

Bacterial Immunity and Host Defense Mechanisms



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Abstract

Microbes are the key players for deteriorating the host defense. They enter inside the host system, colonize the host cells, evade the host immunity and ultimately leads to tissue injury and ultimately disease. But the body cells are having strong immune system to combat with these aliens. There are two basic types of immune responses in body for bacterial degradation. Immune response for extracellular bacteria and immune response for intracellular invaders. The extracellular bacteria leads to cellular death via profound inflammation and by producing toxins. The toxins can be either exotoxins or endotoxins. The exotoxins are cytotoxic or interfere with cell function while the endotoxins which are LPS (component of cell wall) are potent activators of macrophages thereby associated with cellular damage.

Introduction

The bacteria often leads to cell damage mainly by releasing certain virulence factors and suppressors of growth factors and at last interfere with cellular growth regulatory mechanisms

[1,2]. The most common and important mechanisms concerned with bacterial induced cell death are apoptosis and necrosis [3] (Table 1).

Table 1: Intracellular and Extracellular Bacteria [4-6].

S.No.	Bacteria	Toxin	MOA	Effect
Intracellular Bacteria				
1.	<i>Listeria monocytogenes</i>	Listeriolysin	Cell membranes damage	Listeriosis
2.	<i>Mycobacteria</i>	Macrophage activation	Granuloma formation	Leprosy and TB
3.	<i>Legionella pneumophila</i>	cytotoxins	Cell lysis and lung injury	Legionnaires disease
Extracellular Bacteria				
1.	<i>Vibrio cholerae</i>	Cholera toxin ADP ribosylates G protein subunit	Increase cyclic AMP	Enteric infections
2.	<i>Corynebacterium diphtheriae</i>	Diphtheria toxin ADP ribosylate elongation factor 2	Protein synthesis inhibitor	Diphtheria
3.	<i>Staphylococcus aureus</i>	Enterotoxin (superantigen)	Profound T cell activation and thereby cytokine production	Food poisoning and TSS
4.	<i>Streptococcus pyogenes</i>	Streptolysin O	Damage cell membranes	Scarlet fever, impetigo
5.	<i>E.coli</i>	LPS (endotoxin)	Increased cytokine production	GIT and UT infections
6.	<i>Clostridium tetani</i>	Tetanospasmin	Muscle contraction as affect motor end plate at NMJ	Tetanus
7.	<i>Streptococcus pneumoniae</i>	Pneumolysin	Acute inflammation (as like streptolysin O)	Pneumonia and meningitis

Possible Defense Mechanisms To Bacterial Pathogens (Table 2)

Table 2: Possible Defense Mechanisms to Bacterial Pathogens.

S.No.	Innate Immune Response	Adaptive Immune Response
1.	First line.	Second line.
2.	Specific immune response.	Specific immune response.
3.	Not antigen specific immune response as act similarly to all antigens.	Antigen specific immune response.
4.	No memory.	Memory present.
5.	Immediate response.	Take time to react an antigen.
6.	e.g. Neutrophils, macrophages, NK cells, complements, anatomical barriers etc.	e.g. CMI, HMI and classical complement pathway etc.

The innate immunity to extracellular bacteria can involve cellular and non-cellular components. The cellular components comprise of inflammatory and phagocytic processes while non-cellular defenses comprises of anatomical defense mechanisms, tissue bactericides, complement and microbial antagonism. But there is one important factor often associated with host defense called as difference in susceptibility to some of the pathogens. This can be either resistance offered by individual or by some species.

Resistance offered by some individual often affected by age, sex, stress, diet and infections e.g. in stress the chances of infection are often increased because of increased secretion of cortisone by adrenal cortex which decrease the inflammatory reaction, and *Toxoplasma gondii* infection only in fetus. The age related variations are often related to hormonal influences (Table 3).

Table 3: Age related variations are often related to hormonal influences.

S. No.	Factor	Example
1.	Lack of target for the action of toxin	Diphtheria toxin not kill rats while can kill guinea pigs
2.	Absence of specific receptors for colonization	ETEC have different fimbriae to attach with species specific CHO receptors
3.	Lack of nutritional requirements	<i>S. typhimurium</i> requires purines for growth while absent in rat and mice
4.	Host body temperature	Anthrax not affect cold blooded animals (frog), mammalian TB not occur in birds

Nonspecific or innate immune response to bacterial pathogens

Anatomical defense mechanisms

The main anatomical barriers in body contains eye (blinking, tears, and lysozymes), skin (sweat, sebum, lysozyme

and normal flora), respiratory system (coughing, sneezing, mucus membranes, lysozyme and ciliary action), GIT (acidity, peristalsis and flora) and urinary tract (acidic Ph, urine, lysozymes and lactic acid in vagina). The vagina contains *Lactobacillus acidophilus* which produce lactic acid and prevent microbial colonization including fungus (*Candida albicans*). The different mucus membranes of body contains lysozymes, secretory immunoglobins- sIgA (GIT) and normal flora which often antagonize harmful microbes.

