A Review on Microbial Pathogenesis and Host Response

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Himani Meena, Asad Syed, and Busi Siddhardha

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Abstract

Although the prominent convalesce in understanding of microbial pathogenicity and host immune response has been acknowledged still many obstacles has to face for proper solution for the pathogenicity problem. In the present chapter, we have tried to conclude every possible mechanism behind pathogenicity as well as the host immune responses. The relationship between microbe and host is subdivided into mutualism, commensalism, and parasitism. Microbial interaction with host cell is regulated by different routes such as adhesion, internalization,

H. Meena · B. Siddhardha (✉)
Department of Microbiology, School of Life Sciences, Pondicherry University, Puducherry, India

A. Syed
Botany and Microbiology Department, College of Science, King Saud University, Riyadh, Saudi Arabia

B. Siddhardha et al. (eds.), *Model Organisms for Microbial Pathogenesis, Biofilm Formation and Antimicrobial Drug Discovery*,
https://doi.org/10.1007/978-981-15-1695-5_4

colonization, and secretion of toxic molecules and enables bacterial cell development and growth within the host tissue. Host immune system is composed of innate and adaptive immunity. Innate immunity system involves macrophages, neutrophils, and monocytes whereas adaptive immune system provides a detailed mechanism of defense through B lymphocytes, dendritic cells, complement system, and T lymphocytes ($CD4^+$ and $CD8^+$) cells. Therefore, understanding of microbial pathogenesis and host response will enable the scientific community to come up with strategies to fight with dangerous pathogens without any reluctance towards new drug design and development.

Keywords
Microbial infection · Pathogenicity · Cellular immunity · T lymphocytes · Disease

4.1 Introduction

Microbes are the most abundant survivors on the earth with a variety of tactics to subsidize their existence on non-living and living objects. Microbial interaction with the host cell is important for establishment of the infection that lead to infectious disease and eventually death of the affected patients. World Health Organization has declared microbial infection as the second most cause of the deaths worldwide. Microbial infection can be divided into acute and persistent forms; acute infection can be cured within days of infection whereas persistent infection may have a long term effect on host system (Thakur et al. 2019). Outbreak of the pre-occurred disease with the time and antibiotic resistance towards existing drugs has increased the stress in the scientific community in urge to excavate the underlying mechanism of microbial pathogenesis. Exploring microbial pathogenesis is essential to understand the crucial course of microbial adhesion, invasion, and damage to host system. Deciphering the interaction between microbial pathogenic determinants and the factors associated with host defense system has put light on different aspects of treatment for the disease and recovery from the damage caused by the previous medication process (Solanki et al. 2018). This chapter highlights the relationship between host–pathogen, routes of infection and progression, host immune response and host mediated pathogenesis.

4.1.1 Host–Microbe Relationship

Skin is the outer most layer of the host defense system which provides early exposure to microbes and helps immune system to block the infection at initial level of defense. There are three kinds of symbiosis that occurs between pathogen and host cell depending on their constructive arrangement for survival in the host system.

4.1.1.1 Mutualism

Mutualism refers to the relationship between two individual where the host provides nutrition and habitat for the endurance and microbe supplies energy and nutrient for host development and growth. Gut microbiota shares specific relationship with the host body system. The environment and host metabolic routine has an impact on the microbiome survival in the host; a slight variation in the environment or host metabolism can cause severe changes in microbial behavior that may led to different aspects of illness (Visconti et al. 2019; Wu and Wang 2019). Gut microbiota has numerous bacterial species due to its nutrition-rich environment and can be divided into two groups, dominant (*Bacteroidetes*, *Actinobacteria*, *Firmicutes*) and facultative species (*Enterococci*, *Lactobacilli*, *Enterobacteriaceae,* and *Streptococci*). *Bifidobacteria* is a gram-positive, anaerobic bacteria with different beneficial traits such as gut immunostimulation, immunomodulation, reduced lactose intolerance, and cholesterol level in serum (Candela et al. 2008). *Bifidobacterium longum* is an intrinsic bacterium that dominates the gut intestinal tract (GIT) microbiota. Enzymes secreted by *B. longum*, i.e., glycosyl hydrolases and phosphotransferase are linked with carbohydrate utilization and offers high metabolic rate for food consumption and maintain nutritional balance throughout the food cycle (O'Callaghan and van Sinderen 2016). Another well-known microbe, *Lactobacillus* is a part of complex gut microbiome ecosystem but only 4% of the world population harbors *Lactobacillus reuteri*. Apart from playing important role in the digestive process, *L. reuteri* also prevent chances of diarrhea, prevent IgE-associated eczema and sensitization, and boost production of CD4 lymphocytes (Walter et al. 2018).

