International Journal for Research in Applied Sciences and Biotechnology

www.ijrasb.com

ISSN: 2349-8889
Volume-9, Issue-3 (May 2022)

Article Review: Immune Response against Some Bacterial Toxins

Zainab Zamel Khalaf[1] and Heba Khaleel Tawfeeq[2]
[1]Department of Biology, College of Science, University of Baghdad, Baghdad, IRAQ.
[2]Department of Chemistry, College of Science, University of Baghdad, Baghdad, Iraq.

[1]Corresponding Author: zainab.alnaji@sc.uobaghdad.edu.iq

ABSTRACT

Bacterial toxins are considered to be virulence factors due to the fact that they interfere with the normal processes of the host cell in which they are found. The interplay between the infectious processes of bacteria and the immune system is what causes this impact. In this discussion, we are going to focus on bacterial toxins that act in the extracellular environment, especially on those that impair the activity of macrophages and neutrophils. These toxins are of particular interest since they may be found in a wide variety of bacteria. We will be concentrating our efforts, in particular, on the toxins that are generated by Gram-positive and Gram-negative bacteria. These toxins are able to interact with and have an effect on the many different types of immune cells. We utilize the Shiga toxin, cholera toxin (CT), and pertussis toxin as examples of Gram-negative toxins (PT). As examples of Gram Positive toxins, we use Alpha toxin, anthrax toxin, and botulinum toxin (BONT). In total, we look at six different types of bacterial toxins. According to the findings of the study, Shiga toxins, which are associated with the production of cytokines, chemokines, and macrophages, might thus result in post-translational modification. The cholera toxin induced a mucosal response that was mediated by secretory IgA, whereas the pertussis toxin inhibited the migration of macrophages and interacted with phagocytosis. The process by which cells take in and digest foreign material is called phagocytosis. It was revealed that *S. aureus* bacteremia led to an increase in the number of Th17 cells, while at the same time alpha-toxin led to a decrease in the number of Th1 cells. The anthrax toxin inhibits the synthesis of cytokines and chemokines, both of which are involved in the inflammatory response. This, in turn, causes the death of macrophages by necrosis and apoptosis. When being treated with BoNT, it was found that cells produced elevated amounts of TNF and NO in a dose-dependent way. This was determined after the cells were exposed to BoNT. This was the conclusion reached.

Keywords- Shiga toxin, Cholera toxin, Pertussis toxin, Alpha toxin, Anthrax toxin, Botulinum toxin, Immune.

I. INTRODUCTION

In the beginning stages of bacterial infections, macrophages and neutrophils, which are both mediators of the innate immune system, have the ability to phagocytose and degrade pathogens, therefore ridding the body of them (1). The fact that macrophages and neutrophils have certain functional similarities is only half of the story; each cell type also includes distinct and specialized properties that make it efficient in combating infections when working together (2,3). Certain infections target macrophages and neutrophils by secreting toxins that either: (1) cause irreparable damage, resulting in the death of phagocytes; or (2) disrupt signalling pathways, preventing phagocytosis or modifying inflammation (for example, by interfering with the expression of chemokines and cytokines). In either case, the death of phagocytes is the end result (4). Toxins are potent compounds that are produced by a diverse collection of bacteria that are known to cause disease. They launch an assault on the cells of the host, which is an essential aspect of the dynamic that exists between the host and the pathogen. They are essential indicators of virulence that, most of the time, suffice to indicate what the infection will do to the host. Toxins produced by bacteria are classified into a variety of categories according to their properties and modes of action (4).

To begin, pertussis is not a toxin-mediated illness as cholera or diphtheria are. Instead, the bacteria that cause pertussis cause the sickness. Instead, it is the result of the coordinated action of a variety of bacterial factors that allow bacteria to adhere to ciliated respiratory epithelium, persist against the innate immune defense of the host, proliferate, and resist inflammatory cells. In other words, it is the result of a bacterial infection. In addition, the sickness known as whooping cough is not nearly as infectious as other diseases such as cholera or diphtheria (6). All bacterial toxins, whether endotoxins or exotoxins, modify the immune response to bacteria and other antigens. Co-administration of gram-negative bacterial endotoxin lipopolysaccharide (LPS) elicits an immune response to proteins that are normally non-immunogenic (7), and cholera toxin (CT) enhances the immunological response to orally administered antigens (8).

