxin that is composed of 3 subunits, including an active component CDTB and two binding components CDTA and CDTC. The cytotoxic subunit CDTB bears both functional and structural homology to mammalian DNase I, while CDTA and CDTC play a role in binding of the complete toxin to the target cell plasma membrane. The active subunit CDTB is subsequently carried to the nucleus, resulting in a damage to DNA (16). All CDTs share the same action, but their amino acid sequences vary between species of bacteria (17). The CDTB subunit is well conserved in the CDT-producing bacteria while the sequences of the CDTA and CDTC subunits are poorly conserved (17). Cholesterol-binding CDT is released by lymphocytes and macrophages. Cholesterol binding via sequence specificity Cholesterol binding is mediated by the

presence of a cholesterol-recognizing amino acid common motif (CRAC) along the CDTC unit. Diarrheal mutations in CRAC diminish toxin binding, CDTB subunit internalization and CDT-mediated cytotoxicity (18). CDT-induced immunotoxicity also implicates lipid membrane micro domains. Confocal microscopy revealed the presence of these subunits in GM1-enriched membrane (membrane rafts). Additional Western blotting showed the presence of CDT peptides in purified lipid rafts (19).

Cytolethal Distending Toxins Act Like Enzymes CDTB Acts as DNase

There were 3 ways used to study the association of DNase activity with CDTB subunit:

i) demonstration of in vitro DNase activity of CDTB subunit

ii) nuclear localisation of CDTB and

iii) activation of DNA damage response

Few studies have investigated whether CDTB isolated from different bacteria can denature, the data based on plasmid DNA (in vitro) indicates that for many organisms tested they are active as well (18). Active CDTB has to be translocated from the cell surface into the nucleus where it targets its enzyme substrates. *E. coli* CDTB subunits were electroporated and *C. jejune* CDTB subunits were microinjected into Cos-7 cells. These by other bacteria studies show that CDTB subunits possess nuclear localization signals (NLS) to allow their presence inside the nucleus (20). Mutants that lack either of these NLS sequences have reduced nuclear localization and fail to poison the cells. Fahrer et al. studied the impact of CDTs on mammalian fibroblasts to ionizing radiation. In this regard, CDTs are essentially able to trigger the DNA damage response (DDR) and eventually double-strand breaks in contrast with ionizing radiation (IR), which only induces single-strand breaks of DNA (18).

DNA damage response checkpoint is three-phased during activation.

i) Sensor proteins (MRN and Ku complex, RPA) detect DNA damage and activate certain phosphatidylinositol-3-kinase-associated protein kinases (ATM, ATR, and DNA-PK).

ii) Transduction proteins (CHK1, CHK2) amplify the signal.

iii) Effector proteins (p53, CDC25, etc.) activate corresponding cellular responses.

These cellular responses initiate cell cycle regulation, activate DNA repair pathways, and, in some cases, initiate cell death pathways. DNA damage activates two important signaling pathways: the ATMCHK2 pathway and the ATR-CHK1 pathway (16, 19). Guidi et al. have demonstrated that even if cells survive CDT poisoning, DNA damage caused by CDT activity can still lead to genomic instability and promote carcinogenesis (18, 19). Phagocytic activity is also affected, and cytokine production is impaired.

Mouse macrophages were co-cultured with wild-type *A. actinomycetemcomitans* or CDT mutant strains. Macrophages often induce host inflammation during infection. Wild-type strains had lesser phagocytic activity than CDT mutant strains. The co-culture Aa(r)CDT with CDT mutants decreased the phagocytosis functions, indicating that CDT played a role in NO production and elevated expression levels of IL-1β, IL-12, and IL-10. In co-culture, ex-vivo TNF-α production was not modified except with Aa(r)CDT. It seems that Aa-CDT is actively involved in the suppression of phagocytosis and regulation of the ratio between pro-inflammatory cytokines (21). It has been reported that CDT is able to trigger the production of pro-inflammatory cytokines by macrophages, and this response is associated with CDT-induced activation of caspase-1(6), which, in turn, is dependent on NLRP3 inflammasome activation. Murine

macrophages exposed to CDT secreted IL-1β, TNF-α, and IL-6 as early as 5 h post stimulation, and also produced IL-18 48 h after CDT exposure (22).

The impact of Homophiles decry CDT (HdCDT) on circulating human cells of the haematopoietic system (including T cells, B cells, monocytes and PMNs) was examined. HdCDT Block Mitogen-Mediated Proliferation of Circulating Human T and B Cells, and Immunoglobulin Production, and the Immune Response in Host.(23).