4.1.1.2 Commensalism

Commensalism represents the relationship between microbe and host where harmless parasite resides in host body without affecting host health. Commensal microbe can be present on skin (epidermis layer) and mucus layer of respiratory and gastrointestinal tract, for example, *Streptococcus pyogenes* and *Lactobacilli*. *S. pyogenes* is a commonly found bacteria on skin flora and digestive tract that maintain acidic pH level and inhibit other pathogenic strains growth. Under stress condition, *S. pyogenes* move from the normal flora to the epiglottis region and cause swelling and inflammation that lead to sore throat problem (Eloe-Fadrosh and Rasko 2013). Commensal *Lactobacilli* species (*L. iners*, *L. crispatus*, and *L. jensenii*) dwell in the vaginal system, maintain low pH condition, and release toxic compounds for extrusion of harmful microbes to prevent women from urinary tract infection (*Pseudomonas aeruginosa*, *Escherichia coli*, etc.), sexually transmitted disease (STD), and bacterial vaginosis (Antikainen et al. 2007; Eloe-Fadrosh and Rasko 2013).

4.1.1.3 Parasitism

Human provides microbe a favorable environment, protein- and nutrient-rich conditions for proper growth and development. Parasitism can be defined as co-evolution of microbe and host where microbe is totally dependent on host body for its survival. Microbial parasites, *Leishmania*, *Schistosoma*, *Toxoplasma,* and *Trypanosoma*,

are some of the rare disease causing agents which exist in human system and consume food and energy through host metabolic pathways (Tedla et al. 2019). Parasites do not harm the host system as it is required for their own survival. Two main protozoan species, *Schistosoma mansoni* (Philippsen and DeMarco 2019) and *Leishmania major* are able to develop cutaneous leishmaniasis and schistosomiasis. Establishment of the infection is mediated by microbial penetration of dermis layer through secretion of enzyme, i.e., protein disulfide isomerases (PDI) which dissolve extracellular matrix (ECM) in the skin. Matrycryptin endostatin released through PDI and ECM interaction mediates binding of *Leishmania* promastigotes to host cell and promotes their growth (Miele et al. 2019; Philippsen and DeMarco 2019).

4.2 Routes of Infection and Progression

Microbial infection can be transmitted through diverse routes based on their establishment of the disease in the host. Microbial adhesion on outer surface, invasion, colonization, and toxin secretion are some of the well-known routes based on the available literatures (Fig. 4.1).