The immunopathology that is caused by Shiga toxin includes the potential for the toxin to induce damage to the intestinal microvasculature and to trigger local macrophages to create cytokines and chemokines. When macrophages are activated, this causes an inflow of neutrophils and monocytes, both of which can cause the damage to the tissue to become significantly worse. Neutrophils and monocytes, in their capacity as "carrier" cells, are also capable of delivering toxins throughout the circulatory system (9). One of the most significant

ISSN: 2349-8889
Volume-9, Issue-3 (May 2022)

staphylococcal virulence factors is alpha-toxin, which is a staphylococcal virulence factor that is capable of breaking the epithelial barrier and allowing infection to take root. Alpha-toxin is responsible for allowing staphylococcal infections to take hold. Alpha-toxin has been shown to have an effect on a variety of other cell types, including those involved in the immune system. Because protection from S. aureus infection is dependent on CD4+ T cell-mediated immunity, we were especially interested in alpha-ability toxins that directly target CD4+ T cells (10).

Exotoxins such as those generated by Bordetella pertussis, Bacillus anthracis, and Botulinum have also been the topic of investigation. Interleukin-1 (IL-1) and IL-12, for example, have been demonstrated to be key mediators of the inflammatory response to LPS. The latter is the subject of another study that is connected to this Topic, and the fundamental purpose of that review is to exercise control over macrophage activities and especially target them (11). As a consequence of this, the purpose of this review was to investigate the different ways in which bacterial toxins isolated from Gram-negative and Gram-positive bacteria interact with the immune cells of the host and the ways in which these interactions alter the host's immunological responses.

II. IMMUNE RESPONSE AGAINST SOME GRAM NEGATIVE TOXINS

E. coli that produces shiga toxin (STEC):

Escherichia coli (also known as E. coli), like the one that is present at this location, has the potential to contaminate both food and water and should be avoided. This strain of E. coli is also referred to as Shiga toxin-producing E. coli (STEC) and Verotoxin-producing E. coli. Both of these names refer to the same strain (VTEC). Some STEC clinical isolates are capable of producing Shiga toxin types 1 (Stx1) and 2 (Stx2), whereas others, in highly unusual cases, are only capable of producing Stx1 (12, 13). The additional components that are generated by STEC are thought to have a local impact in the gut, in contrast to the Shiga toxins, which are thought to have a systemic effect. Escherichia coli O157:H7, which generates the Shiga toxin, has a low infectious dose yet nevertheless causes considerable disease in humans. It has been connected to HUS epidemics as well as sporadic incidences of the disease (14,15).

The most essential component in the pathogen's pathogenicity is the capacity to generate Shiga toxins (Stx), which play a vital role in the development of HUS [9]. Stx are made in the mucosal colonization process and subsequently moved to the blood. One 32 kDa enzymatically active A subunit is linked to a pentamer of 7.5 kDa B subunits to form these enzymes (16).

It is hypothesized that protective immunity against STEC infection would come from the cross-talk between antibodies that impede intestinal colonization and those that neutralize Stx (17). Experimental and clinical evidence suggest that Stx antibodies may contribute to the formation of HUS resistance and the protective immune response (17-18).

Numerous variables, such as weather, contact with infected animals, and food processing practices, might affect the epidemiological pattern of STEC infections and HUS (19). Anti-Stx antibodies have also been shown to reduce the likelihood of getting HUS. Both animal and human research provide credence to the concept that these antibodies have a protective function in the immune system (17). It has been shown by several studies that the elderly are developing Stx-antibodies and are thus resistant to HUS (17, 20). According to the findings of research conducted in vitro, Stxs control signaling pathways at both the transcriptional and post-transcriptional levels that are important in the production of cytokines and chemokines by human and murine macrophages, as well as cell lines that behave like macrophages (21-22). The immunomodulatory effects of Stxs appear to be clinically significant for monocytes and neutrophils. On the other hand, the cytotoxic effects of the toxins examined in ref appear to be a major target for renal and central nervous system microvascular endothelial cells as well as renal tubular epithelial cells (23). On the other hand, it's possible that all of these cell types are able to create cytokines when they come into contact with the toxins. The activation of innate immunity by Stxs has several pathophysiological effects. Three mechanisms contribute to Stx entry into the lamina propria: I altered cell morphology and intercellular tight junctions in the intestinal epithelial barrier, which allows Stxs to cross into the lamina propria and damage colonic blood vessels and initiate hematogenous spread; ii) facilitated chemotactic infiltration of inflammatory cells into the gut lamina propria and into the kidneys; and iii) up-regulated expression of genes involved in innate immunity and (21–24).