Substances in host tissues with antimicrobial action

Most of these antimicrobial substances are either glycoproteins or proteins in nature and are quite capable to prevent bacterial growth and associated damage (Table 4).

Table 4: Substances in host tissues with antimicrobial action.

S. No.	Chemical Nature	Antimicrobial Substance
1.	Glycoproteins	Iron holder (lactoferrin, transferrin), opsonizers (fibronectin)
2.	Proteins	Lysozyme (Bacterial cell lysis), peroxidases (cellular oxidation), interleukins (immune system activator) and basic proteins (beta lysins, histones etc.)
3.	Protein-carbohydrate complex	Complement (Inflammation, opsonization and cell lysis)

The most of the substances among these are present in serum (complement, fibronectin, basic proteins, and lysozymes), body secretions (lactoferrin, transferrin), mucosal surfaces (fibronectin) and secreted by inflammatory cells like macrophages and lymphocytes (interleukins). The lysozymes were first discovered by Alexander Fleming in body fluids except CSF, sweat and urine. The highest concentration is often seen in tears and egg white. The lysosomes are often having antibacterial action (at Ph 3-6) otherwise can act as opsonins.

Many bacteria like *Staphylococcus aureus*, *E. coli*, *Mycobacterium tuberculosis*, etc. require iron for their growth and proliferation. But the body is having a strong system to withhold this iron to be utilized by bacteria. The key players in this are Fe binding proteins namely transferrin, lactoferrin, ferritin and hepatoglobin. If any bacteria get entry into our system the production of IL-1 is foremost step which further increase the level of transferrin and hepatoglobin in liver. Thus the level of Fe in serum get declined and the absorption of iron from intestine also get decreased. So, ultimately the bacterial growth get inhibited. Similarly, if mammary gland harbor any bacterial infection the neutrophils present over there releases lactoferrin and thus inhibit bacterial growth. But there are some bacteria which produces certain proteins having affinity for iron called as siderophores e.g. *Mycobacterium tuberculosis* produces Mycobactin and *E. coli* produces Enterocholin.

Immune Response to Extracellular Bacteria

Innate immune response (IIR) to extracellular bacteria

This principle mediators involved with this type of immune response includes:

- o Complement activation
- o Inflammatory process
- o Phagocytosis

Complement activation

Complement system is a part of innate as well as adaptive immune response (AIR). It comprises of 3 basic pathways including alternate or properdin pathway, classical pathway and lectin pathway. Classical pathway is a part of adaptive immune response while other 2 pathways are included under innate immune response. As the classical complement pathway requires immunoglobulin molecule (IgG or IgM) for their activation, while antigenic entities (LPS, teichoic acid and other peptidoglycans) can directly activate alternate pathway. Thus only the classical pathway is Ab (antibody) dependent pathway. Otherwise the ultimate aim of all these pathways is same.

Functions of complement components involved in different complement pathways

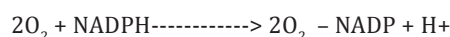
- o Osmotic lysis by MAC (Membrane attacking complex) formation and only Gram negative bacteria are lysed in the presence of lysozyme.
- o Chemotactic action for withdrawing the inflammatory cells at the site of inflammation (C3a, C5a).
- o Opsonization which helps in phagocytosis (C3b which binds with Fc portion of IgM), thereby help in phagocytosis.
- o Complement components (C3a, C5a) also having role in inflammation as help in release of histamine from mast cells by increasing vascular permeability.

Inflammatory process

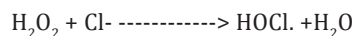
The basic mechanisms opted by phagocytes to kill bacterial entities are quite complex. The bacteria are having some patterns called as PAMPS which are recognized by phagocytes (mainly macrophages) with the help of certain receptors called as TLRs (toll like receptors). Out of all defense mechanisms inflammation is most important. Inflammatory reactions can either be involved in antimicrobial action as well as important for damage induced by pathogens in tissues. The two basic types of mechanisms followed by phagocytes to kill microbes are oxygen dependent killing and oxygen independent killing. Oxygen dependent killing mechanism is further divided into two categories namely MPO dependent killing mechanism and MPO independent killing mechanism.