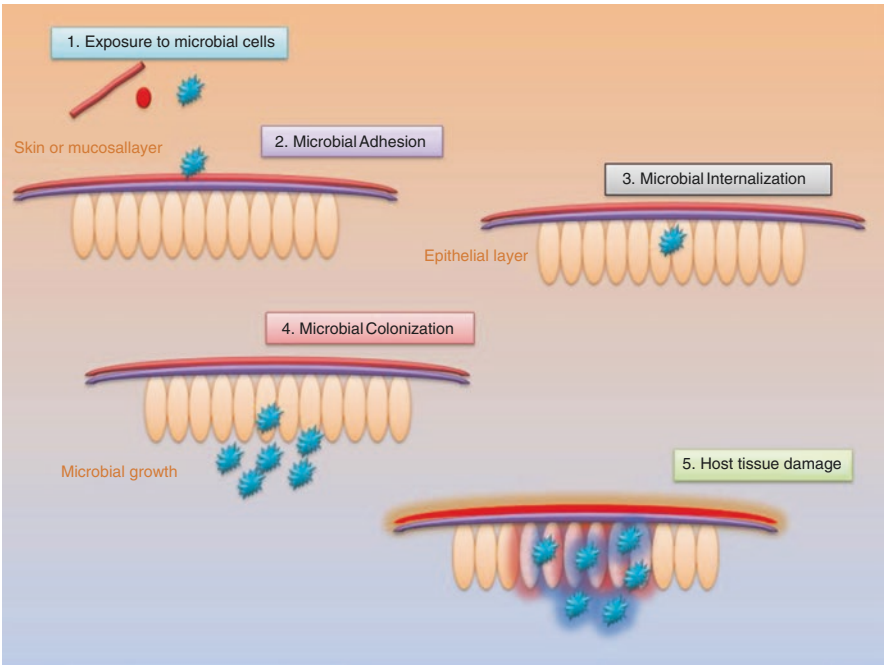

Fig. 4.1 Graphical representation of microbial infection to the host cells via different routes of pathogenesis

4.2.1 Adhesion

Microbial adhesion on the host cell membrane is the most traditional mode of establishing an infection in the host. Microbial surface protein recognizes cell surface protein that initiates microbial infection, understands different signaling pathways involved in pathogenesis, helps to achieve persistent infection, and enhances microbial invasion (Boyle and Finlay 2003). Bacterial adherence is mediated by lectin projectors that specifically bind to glycan molecules present on the host cell surface. Bacterial lectins can modify with changing glycome dynamics and environmental conditions. Lectins produced from different microorganisms are responsible for different assignment, for example, Lectin A or B from *P. aeruginosa* help to establish biofilm or botulinum from *Clostridium botulinum* which act as bacteriocins (Moonens and Remaut 2017). Surface anchored molecules are reported for their adherence towards host tissues such as in *Campylobacter flaA*, *ciaB*, *cadF*, and *pldA* and are identified to be involved in adherence and invasion of the bacteria in epithelial cells. Flagellin encoded by *flaA* gene participates in the cell adherence and fibronectin-associated surface protein is encoded by *cadF* gene. Another outer membrane phospholipase synthesizer is reported in *Campylobacter* for cell invasion (Ganan et al. 2010). Seven cell adhesion genes *ompA*, *inv*, *sip*, *aut*, *hly*, *fliC*, and *cpa* were distinguished among *Cronobacter sakazakii* and *C. malonaticus* species based on their role in adhesion and invasion process (Holy et al. 2019). Enteropathogenic *E. coli* (EPEC) one of the causative agent of diarrhea expressed *pilS* gene during adherence to intestinal epithelium and microvilli effacement and is responsible for histopathological attaching and effacing" (A/E) lesion (Garcia et al. 2019). Another example of cell adhesion protein is extracellular adherence protein (Eap) (Palankar et al. 2018) from *Staphylococcus aureus*.

4.2.2 Internalization

Bacterial invasion or internalization facilitates microbial entry to host cells and allows to multiply which results in bacterial pathogenesis. Based on the genetic and physiological features, gram-negative and gram-positive bacteria possess different structural arrangement on the cell surface. Adhesion and internalization in gram-negative bacteria is regulated through membrane channel which provides translocation of cellular molecule to host cell. Bacterial invasion system can be categorized in two specific types based on the intrusion mechanism used by the pathogen, i.e., trigger and zipper mechanism. Type III secretion system (T3SS) allows bacterial cells to invade host cell using trigger mechanism. In the process, bacterial cell accumulates their effectors into cytoplasm, releases effector protein to host cell, rearranges the host cell membrane, and allows invasion without encountering the outer membrane defense system (for example, type III secretory systems of *P. aeruginosa* and *Salmonella*) (Bohn et al. 2019, Kochut and Dersch 2012). Additional bacterial species which follows this invasion technique to infiltrate the host cells are *Salmonella*, *Shigella*, *Yersinia*, *E. coli*, and opportunistic pathogen *Citrobacter*