Numerous clinical studies on humans and animals have demonstrated that toxins particularly target the epithelial cells of the renal proximal tubule, and these studies have also revealed that the localized synthesis of cytokines by renal cells may make the damage to the tubules even more severe (25–26). According to the findings of our study, Stxs have the ability to stimulate the innate immune response in macrophage-like cell lines, which results in an inflammatory response that is both pro- and anti-inflammatory in nature. The findings of our study demonstrated that this is really the case (22,27).

Cholera toxin:

Vibrio cholerae produces a multimeric protein called cholera toxin (CT), which is made up of a pentameric ring of B subunits and a single A subunit (CT-A). CT-B subunits attach to intestinal epithelial cells and mediate the poisonous A subunit's entry (28).

ISSN: 2349-8889
Volume-9, Issue-3 (May 2022)

Several different antigens produced cutaneous immune responses in cholera patients. These antigens included the cholera toxin B subunit (CTB), lipopolysaccharide (LPS), and the toxin-coregulated pilus (TCP).

A protective mucosal response against Vibrio cholerae is thought to be mediated by the secretory IgA (sIgA) system of the gut-associated lymphoid tissue (GALT). Since V. cholerae is a strictly intracellular pathogen, this is the case (29). Several putative avenues for adjuvanticity (30) are made available by CT's capacity to significantly alter the physiology of different cell types.

1. Induction of IL-1 production.
2. The costimulatory molecules CD80 and CD86 are expressed.

There is evidence that LPS and CT are not the same in terms of adjuvanticity (for example, the induction of IL-1), despite the fact that there are certain parallels between the two. The adjuvanticity of CT has been associated with a response of the Th2-type cytokine as well as the production of immunoglobulin E (IgE), and it is possible that it also reduces the release of Th1 cytokines (31).

According to the findings of the vast majority of research, Cholera Toxin appears to stimulate a strong T helper cell type 2 (Th2)-biased immune response to both itself and bystander antigens. The findings that Ig E and larger titers of IgG1 than IgG2a [33] are formed following vaccination with antigens in the presence of CT supports the conclusion that this is the case. The response is mostly a Th2 response; however, CT also creates a population of IL-10-producing T cells that have a regulatory function. This is despite the fact that some IFN- is produced.

Pertussis toxin:

The bacterium Bordetella pertussis is the agent responsible for the creation of the pertussis toxin, which is an AB-toxin composed of several subunits. The capacity of the toxin to attach to any sialic acid-containing glycoprotein that is present on the cell surface is due to the presence of the toxin's B-subunits, which are located on the surface of the toxin (34). Intranasal treatment with pertussis toxin (PT) resulted in ADP-ribosylation of airway macrophage Gi-proteins (6). This suggests that the toxin's immunosuppressive qualities in vitro are the cause of its inhibitory impact on macrophages in vivo. It was discovered that PT inhibits macrophage and neutrophil motility as well as phagocytosis and the cytokine response in macrophages and neutrophils when tested in vitro (35,36). In the early stages of an infection, PT targets airway macrophages in order to restrict neutrophil recruitment to the site of the infection (37). Only mice that had previously been infected and mice that had antibodies against B. pertussis were shown to have a protective role against B. pertussis (38), which suggests that PT disrupt neutrophil recruitment to the airways, which slows down antibody-mediated clearance of the virus. Only mice that had previously been infected and mice that had antibodies against B. pertussis were shown to have a protective role against B. pertussis. At the height of infection, mice that have been infected with the wild type strain draw a significant number of neutrophils to their lungs, but mice that have been infected with the PT-deficient strain do not exhibit this behavior (39).