The MPO dependent killing mechanism is also called as H₂O₂-MPO halide system. For this system the phagosome and

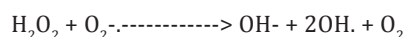
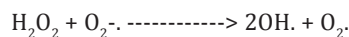
lysosomal fusion is necessary which is not required in MPO independent killing. In this system the phagocytes having FcR bind with microbes and thereby leads to the increase consumption of oxygen called as respiratory burst. The activity of NADPH oxidase present in the phagocytic membrane get increased leads to oxidation of O₂ in the presence on NADPH into superoxides (O₂⁻). These superoxides later on converted into H₂O₂ and at last forms hypochlorous free radical (HOCl) in the presence of myeloperoxidase (MPO). But the important factor for this entire mechanism is the presence of NADPH oxidase. If this enzyme is absent it leads to conditions like CGD (chronic granulomatous disease). This type of MPO halide system is present in neutrophils while absent in macrophages which are only having H₂O₂ mechanism of killing.



But H₂O₂ is not individually capable to kill bacteria, while O₂⁻ and OH⁻ can.



As macrophages are not having MPO halide system of killing in place of that these phagocytes are having a very efficient killing mechanism called as NO induced killing. Where the NO synthetase enzyme plays an important role in the production of nitric oxide and its derivatives like nitrates and nitrites. While in MPO independent killing system (Haber-Weiss reaction) requirement of oxygen is there but this process is slower. In this process O₂⁻, OH⁻, O₂ are also required.



Mechanisms involved in oxygen independent killing (Table 5)

Table 5: Mechanisms involved in oxygen independent killing.

S. No.	Mechanism Involved	Role
1.	Bactericidal permeability increasing protein (BPI)	Phospholipase activation thereby phospholipid membrane degradation
2.	Lysozyme	Hydrolysis of muramic acid -N-acetyl glucosamine bond present in the glycopeptide coat of bacteria
3.	Lactoferrin	Iron binding protein prevent bacterial proliferation and invasion
4.	Major basic protein (MBP)	Present in eosinophilic granules having cytotoxic action to parasites and possess little bactericidal action
5.	Defensins	Arginine rich granules forms hole in bacterial membranes

Adaptive immune response to extracellular bacteria:

The principal protective immune response mechanism associated with this is humoral mediated immune response (HMI), which is associated with the production of antibodies (Abs). The HMI mainly produce effective immune response against polysaccharide rich capsulated bacteria. The protection offered by HMI is because of antibodies which having following functions:

- o The antibody molecules bind with toxin and neutralize it.
- o These are capable of neutralizing bacterial spreading

factors like hylaurinidase, fibrin etc.

- o Secretory antibodies (IgAs) can bind with mucosal surface and prevent attachment of harmful bacteria.
- o These can act as an opsonizing substances for bacterial killing.
- o These are capable of Fe transport and utilization by bacteria.
- o These can fix complement for killing mainly IgG1, IgG3 and IgM.

Extracellular bacteria: (Figure 1)