(Hu and Wai 2017). Human α-defensin protein is responsible for intestinal homeostasis and innate immunity. Then, it channelizes the entry of *Shigella* for adhesion, internalization, and hence enhances the pathogenicity (Xu et al. 2018). *Yersinia pestis*, *Y. enterocolitica*, and *Y. pseudotuberculosis* mediate effector translocation via cell surface appendages such as invasin (Inv), *Yersinia* adhesion A (YadA), and attachment and invasion locus (Ail). This combination of adhesion and invasion protein confers host cell interaction through leukocytes directing towards myeloid cells. On the other hand, gram-positive bacteria possess invasion molecules which are attached at C-terminus with LPXTG motif to interact with host cell receptors reservoir. Zipper mechanism involves ligand–protein binding approach. The zipper mechanism could be categorized into three different phases, first phase: interaction between bacterial cell-anchored ligand with specific cell receptor on host cell surface, second phase: activation of signaling pathways, third phase: involvement of membrane bound vacuole that help bacterial cell to be internalized by the host cell (Kochut and Dersch 2012). Gram-positive bacteria, *Listeria monocytogenes,* causative agent for listeriosis, exploit zipper mechanism involving two surface invasion factors, InlA and InlB and pore forming enzyme listeriolysin O which help bacterial cells to infect epithelial cell or blood–cerebrospinal fluid barrier and allow to proliferate in the host cytoplasm by promoting the phagolysis (Phelps et al. 2018; Grundler et al. 2013). Another bacterial surface molecule with C-terminus anchored PfbA (plasmin and fibronectin-binding protein A) via LPKTG motif from *Streptococcus pneumoniae* identifies the host cell receptors such as fibronectin, plasminogen, and serum albumin and modulates infection process (Beulin et al. 2014).

4.2.3 Colonization

Microbial colonization is defined as establishment of microorganisms on host tissue and they eventually overcome the host defense system for their proliferation and growth. Bacterial colonization can be categorized in three phases, adherence to the host cell surface, invading the host cell and suppress the host immune system for their proper reproduction or multiplication (Ribet and Cossart 2015). Failure in cell surface recognition patterns and cellular signaling pathways in host during adhesion and invasion process might have negative impact on bacterial metabolic rate ultimately leading to lack of production of virulence factors and debilitated colonization (Stones and Krachler 2016). Plaque formation on tooth enamel is one of the best examples for bacterial colonization. Bacterium, *Porphyromonas gingivalis* regulates microbial succession in the dental health where it allows growth of other bacterial species such as *S. oralis*, *S. gordonii*, *Actinomyces oris*, *Veillonella* sp., *Fusobacterium nucleatum,* and *Aggregatibacter actinomycetemcomitans* and forms biofilm on enamel (Periasamy and Kolenbrander 2009). *Bifidobacterium* is the primary bacterial species transmitted through mother's placenta to infant during delivery. It is mostly present in the epithelial layer of skin, urinary tract, or gastrointestinal tract. Several factors are available that favors colonization of *B. longum* such as availability for carbohydrate consumption via glycosyl hydrolases

and phosphotransferase, adaptation towards bile salt concentration, and abundance of adhesins and pili for bacterial entrapment on mucus layer (Gonzalez-Rodriguez et al. 2013; Grimm et al. 2014; Zhang et al. 2019a). Gut microbiome forms microbial network which maintains specific niche for microbial succession and provides nutritional support (Cui et al. 2019; Suskind et al. 2019). Gram-negative bacteria, *E. coli* colonizes epithelial layer of skin, respiratory tract, and soft tissue via penetration. *E. coli* is a causative agent for bacterial infection in urinary tract, meningitis, and bacteremia (Alfaro-Viquez et al. 2019). *Enterococcus faecalis* and *E. faecium* occupies human gastrointestinal tract and can have transitional state changes between beneficial microorganism to pathogenic strain based on the environment conditions (Banla et al. 2019). *P. aeruginosa* causes infection and injury in the epithelial layer of cornea, further followed by microbial keratitis. Microbial keratitis in another opprobrium of biofilm and colonization on the epithelial cells (Wu et al. 2019). Gram-positive bacteria, *S. aureus* is a well-known colonizer that resides within epithelial layer of nasal cavity via zipper mechanism. Bacterial cell surface adhesins, iron-regulated surface determinant A and clumping factor B (ClfB) interacts with loricrin, cytokeratin 10 (K10), involucrin, filaggrin, and small proline-rich proteins to establish an intense infection (Mulcahy and McLoughlin 2016).