III. IMMUNE RESPONSE AGAINST SOME GRAM POSITIVE TOXINS

1. Alpha-toxin

Staphylococcus aureus is a gram-positive, rod-shaped bacterium that may invade and live in host cells. (40-44) Some of the extracellular virulence factors produced by S. aureus have immunomodulatory properties. Toxic shock syndrome toxin 1, a staphylococcal superantigen, activates T cells and leads to severe inflammation (45). Initially identified for its lytic effect on rabbit erythrocytes, alpha-toxin (also known as alphahemolysin or hla) is a major virulence factor of S. aureus (46). Monomeric alpha-toxin is released into the environment, where it attaches to the host cell membrane and forms lethal heptameric holes (47). The target cell is destroyed when the monomer form of alpha-toxin is produced and attaches to the cell membrane of the host cell. This results in the formation of heptameric holes (48). The initial binding factor is cellular ADAM10, which is also known as a disintegrin and metalloproteinase domain-containing protein 10. (49). S. aureus alpha toxin (AT) is a cytolytic pore-forming toxin that has been demonstrated to play a significant role in S. aureus illness in mouse and rabbit models .These diseases include dermonecrosis, pneumonia, and sepsis(50–53).

We were interested in alpha-ability toxins that may directly change CD4+ T cells as a means of protecting against S. aureus infection. This is because CD4+ T cell-mediated immunity is necessary for providing protection against S. aureus infection. To no one's astonishment, it was discovered that alpha-toxin was the cause of death in Th1-polarized cells, but Th17-polarized cells demonstrated a substantial resistance to increasing doses of this toxin. This discovery came as a complete surprise to everyone. The changes in the expression of the cellular alpha-toxin receptor ADAM10 or the activation of caspase could not explain these effects; nonetheless, it is probable that they are the result of Th1 cells' higher vulnerability to Ca2+-mediated activation-induced cell death (10). The host's immune response to cutaneous infections caused by S. aureus is characterized by the infiltration of neutrophils and the formation of abscesses (54,55). In addition, cd and CD4+ T cells have been found to have a role in the immune response to a cutaneous infection caused by S. aureus (55, 56). There was a decrease in Th1 cells during S. aureus bacteremia that was reliant on alpha-toxin, and

ISSN: 2349-8889
Volume-9, Issue-3 (May 2022)

an increase in Th17 cells. As well as targeting Th1 cells, S. aureus also affected related subsets of innate lymphoid cells (ILCs) and gd T cells. This suggests that S. aureus has established a universal approach to regulate both type 1 and type 3 immune responses (10).

2. Anthrax toxin

Bacillus anthracis is responsible for the production of three distinct exotoxins, which are referred to as the protective antigen (PA), the edema factor (EF), and the lethal factor (LF) (LF). PA is responsible for the production of the binary poisons edema toxin (ETx) and lethal toxin (LTx) when it combines with EF and LF (57). The toxins are able to penetrate most cell membranes, but the only cells that pose a threat are macrophages derived from particular congenitally altered mouse strains (58). Anthrax toxins contribute to the bacterium's ability to evade the body's immune system by disrupting both the body's innate and adaptive immune responses. The development of necrosis and apoptosis in macrophages is inhibited by LT, as well as the production of pro-inflammatory cytokines and chemokines. LT not only causes DCs to apoptose, which removes them physically from the system, but it also stops DCs from developing, which stops them from activating B and T cells. This is because DCs cannot mature while LT is present (59). LT also attacks the adaptive immune system by preventing the development of B cells and the production of antibodies, in addition to preventing T cells from activating and multiplying (60). The humoral immune response to anthrax (61), on the other hand, is well established; nevertheless, the influence of bacterial toxins on the adaptive immune response is only partially characterized.

3. Botulinum toxin:

Clostridium botulinum is responsible for the production of botulinum neurotoxin (BoNT), which is often considered to be the most poisonous molecule found in nature. The toxin has been separated into seven distinct serotypes, labeled A through G, based on their immunological properties (62). Because of its action on presynaptic vesicles, this toxin results in a flaccid kind of muscle paralysis (63).

Because the body of the host recognizes botulinum toxin as an alien substance, it has the potential to provoke an immune response, particularly when it is employed frequently; this can lead to the ineffectiveness of the therapy non question as a secondary measure (64).

When a human is exposed to BoNT, the toxin is absorbed into the circulation through a mucosal surface. It then makes a direct and rapid impact on the presynaptic terminal, which it does before the host immune system is engaged. Additionally, reports indicate that exposure to BoNT results in relatively mild discomfort (60). The presence of these traits continues to be a significant obstacle in the way of research into the inflammatory effects of the active toxin in vivo. In vitro studies have also been conducted, albeit on a much smaller scale, to investigate the effects of botulinum toxin on the immune cells of the host. It was demonstrated that BoNT caused an increase in TNF and NO production in cells in a way that was dependent on the dosage administered. Only after cell activation with doses of BoNT greater than 5 nM was IL-6 found to be present in the sample. The highest concentration of bovine neurotoxin T, on the other hand, rendered IL-1 and IL-12 undetectable (65).