Recent Discoveries: Deciphering the Role of TA Modules and CDTs in the Development of Chronic Diseases

Bacterial toxins protect bacteria. Studying the activity of these toxins is crucial for predicting the occurrence of certain diseases. Bacteria encode both toxins and antitoxins.

They were first related to plasmid maintenance and were involved in specific bacterial cellular processes, such as DNA replication, t RNA biogenesis. TA modules can be grouped into 6 classes. TA modules on the contrary, act within the cell producing them and not within the host organism in which they are part of. TA modules are composed of a stable toxin and a degradable antitoxin (either RNA or protein). Antitoxins either bind directly to toxins as inhibitors or regulate toxin production. The regulation of TA modules allowed bacterial community to survive under harsh conditions including the induction of persistence phenomenon, the formation of biofilm and favor the resistance to infection by maintaining multidrug resistance. The medical potential of bacteriophages was already known and applied to treatment during WWI when the soldiers' camps were faced with dysentery. Bacteriophages were employed as antibacterial agents before antibiotics became available. These studies suggested for the first time in “phage-history” that so called “infection cessation” could protect bacteria from bacteriophage attack (at least in laboratory cultures) and, thus limiting the use of bacteriophages as therapeutic agents (prophylaxis) otherwise referred to as phage-therapy. As a contrasting system, TA modules provide a reverse with the same effect to phage in bacteria. Several works with TA models have also demonstrated that TA modules play a key role in promoting the reduction of bacterial metabolism and act as effectors of PGCD on defined bacterial populations. Bacteria persistence and biofilm formation are also believed to be responsible for the next survival of a small fraction of bacteria, by assuring the stoichiometric value between toxins and antitoxins. Pathogenic bacteria's TA systems can cause multidrug resistance, which adds an additional challenge for treating diseases. Ideal therapy for diseases resulting from pathogenic microorganisms remains elusive. The action of TA modules may enhance the pathogenicity of microorganisms. At present Mycobacterium tuberculosis have about 88 diverse TA modules. In particular, it has been demonstrated that these systems are involved in the pathogenicity via bacterial persistence and multidrug resistance. Dormancy and multidrug resistance make the treatment of tuberculosis difficult. (24) Thus, CDT impedes the human immune response and contributes to proliferation of pathogenic bacteria although low doses of CDT induces DNA damage shows that damaged caused by CDT at low levels result in replication-dependent DSBs. This implies the presence of DSB-independent repair pathways that are involved in CDT-resistance. They established that CDT-induced damage is repaired mainly by two DSB repair processes: HR and NHEJ. Experiments demonstrated that SSBR deficient cells were sensitized to CDT but not to nucleotide excision repair. These findings is indicative cells could escape CDT-induced DNA damage by multiple mechanisms. Repair systems are essential

in the resistance to CDT-induced DNA damage and also for persistence inside host cells. Thus, what is currently being investigated by investigators are the real mechanisms of action of CDT: how pathogenic bacteria activate infection to trigger resistance towards CDT through endogenous repair processes (24). Certain Gram-negative bacteria, including for example E. coli—shown to be part of normal human microflora of the bowels—may produce CDTs. CDTs of E. coli (Ec-CDTs) may be generated by *E. coli*.(25)

In vitro study revealed the role of Ec-CDTs in promoting colorectal cancer in human colonic epithelial cells. (26).

Nanoparticles as innovative approaches for bacterial toxin neutralization

Nanoparticles coated with host cell-like substances, such as erythrocyte membranes, can bind to and neutralize bacterial toxins, thereby protecting the host. They can attract toxins, deflect them from their target structures, and stimulate the body to produce an immune response against bacteria. (27,28) Cell membrane-coated nanoparticles, the so-called "cellular nanosponges," are coated with various cell membranes, including erythrocyte membranes, platelet membranes, leukocyte membranes, and macrophage membranes. Depending on the type of membrane, they can specifically target different toxins and microorganisms. Erythrocyte membrane-coated nanoparticles can neutralize pore-forming toxins produced by Staphylococcus aureus and Streptococcus pyogenes (Fig. 2A). These toxins can cause serious diseases such as pneumonia, skin infections, and necrotizing fasciitis. (29) Macrophage membrane-coated nanoparticles can neutralize endotoxins (Fig. 2B). (30) Other nanoparticles coated with the main host receptor of cholera toxin—monosialotetrahexosy lganglioside (GM1)—can act as toxin inducers by selectively and persistently binding to cholera toxin and neutralizing its effects on epithelial cells in vitro and in vivo. (31) These nanoparticles can also activate the immune system and induce antibacterial immunity. These are some innovative applications of nanoparticles in combating bacterial infections (32).