4.2.4 Microbial Secretion System

P. aeruginosa produces a variety of toxins during infection but redox-active phenazine compounds (pyocyanin and pyoverdine), cell-lytic enzymes (protease, elastase, chitinase), exotoxin A, and exoenzymes are main virulence factors secreted during critical infection phase. Type 3 secretory system is a well described system known as needle complex in *P. aeruginosa* to passage effectors protein to the host cell through needle-shaped pipeline (Fig. 4.2). First, formation of the basal compartment on the bacterial surface, followed by accumulation of effector proteins in cytoplasm and formation of needle-shaped bridge outward by initiating configuration changes on the host cell surface to form a pore. In the end, energy driven translocation of the effector proteins from the bacterial cell to host cell cytoplasm (Lombardi et al. 2019). T3SS system is regulated by an operon known as exsCEBA operon whose expression is controlled by ExsA transcriptional regulator to facilitate the translocation process. ExsD acts as an anti-activator and ExsC serves as anti-antiactivator synchronized under the influence of calcium concentration in the cellular medium. Among four effector proteins, ExoU is known for phospholipase activity and possess cytotoxic effect which causes immunosuppression and activates inflammatory cascades. ExoY harbors an adenylate cyclase activity and it maintains cyclic adenosine monophosphate (cAMP) level in the cell. Bifunctional effector proteins, ExoS and ExoT, are responsible for rounding of cell and have detrimental effect on wound healing process (Dela Ahator and Zhang 2019; Sawa 2014). Pathogenic bacterium, *Vibrio cholera* spread through contaminated water consumption and produce cholera toxin, a virulence factor determined to have great impact on pathogenicity. Pili-mediated bacterial cell adhesion to the microvilli of small intestinal mucus layer leads to the release of cholera toxin from *V. cholera* at

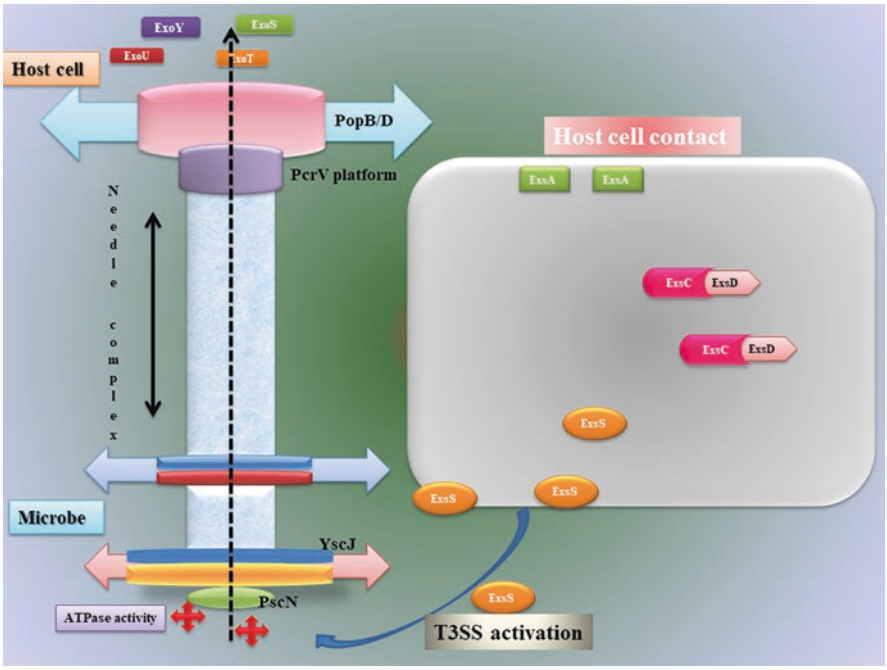

Fig. 4.2 Type III secretion system (T3SS) mediated pathogenicity in gram-negative bacteria, *Pseudomonas aeruginosa* that requires activation via exsACDE operon. During interaction with host cell, ExsC binds with ExsD to form complex and release bound ExsE for activation of T3SS