REFERENCES

[1] **Wynn** T. A., Chawla A., Pollard J. W. (2013). Macrophage biology in development, homeostasis and disease. *Nature* 496 445–455. 10.1038/nature12034.

[2] **Silva** M. T. (2010). When two is better than one: macrophages and neutrophils work in concert in innate immunity as complementary and cooperative partners of a myeloid phagocyte system. *J. Leukoc. Biol.* 87 93–106.

[3] **Silva** M. T., Correia-Neves M. (2012). Neutrophils and macrophages: the main partners of phagocyte cell systems. *Front. Immunol.* 3:174

[4] **Lemichez** E., Barbieri J. T. (2013). General aspects and recent advances on bacterial protein toxins. *Cold Spring Harb Perspect. Med.* 3:a013573 10.1101

[5] **Pittman** M. (1984). The concept of pertussis as a toxin-mediated disease. *Pediatr. Infect. Dis.* 3 467–486. 10.1097

[6] **Carbonetti** N. H. (2007). Immunomodulation in the pathogenesis of *Bordetella pertussis* infection and disease. *Curr. Opin. Pharmacol.* 7 272–278.

[7] **Johnson**, A. G., S. Gaines, and M. Landy. 1956. Studies on the O antigen of *Salmonella typhosa*. V. Enhancement of antibody response to protein antigens by the purified lipopolysaccharide. J. Exp. Med. 103:225–246.

[8] **Lycke**, N., and J. Holmgren. 1986. Strong adjuvant properties of cholera toxin on gut mucosal immune responses to orally presented antigens. Immunology 59:301–308.

[9] **Moo-Seung** Lee and Vernon L. Tesh. (2019). Roles of Shiga Toxins in Immunopathology. Toxins, 11, 212; toxins11040212.

[10] **Bonifacius** A, Goldmann O, Floess S, Holtfreter S, Robert PA, Nordengrün M, Kruse F, Lochner M, Falk CS, Schmitz I, Bröker BM, Medina E and Huehn J (2020) Staphylococcus aureus Alpha-Toxin Limits Type 1 While Fostering Type 3 Immune Responses. Front. Immunol. 11:1579. doi: 10.3389/fimmu.2020.01579

[11] **Barth** H., Fischer S., Moglich A., Fortsch C. (2015). Clostridial C3 toxins target monocytes/macrophages and modulate their functions. *Front. Immunol.* 6:339

[12] **Strockbine,** N.A.; Jackson, M.P.; Sung, L.M.; Holmes, R.K.; O'Brien, A.D. Cloning and sequencing of the genes for Shiga toxin from Shigella dysenteriae type 1. *J. Bacteriol.* 1988, *170*, 1116–1122**.**

[13] Imamovic, L.; Jofre, J.; Schmidt, H.; Serra-Moreno, R.; Muniesa, M. Phage-mediated Shiga toxin 2

ISSN: 2349-8889
Volume-9, Issue-3 (May 2022)