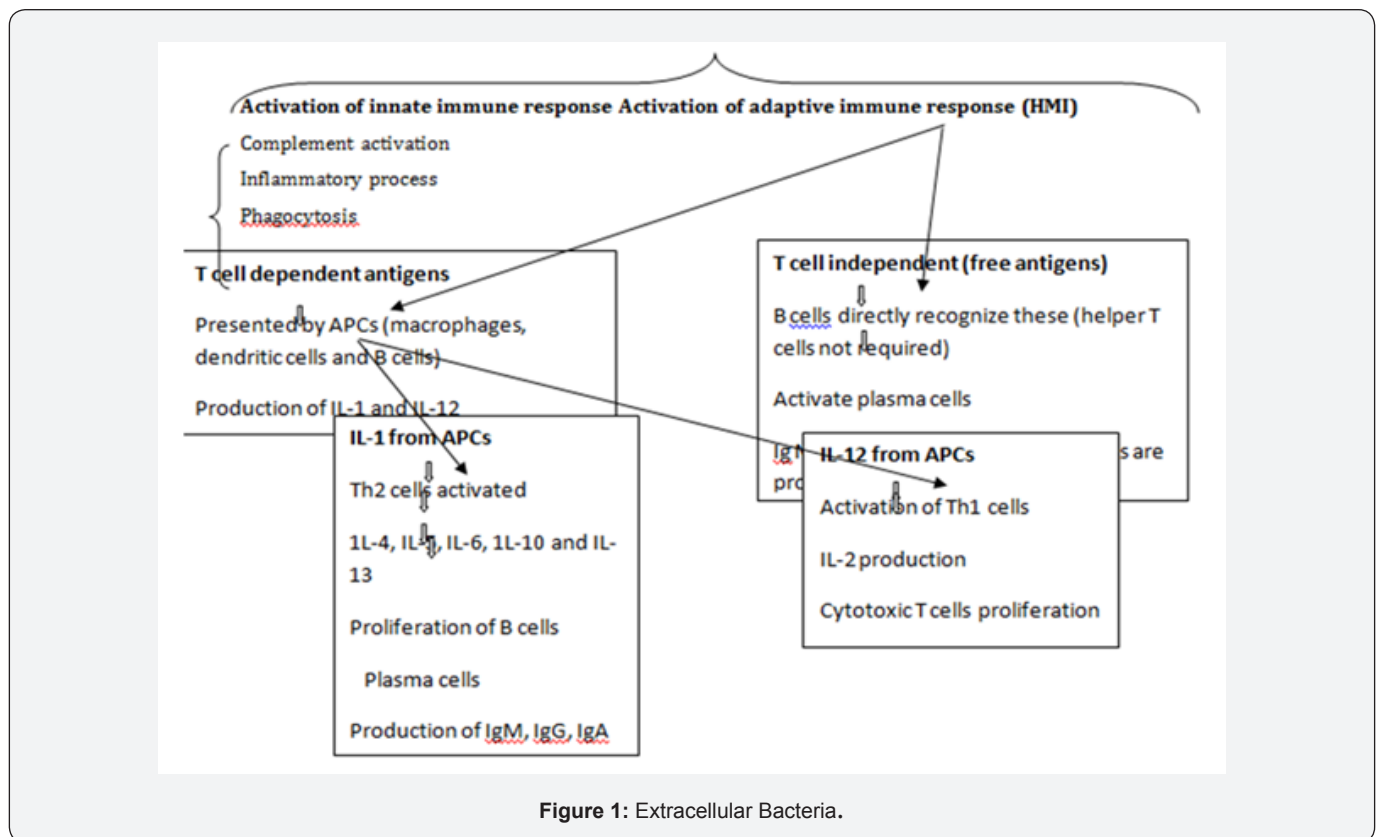


Figure 1: Extracellular Bacteria.

However the HMI is associated with strong immune mediated response to pathogens while it can also leads to damage in the form of severe inflammatory reaction, septic shock and overstimulation of T cells by some super antigens if any. The super antigens are basically microbial toxins which binds with variable beta chain of T cell receptor (TCR) and without processing and presentation these leads to stimulation of large number of T cell subsets. These activated T cells now produce increased production of cytokines and leads to toxic shock syndromes. The one of the most important known super antigen is enterotoxin by *Staphylococcus aureus*. In septic shock TNF is most important mediator associated. Both the inflammation and septic shock together can lead to overstimulation of T cells and thereby overproduction of cytokines.

Immune response to intracellular bacteria

Innate immune response to intracellular bacteria: The principal cells involved in this mechanism are NK cells (natural killers) and phagocytes (mainly macrophages and lymphocytes). The intracellular bacteria are capable to live and replicate inside phagocytes and are not accessible to circulatory molecules i.e. Abs. The intracellular bacteria are first engulfed by neutrophils but they are not capable to destroy these bacteria. After neutrophils this work is taken by macrophages. The activated macrophages produce IL-12 the potent activator of NK cells. Once the NK cells are activated these leads to the production of IFN-gamma which in turns activate further more number of macrophages. Thus both macrophages and NK cells activate each

other and thereby act together to limit intracellular pathogens. The innate immune response for intracellular bacteria can only reduce the bacterial population but for complete elimination of intracellular bacteria specific adaptive immune response is needed.