host body temperature. Cholera toxin is mucolytic by nature that disrupts the mucus layer integrity and controls bacterial penetration to the host cell. Cholera toxin is a complex structure composed of single A subunit and five B subunits. Both subunits are assigned with specific functions such as A subunit possess adenylate cyclase activity while B subunit acts as binding factor. Binding subunits binds to host surface receptor of mucus layer, called as GM1 ganglioside which forms complex to initiate phagocytosis. The cAMP concentration reaches to a threshold level and mediates release of internal Na^+, H_2O, and K^+ through increased permeability of chloride channel. Accumulation of Na^+, H_2O, and K^+ in the cytoplasm intensifies dehydration level in the infected host and causes severe diarrhea (Tirumale and Tessy 2018).

4.3 Microbial Pathogenesis and Host Immune Response

4.3.1 Innate Immune Response

The skin layer is a first line of defense as it covers the entire body as a physical barrier against environmental factors and regulates secretion of various immune response under stress conditions. It is composed of three layers, epidermis, dermis,

and hypodermis, which maintain tissue homeostasis and provoke innate defense system during infection. The outermost layer of the epidermis region is made up of stratum corneum responsible for keratinization. Keratinocytes are capable of converting themselves into corneocytes by replacing outer membrane with cornified envelope under special conditions. Corneocytes retrieve water from the external environment and maintain membrane integrity by providing moisture. Corneocytes prevents bacterial colonization by supplanting themselves via desquamation process within 2–4 weeks (Egawa and Kabashima 2018). Keratinocytes are present at epidermis layer that secretes immunostimulators like cytokines, chemokines, and Toll-like receptors and are able to recruit innate immune cells which provide temporary tolerance towards pathogens (Guttman-Yassky et al. 2019) (Fig. 4.3). Mucosal layer is primary defense line for internal organs, gives protection against pathogenic agents. It possesses typical immune cells, i.e., dendritic cell and macrophages which trigger immune responses. Immune cells identify microbial cells using pattern recognition receptors (PPRs) which determine presence of microbes via microorganism-associated molecular patterns (MAMPs). PPRs can be categorized into three different classes: surface cell-anchored molecules (CD14, CD209, CLEC4E, TLR4) and intracellular-associated (NAIP, IFIH1, DAI) and soluble (PTX4, SAA1) based on their structural motifs (Gonzalez et al. 2018). Inflammation response is an organized mechanism where chemical factors released from different immune cells activate inflammatory response system that triggers pain sensors,

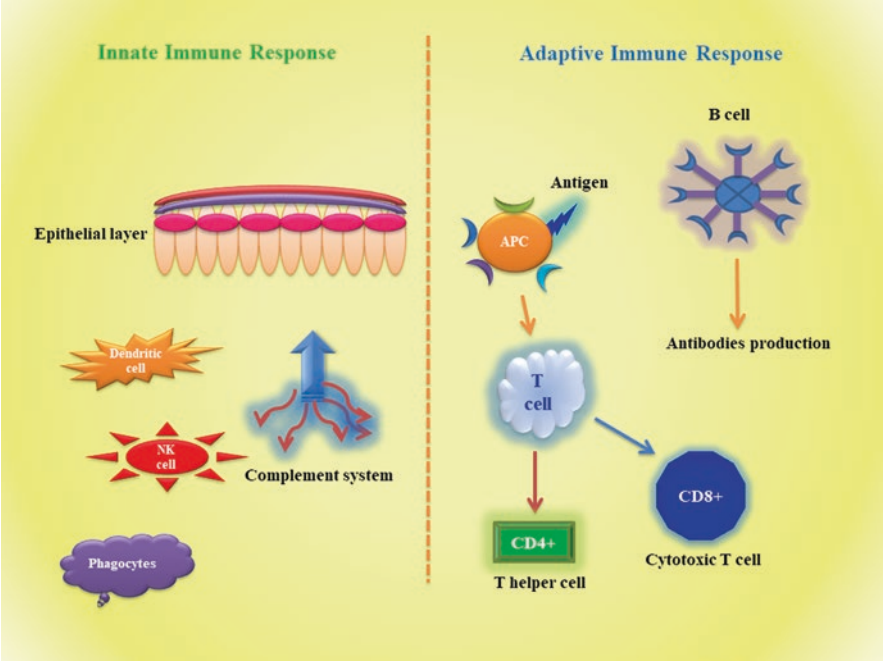

Fig. 4.3 Illustration of host immune system comprised of innate immune response and adaptive immune response