gene transfer in food and water. *Appl. Environ. Microbiol.* 2009, *75*, 1764–1768.
[14] Johnson KE, Thorpe CM, Sears CL: The emerging clinical importance of non-O157 Shiga toxin-producing Escherichia coli. Clin Infect Dis 2006, 43(12):1587–1595.
[15] Bettelheim KA: Non-O157 Shiga-toxin-producing Escherichia coli. Lancet Infect Dis 2012, 12(1):12.
[16] O'Brien AD, Tesh VL, Donohue-Rolfe A, Jackson MP, Olsnes S, Sandvig K, Lindberg AA, Keusch GT: Shiga toxin: biochemistry, genetics, mode of action, androle in pathogenesis. Curr Top Microbiol Immunol 1992, 180:65–94.
[17] Karmali MA, Mascarenhas M, Petric M, Dutil L, Rahn K, Ludwig K, Arbus GS, Michel P, Sherman PM, Wilson J, Johnson R, Kaper JB: Age-specific frequencies of antibodies to Escherichia coli verocytotoxins (Shiga toxins) 1 and 2 among urban and rural populations in southern Ontario. J Infect Dis 2003, 188(11):1724–1729.
[18] Karmali MA, Petric M, Winkler M, Bielaszewska M, Brunton J, van de Kar N, Morooka T, Nair GB, Richardson SE, Arbus GS: Enzyme-linked immunosorbent assay for detection of immunoglobulin G antibodies to Escherichia coli Vero cytotoxin 1. J Clin Microbiol 1994, 32(6):1457–1463.
[19] **Tesh**, V.L. The induction of apoptosis by Shiga toxins and ricin. Curr. Top. Microbiol. Immunol. 2012, 357, 137–178.
[20] **Barrett** TJ, Green JH, Griffin PM, Pavia AT, Ostroff SM, Wachsmuth LK: Enzyme linked immunosorbent assays for detecting antibodies to Shiga-like toxin I, Shiga-like toxin II, and Escherichia coli O157:H7 lipopolysaccharide in human serum. Curr Microbiol 1991, 23:189–195.
[21] **Tesh**, V.L.; Ramegowda, B.; Samuel, J.E. Purified Shiga-like toxins induce expression of proinflammatory cytokines from murine peritoneal macrophages. Infect. Immun. 1994, 62, 5085–5094.
[22] **Leyva-Illades**, D.; Cherla, R.P.; Lee, M.S.; Tesh, V.L. Regulation of cytokine and chemokine expression by the ribotoxic stress response elicited by Shiga toxin type 1 in human macrophage-like THP-1 cells. Infect. Immun. 2012, 80, 2109–2120.
[23] **Legros**, N.; Pohlentz, G.; Steil, D.; Müthing, J. Shiga toxin-glycosphingolipid interaction: Status quo of research with focus on primary human brain and kidney endothelial cells. Int. J. Med. Microbiol. 2018, 308, 1073–1084.
[24] **Keepers**, T.R.; Gross, L.K.; Obrig, T.G. Monocyte chemoattractant protein 1, macrophage inflammatory protein 1_, and RANTES recruit macrophages to the kidney in a mouse model of hemolytic-uremic syndrone. Infect. Immun. 2007, 75, 1229–1236.
[25] **Wadolkowski**, E.A.; Sung, L.M.; Burris, J.A.; Samuel, J.E.; O'Brien, A.D. Acute renal tubular necrosis and death of mice orally infected with Escherichia coli strains that produce Shiga-like toxin type II. Infect. Immun. 1990, 58, 3959–3965.
[26] **Porubsky**, S.; Federico, G.; Müthing, J.; Jennemann, R.; Gretz, N.; Büttner, S.; Obermüller, N.; Jung, O.; Hauser, I.A.; Gröne, E.; et al. Direct acute tubular damage contributes to Shigatoxin-mediated kidney failure. J. Pathol. 2014, 234, 120–133.
[27] **Lee, M.S.**; Kwon, H.; Lee, E.Y.; Kim, D.J.; Park, J.H.; Tesh, V.L.; Oh, T.K.; Kim, M.H. Shiga toxins activate the NLRP3 inflammasome pathway to promote both production of the proinflammatory cytokine interleukin-1beta and apoptotic cell death. Infect. Immun. 2016, 84, 172–186.
[28] **Spangler** B D. Structure and function of cholera toxin and the *Escherichia coli* heat-labile enterotoxin. Microbiol Rev. 1992;56:622–647
[29] **Svenner** holm AM, Gothefors L, Sack DA, Bardhan PK, Holmgren J. Local and systemic antibody responses and immunological memory in humans after immunization with cholera B subunit by different routes. Bull World Health Organ 1984; 62:909 –18.
[30] **Snider**, D. P. 1995. The mucosal adjuvant activities of ADP-ribosylating bacterial enterotoxins. Crit. Rev. Immunol. 15:317–348.
[31] **Marinaro** M, Staats H F, Hiroi T, Jackson R J, Coste M, Boyaka P N, Okahashi N, Yamamoto M, Kiyono H, Bluethmann H, Fujihashi K, McGhee J R. Mucosal adjuvant effect of cholera toxin in mice results from induction of T helper 2 (Th2) cells and IL-4. J Immunol. 1995;155:4621–4629.
[32] **Simecka**, J. W., Jackson, R. J., Kiyono, H., McGhee, J. R. (2000) Mucosally induced immunoglobulin E-associated inflammation in the respiratory tract. Infect. Immun. 68, 672–679.
[33] **Richards**, C. M., Shimeld, C., Williams, N. A., Hill, T. J. (1998) Induction of mucosal immunity against herpes simplex virus type 1 in the mouse protects against ocular infection and establishment of latency. J. Infect. Dis. 177, 1451–1457.
[34] **Stein**,P.E.,Boodhoo,A.,Armstrong,G.D.,Heerze,L. D.,Cockle,S.A.,Klein, M. H.,etal.(1994). Structure of a pertussis toxin-sugar complex as a model for receptor binding. *Nat.Struct.Biol.* 1, 591–596.doi:10.1038/nsb0994-591.
[35] **Meade**,B.D.,Kind,P.D.,Ewell,J.B.,McGrath,P.P.,an dManclark,C.R.(1984). In vitro inhibition of murine macrophage emigration by *Bordetella pertussis* lymphocytosis-promoting factor. *Infect. Immun.* 45, 718–725.
[36] **Mork**, T.,andHancock,R.E.(1993).Mechanisms of non opsonicphagocytosis of *Pseudomonas aeruginosa*. *Infect. Immun.* 61, 3287–3293.
[37] **Andreasen**, C.,and Carbonetti,N.H.(2008). Pertussis toxin inhibits early chemokine production to delay neutrophil recruitment in response to *Bordetella pertussis* respiratoryt ract infection in mice. *Infect. Immun.* 76, 5139–5148.doi:10.1128/IAI.00895-08.