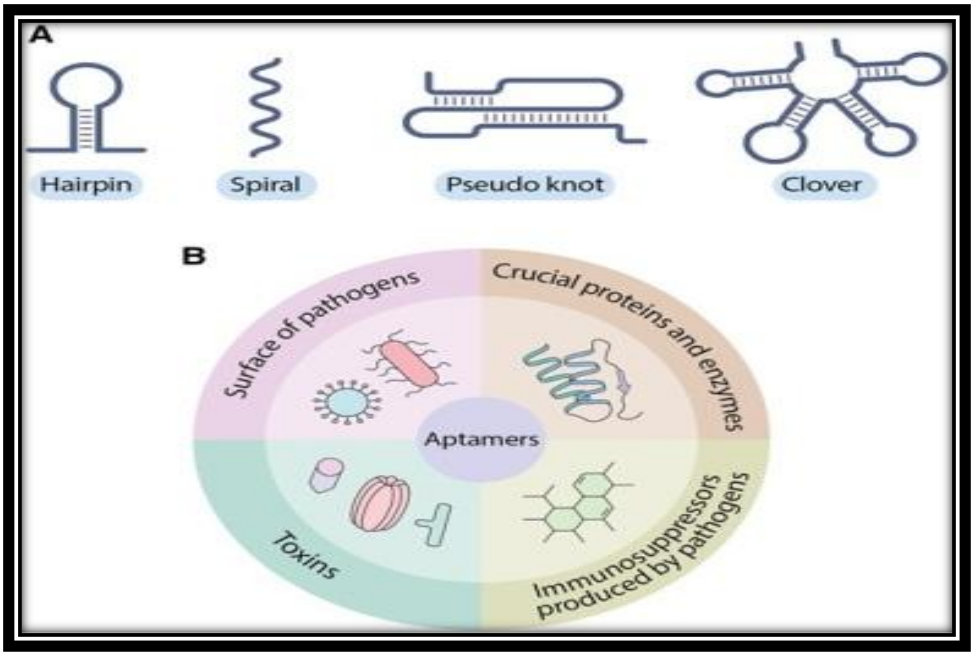

Image (2).(A) shows the aptamer structure, and (B) shows its potential therapeutic applications, including: (1) targeting structures or molecules on the surface of pathogens or host cell receptors to inhibit their penetration or facilitate drug delivery; (2) inhibiting pathogen replication by targeting essential proteins and enzymes; (3) alleviating symptoms caused by microbial toxins; and (4) enhancing the efficiency of the host immune system by targeting immunosuppressants or related molecules.(5)

Conclusion

Toxins produced by pathogenic bacteria play a crucial role in the interaction between microbes and the host, and promote the progression of host diseases. As previously mentioned, bacterial toxins alter the toxin-antitoxin (TA) module of pathogenic bacteria, leading to programmed cell death (PCD) or a reduction in metabolic levels. These toxins help reduce the number of bacteria within the host, allowing a small number of bacteria to survive. Therefore, programmed cell death induced by the bacterial TA module is the optimal survival strategy for pathogenic bacteria under stress.

While cell cycle toxins (CDTs) disrupt host cells by altering the eukaryotic cell cycle, they can also attack the host's immune system and cells, allowing dangerous bacteria to survive. Some studies have shown that CDTs are involved in the carcinogenic process.

Escherichia coli, part of the normal flora of the human gut, is capable of producing CDTs; researchers have demonstrated that CDTs may play a role in the progression of colorectal cancer. Interestingly, these two toxin systems exhibit distinctly different mechanisms and target structures in inducing host diseases. The toxin-antitoxin (TA) system acts on the bacterial cells themselves, while the cytotoxic toxin (CDT) system acts on host cells. However, both contribute to bacterial survival within the host. Therefore, in-depth research into toxins and their molecular processes can provide crucial information for discovering new applications in the field of biotechnology. In turn, this can facilitate the development of new treatments to counteract the negative effects of these toxin systems during infection.