Adaptive Immune Response for Intracellular Bacteria (Cell Mediated Immune Response/CMI)

This immune response mechanism can be operated by 2 different modes i.e. activation of macrophages and CTCs. Both CD4+ (Th) and CD8+ cells (Tc) have role in this immune response. Once the MHC bound antigen is presented by APCs (antigen presenting cells) to Th cells, which type of Th cell subset is to be activated is being decided by type of IL molecule released by APCs (antigen presenting cells). The production of IL-1 and IL-12 by APCs activate Th2 and Th1 subsets respectively. If Th1 cells are activated these lead to the production of cytokines like IL-2, IFN-gamma, TNF etc. which leads to activation of CD8+ cells thereby killing. IFN-gamma is an important cytokine which can lead to activation of macrophages and thus killing. While if Th2 subset is activated many cytokines like IL-10, IL-4, IL-3, IL-13 etc. are produced which are often having inhibitory action for macrophages activation. But the cytokines (IL-3, IL-4) produced by Th2 cells are having role in HMI for the B cells and thereby antibody production. So, the overall outcome of immune response depends upon the subset of Th cells being activated.

How the Outcome of Infection Depends upon Type of Th Cells Activated?

It can be best understood by taking an example of Leprosy. There are 2 forms of this bacteria, lepromatous and tuberculoid leprosy. The lepromatous form is more harmful as compare to tuberculoid leprosy, both the forms are caused by same bacteria but in tuberculoid form the CMI response is more prominent, as in this form Th1 subset is activated. Hence macrophages are activated because of associated cytokines (IL-2, IFN-gamma). While in lepromatous form the Th2 subset is being activated, so the cytokines produced are having suppressive role towards CMI and only HMI can be produced. The cytokines produced during Th2 activation in lepromatous form are IL-4 and IL-10, which decreases the production of IFN-gamma, so no activation of macrophages and suppress the function of macrophages. Thus the CMI is being inhibited by activation of Th2 subset and the chances of infection are more in lepromatous form of leprosy. Although host defense mechanisms are quite efficient to get rid of pathogens but still there are various strategies followed by these to evade host immune system.

Strategies to Evade Host Immune Response

Extracellular bacteria

- o Some extracellular bacteria shows antigenic variations (*Neisseria gonorrhoeae*, *Salmonella typhimurium*, *E. coli*).
- o Inhibition of phagocytosis.

- o Scavenging of oxygen free radicals e.g. *S. aureus* containing one yellow pigment which quench the singlet oxygen, so not destroyed during respiratory burst.
- o Inhibition of complement system (*E. coli*, *Salmonella*).
- o Some bacteria like *Shigella flexneri* increase the apoptosis of macrophages.

Intracellular Bacteria

- o Scavenging of oxygen free radicals by *Mycobacterium leprae*.
- o Inhibition of phagolysosome formation by *Mycobacterium tuberculosis*, *Legionella pneumophila*.
- o Disruption of phagolysosome membrane and escape into cytoplasm e.g. *Listeria monocytogenes*.
- o Prevention of fusion of phagosome and lysosome (*Mycobacterium tuberculosis*, *Chlamydia trachomatis*).

When Th1 subset is activated, IFN-gamma leads to activation of macrophages which firstly engulf the bacteria within phagosome and thereby the killing mechanism is initiated with the fusion of phagosome to lysosome i.e., phagolysosome formation. Within phagolysosome the bacteria are lysed by the production of oxygen free radicals (OFRs), lysosomal enzymes and by nitric oxides (NOs). But there are certain bacteria which release certain factors leads to escaping from these killing mechanisms e.g. *Listeria monocytogenes* an intracellular Gram + bacteria leads to the production of hemolysin and phospholipase which break the phagolysosomal membrane thereby enters into the cytoplasm. In the cytoplasm of phagocytes it divides, produce acting tail and extend towards the peripheral surface and by projections taken by nearby macrophages. So not killed by CMI and capable to infect more and more macrophages.

Tuberculosis: An example for co-existence between protective immunity and pathological response

The tuberculosis bacilli, does not produce any exotoxins and endotoxins. The lesions produced in TB patients are basically as a result of host response. The bacteria resist killing within macrophages, so chronic continuous antigenic stimulation takes place which leads to activation of Th cells and macrophages. When the bacilli spread from lungs to regional lymph nodes, leads to the activation of CD4+ (Th1 mainly) cells. IFN-gamma produced by Th1 cells lead to the activation of macrophages, while TNF-alpha is having role in inflammation and decreasing the appetite (cachexia). This continuous activation leads to formation of granuloma which is a histologic hallmark for intracellular bacterial infection. The central area of necrosis is also having role in the removal of microbe as produce anoxic conditions which is not favorable for this bacilli as being aerobe. Thus granuloma formation prevents spread of bacilli, so having protective role also.

Conclusion

Bacterial pathogens are often associated with many health issues globally and are capable to cause diseases irrespective of host species involved. Although there are principal protective immune response mechanisms associated like HMI, CMI and many more which are capable of defending our system from these harmful invaders.

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