ISSN: 2349-8889
Volume-9, Issue-3 (May 2022)

[38] **Andreasen**, C., and Carbonetti,N.H.(2009). Role of neutrophils in response to *Bordetella pertussis* infection in mice. *Infect. Immun.* 77, 1182–1188.doi: 10.1128/IAI.01150-08

[39] **Andreasen**,C.,Powell,D.A.,andCarbonetti,N.H.(2009).Pertussis toxin stimulates IL-17production in response to *Bordetella pertussis* infection in mice. *PLoSONE* 4:e7079.doi:10.1371.

[40] **Lowy FD**. Staphylococcus aureus infections. N Engl J Med. (1998) 339:520–32. doi: 10.1056/NEJM199808203390806

[41] **Wertheim** HF, Melles DC, Vos MC, Van Leeuwen W, Van Belkum A, Verbrugh HA, et al. The role of nasal carriage in Staphylococcus aureus infections. Lancet Infect Dis. (2005) 5:751–62. doi: 10.1016/S1473-3099(05)70295-4

[42] **Baker** S, Thomson N, Weill FX, Holt KE. Genomic insights into the emergence and spread of antimicrobial-resistant bacterial pathogens. Science. (2018) 360:733–8. doi: 10.1126/science.aar3777

[43] **Cassini** A, Högberg LD, Plachouras D, Quattrocchi A, Hoxha A, Simonsen GS, et al. Attributable deaths and disability-adjusted life-years caused by infections with antibiotic-resistant bacteria in the EU and the European Economic Area in 2015: a population-level modelling analysis. Lancet Infect Dis. (2018) 19:56–66. doi: 10.1016/S1473-3099(18) 30605-4

[44] **Lakhundi** S, Zhang K. Methicillin-resistant Staphylococcus aureus: molecular characterization, evolution, and epidemiology. Clin Microbiol Rev. (2018) 31: e00020-18. doi: 10.1128/CMR.00020-18

[45] **Calvano** SE, Quimby FW, Antonacci AC, Reiser RF, Bergdoll MS, Dineen P. Analysis of the mitogenic effects of toxic shock toxin on human peripheral blood mononuclear cells in vitro. Clin Immunol Immunopathol. (1984) 33:99– 110. doi: 10.1016/0090-1229(84)90296-4

[46] **Glenny** AT, Stevens MF. Staphylococcus toxins and antitoxins. J Pathol Bacteriol. (1935) 40:201–10. doi: 10.1002/path.1700400202

[47] **Berube** BJ, Bubeck Wardenburg J. Staphylococcus aureus alpha-toxin: nearly a century of intrigue. Toxins. (2013) 5:1140–66. doi: 10.3390/toxins5061140