In summary, the articles demonstrate the complexity of the interactions between bacterial toxins and numerous organisms and immune cells. Of particular note is the sophisticated mechanisms bacteria have evolved to precisely, strain-specifically, and selectively modulate immune cell function. This highlights how invading pathogens employ entirely different strategies to evade the immune system during bacterial infection. Given the increasing severity of antibiotic resistance in bacteria globally, current articles focuses on developing more targeted strategies to combat and prevent infection, such as enhancing the host's immune system. A deeper understanding of how bacteria regulate the immune system will contribute to a better understanding and ultimately, identification of diseases. A deeper understanding of how bacteria manipulate the immune system will contribute to a better understanding of diseases and ultimately, the discovery of better treatments.

Reference

1. Los FC, Randis TM, Aroian RV, Ratner AJ. Role of pore-forming toxins in bacterial infectious diseases. Microbiol Mol Biol Rev (2013) 77:173–207. doi:10.1128/MMBR.00052-12
2. Ribet D, Cossart P. Post-translational modifications in host cells during bacterial
3. Tortora G, Funke B, Case C. Chapter 15 - Microbial mechanisms of pathogenicity, In: Beauparlant, editor. Microbiology an introduction. 13th ed. Boston: Pearson; 2019; pp. 423–444
4. Wilson B, Salyers A, Whitt D, Winkler M. Bacterial pathogenesis a molecular approach.3rd ed. Washington, DC: American Society for Microbiology Press; 2011. pp. 225–255.
5. Zhang, Y., et al. (2022). Exotoxin-Targeted Drug Modalities as Antibiotic Alternatives. ACS Infectious Diseases, 8(1), 1-20.
6. Levinson W. Review of medical microbiology and immunology. 13th ed. New York: McGraw- Hill Education; 2014; pp. 80–124. https://lib.hpu .edu.vn/handle/123456789/32671
7. Talaro KP, Chess B. Foundations in microbiology. 10th ed. New York: Mc-Graw Hill Education, 2018; pp. 397–436.
8. Wang X, Wood T. Toxin-antitoxin systems influence biofilm and persister cell formation and the general stress response. Appl Environ Microbial. 2011;77(16):5577. https://doi.org/10 .1128/AEM.05068-11
9. Yamaguchi Y, Park JH, Inouye M. Toxin-antitoxin systems in bacteria and archaea. Annu Rev Genet. 2011;45:61–79. https://doi.org/10.1146/annurev -genet-110410-132412
10. Harms A, Brodersen D, Mitarai N, Gerdes K. Toxins, targets, and triggers: an overview of toxinantitoxin biology. Mol Cell. 2018;70(5):768–784.https://doi.org/10.1016/j.molcel.20 18.01.003
11. Fernández-García L, Blasco L, Lopez M, Bou G, García-Contreras R, Wood T, et al. Toxinantitoxin systems in clinical pathogens.Toxins. 2016;8:227. https://doi.org/10.3390/ toxins8070227
12. Wen Y, Behiels E, Devreese B. Toxin-antitoxin systems: their role in persistence, biofilm formation, and pathogenicity. Pathog Dis. 2014;70(3):240–249. https://doi.org/10.1111/2049-2X.12145
13. Pons B, Vignard J, Mirrey J. Cytolethal distending toxin subunit B: a review of structure–function relationship. Toxins. 2019;11(10): 595. https://doi.org/10.3390/toxins1110059 5
14. Gargi A, Reno M, Blanke S. Bacterial toxin modulation of the eukaryotic cell cycle: are all cytolethal distending toxins created equally? Front Cell InfectMicrobiol2012;2(124):1–11. https://doi.org/10.3389/fcimb.2012.001 24
15. Pérès SY, Marchès O, Daigle F, Nougayrède JP, Herault F, Tasca C, et al. A new cytolethal distending toxin (CDT) from *Escherichia coli* producing CNF2 blocks HeLa cell division in G2/M phase. Mol Microbiol. 1997;24(5):1095– 1107. https://doi.org/10.1046/j.1365-2958.1997 .4181785.x
16. Bezine E, Vignard J, Mirey Gladys. The cytolethal distending toxin effects on mammalian cells: a DNA damage perspective. Cells. 2014;3(2):592– 615. https://doi.org/10.3390/cells3020592
17. Guerra L, Cortes-Bratti X, Guidi R, Frisan T. The biology of the cytolethal distending toxins. Toxins. 2011;3(3):172–190. https://doi.org/10 .3390/toxins3030172

18. Scuron M, Boesze-Battaglia K, Dlakic M, Shenker B. The cytolethal distending toxin contributes to microbial virulence and disease pathogenesis by acting as a tri-perditious toxin. Front Cell Infect Microbiol. 2016;6:168. https://doi.org/10.0.3389/fcimb.2016.00168

19. Fahrer J, Huelsenbeck J, Jaurich H, Dörsam B, Frisan T, Eich M, et al. Cytolethal distending toxin (CDT) is a radiomimetic agent and induces persistent levels of DNA double-strand breaks in human fibroblasts. DNA Rep. 2014;18:31–43. https://doi.org/10.1016/j.dnarep.2014.03.002

20. Elwell C, Dreyfus L. DNase I homologous residues in CDTB are critical for cytolethal distending toxin-mediated cell cycle arrest. Mol Microbiol. 2000;37(4):952–963. https://doi.org/10.1046/j.1365-2958.2000.02070.x

21. Dlakic M. Is CdtB a nuclease or a phosphatase? Science. 2001;291(5504):547. https://doi.org/10.1126/science.291.5504.547a

22. Shenker B, Dlakic M, Walker L, Besack D, Jaffe E, LaBelle E, et al. A novel mode of action for a microbial-derived immunotoxin: the cytolethal distending toxin subunit B exhibits phosphatidylinositol 3,4,5-triphosphate phosphatase activity. J Immunol. 2007;178(8):5099–5108. https://doi.org/10.4049/jimmunol.178.8.5099

23. Suguimoto E, Silva M, Kawamoto D, Chen C, DiRienzo J, Mayer M. The cytolethal distending toxin of Aggregatibacter tinomycetemcomitans inhibits macrophage phagocytosis and subverts cytokine production. Cytokine. 2014;66(1):46– 53. https://doi.org/10.1016/j.cyto.2013.12.014

24. Kedzierska B, Hayes F. Emerging roles of toxinantitoxin modules in bacterial pathogenesis. J Molecules. 2016;21(6):790. https://doi.org/10.3390/molecules21060790

25. Bonnet M, Buc E, Sauvanet P, Darcha C, Damien D, Bruno P, et al. Colonization of the human gut by E. coli and colorectal cancer risk. Human Cancer Biol. 2014;20(4):859–867. https://doi.org/10.1158/1078-0432.CCR-13-1343

26. Bezine E, Malaisé Y, Loeuillet A, Chevalier M, Boutet-Robinet E, Salles B, et al. Cell resistance to the cytolethal distending toxin involves an association of DNA repair mechanisms. Sci Rep. 2016;24;6:36022. https://doi.org/10.1038/ srep36022

27. Doroudian M, MacLoughlin R, Poynton F, Prina-Mello A, Donnelly SC. Nanotechnology based therapeutics for lung disease. Thorax 2019; 74:965–76.Google ScholarCrossrefPubMedWorldCat

28. Doroudian M, O' Neill A, Mac Loughlin R, Prina-Mello A, Volkov Y, Donnelly SC. Nanotechnology in pulmonary medicine. Curr Opin Pharmacol 2021; 56:85–92.Google Scholar Crossref Pub Med World Cat

29. Wang X, Xia Z, Wang H, Wang D, Sun T, Hossain E, et al. Cell-membrane-coated nanoparticles for the fight against pathogenic bacteria, toxins, and inflammatory cytokines associated with sepsis. Theranostics 2023; 13:3224–44.Google Scholar Crossref PubMedWorldCat

30. Liu WL, Zou MZ, Qin SY, Cheng YJ, Ma YH, Sun YX, et al. Recent advances of cell membrane-coated nanomaterials for biomedical applications. Adv Funct Mater 2020.

31:2003559.GoogleScholarCrossrefWorld Cat 30. Fang RH, Gao W, Zhang L. Targeting drugs to tumours using cell membrane-coated nanoparticles. Nat Rev Clin Oncol 2023; 20:33–48.Google ScholarCrossrefPubMedWorldCat

32. I. H. Ali, R. T. Kadhim, D. F. A. Alasady, R. O. Abdulsada, M. H. Jawad. GREEN SYNTHESIS OF CUO NANOPARTICLES AND THEIR ANTIBACTERIAL PROPERTIES . Theoretical and Experimental Chemistry, Vol. 61, No. 2, May, 2025 , DOI 10.1007/s11237-025-09861-9