[48] **Berube** BJ, BubeckWardenburg J. Staphylococcus aureus alpha-toxin: nearly a century of intrigue. Toxins. (2013) 5:1140–66. doi: 10.3390/toxins5061140

[49] **Wilke** GA, BubeckWardenburg J. Role of a disintegrin and metalloprotease 10 in Staphylococcus aureus alpha-hemolysin-mediated cellular injury. Proc Natl Acad Sci USA. (2010) 107:13473–8. doi: 10.1073/pnas.1001815107

[50] **Kobayashi** SD, Malachowa N, Whitney AR, Braughton KR, Gardner DJ, et al. (2011) Comparative analysis of USA300 virulence determinants in a rabbit model of skin and soft tissue infection. J Infect Dis 204: 937–941.

[51] **Kennedy** AD, Bubeck Wardenburg J, Gardner DJ, Long D, Whitney AR, et al. (2010) Targeting of alpha-hemolysin by active or passive immunization decreases severity of USA300 skin infection in a mouse model. J Infect Dis 202: 1050–1058.

[52] **Kernodle** DS, Voladri RK, Menzies BE, Hager CC, Edwards KM (1997) Expression of an antisense hla fragment in staphylococcus aureus reduces alphatoxin production in vitro and attenuates lethal activity in a murine model. Infect Immun 65: 179–184.

[53] **Bubeck** Wardenburg J, Schneewind O (2008) Vaccine protection against staphylococcus aureus pneumonia. J Exp Med 205: 287–294.

[54] **Miller** LS, Cho JS (2011) Immunity against staphylococcus aureus cutaneous infections. Nat Rev Immunol 11: 505–518.

[55] **Molne L**, Verdrengh M, Tarkowski A (2000) Role of neutrophil leukocytes in cutaneous infection caused by staphylococcus aureus. Infect Immun 68: 6162–6167.

[56] **Molne** L, Corthay A, Holmdahl R, Tarkowski A (2003) Role of gamma/delta T cell receptor-expressing lymphocytes in cutaneous infection caused by staphylococcus aureus. Clin Exp Immunol 132: 209–215.

[57] **Singh** Y, Klimpel KR, Goel S, Swain PK, Leppla SH. Oligomerization of anthrax toxin protective antigen and binding of lethal factor during endocytic uptake into mammalian cells. Infect Immun1999; 67:1853–9.

[58] **Singh**, Y., S. H. Leppla, R. Bhatnagar, and A. M. Friedlander. 1989. Internalization and processing of Bacillus anthracis lethal toxin by toxin-sensitive and -resistant cells. J. Biol. Chem. 264:11099–11102.

[59] **Marinaro**, M., Staats, H. F., Hiroi, T., Jackson, R. J., Coste, M., Boyaka, P. N., Okahashi, N., Yamamoto, M., Kiyono, H., Bluethmann, H., et al. (1995) Mucosal adjuvant effect of cholera toxin in mice results from induction of T helper 2 (Th2) cells and IL-4. J. Immunol. 155, 4621– 4629

[60] **Taysse** L, Daulon S, Calvet J, Delamanche S, Hilaire D, Bellier B, et al. Induction of acute lung injury after intranasal administration of toxin botulinum a complex. Toxicol Pathol. 2005; 33: 336–42

[61] **Pitt**, M. L., S. Little, B. E. Ivins, P. Fellows, J. Boles, J. Barth, J. Hewetson, and A. M. Friedlander. 1999. In vitro correlate of immunity in an animal model of inhalational anthrax. J. Appl. Microbiol. 87:304.

[62] **Hatheway** CL, Toxigenic clostridia. Clinical Microbiology Reviews 1990; 3: 66–98.

[63] **Schiavo** GG, Benfenati F, Poulain B, Rossetto O, de Laureto PP, Tetanus and botulinum-B neurotoxins block neurotransmitter release by proteolytic cleavage of synaptobrevin. Nature 1992; 359: 832–835.

[64] **Benecke**, R.(2012). Clinical Relevance of Botulinum Toxin Immunogenicity. Biodrugs 2012; 26 (2): e1-e9

[65] **Kim** YJ, Kim J-H, Lee K-J, Choi M-M, Kim YH, Rhie G-e, et al. (2015) Botulinum Neurotoxin Type A Induces TLR2-Mediated Inflammatory Responses in Macrophages. PLoS ONE 10(4): e0120840.