expands the blood vessels, and recruits phagocytic cells for proper immune response. Cytokines and chemokines enable the activation of macrophages and neutrophils that further magnify the immune system by involving adaptive immune response (leukocytes, lymphocytes). Innate immune response involves monocytes, macrophages, neutrophils, and natural killer cells that mediate overall production of immune response molecule for protection. Toll-like receptors (TLRs, i.e., TLR3, TLR8, TLR9) and RIG-like receptors (RLRs, i.e., RIG1) are able to identify the Zika virus and activate innate immune response against the virus. Zika virus attachment on host cell leads to high expression of interferon production (IFN-α, IFN-β, IFN-γ), cytokines (IL-1β, IL-2, IL-4, IL-6, IL-9, IL-10, IL-13, IL-17, and TNF-α,), and chemokines (CXCL-10, CXCL-12, CCL-2, and CCL-3) which have stimulatory effect on STAT1 and STAT2 phosphorylation. STAT1 and STAT2 proteins are involved in JAK-STAT pathway where signaling pathway is initiated by phosphorylation of heterodimer, STAT1 and STAT2 combined with IFN-regulatory factor 9 (IRF9) which activates transcription for anti-viral immune response (da Silva et al. 2019).

4.3.2 Adaptive or Specific Immune Responses

Adaptive immunity is an acquired immunity mechanism and can be divided into two sub-categories, humoral and cellular immunity. Humoral immunity deals with activation of B cell and maturation of B cell and involves antibodies and complement system for specific antigen clearance. While cellular immunity enables production of T cell (helper cell CD4, mature T cell) and involves antigen-presenting cells. Natural killer (NK) cell are innate lymphoid cells that can destroy foreign material without any perturbation of antigen. It induces production of different immunity cells such as cytokines, IFN-γ, tumor necrosis factor-beta (TNF-β), tumor necrosis factor-alpha (TNF-α), and granulocyte macrophage-colony stimulating factor (GM-CSF) that participate in adaptive immunity (Veerman et al. 2019; Han et al. 2019) (Fig. 4.3). B cell is the key component of humoral immune response and is bifunctional in nature as it can act as effectors as well as regulators for other immune response elements. B cell maturation, activation, and differentiation takes place in bone marrow via hematopoiesis process (Sebina and Pepper 2018). B cells are classified as B1 and B2 cells; B1 cells are innate cells originated from fetal liver derived hematopoietic stem cell (HSC). B cell which is nurtured from bone marrow HSC participates in humoral immune response. Two specific routes are assigned for B cell activation: B cell receptor stimulation (T cell dependent) and TLRs (T cell independent). B cell differentiation is able to produce various immune cells such as primary cells, memory cells, and cytokine releasing cells (Zhang et al. 2019b). B cell produces immunoglobulins, IgG and IgM responsible for opsonization and neutralization (Ganeshpurkar and Saluja 2018). Dendritic cell (DC) is involved in both innate and adaptive immune system and acts as antigen-presenting cells for T cells. After infection, DC incorporates the whole antigen or specific peptides on the cell surface and represents it to antigen specific T cell for further immune

response for microbial clearance (Heath et al. 2019). DC complex with major histocompatibility complex (MHC)-peptide stimulates production of $CD4^+$ (helper cell) and $CD8^+$ (cytotoxic cell) T cell production. Activation of cytotoxic T cell may require interaction with mature DC cell associated with $CD4^+$ cell to produce $CD8^+$ memory cells. Production of T follicular helper lineage (Tfh cells) takes place when B lymphocytes are presented with surface associated MHC II complex (Christoffersson and von Herrath 2019). Moreover, Tfh cells are linked with B cell maturation and differentiation in bone marrow with concomitant production of interleukin 4 (IL-4), interleukin 21 (IL-21), and membrane-anchored CD40 ligand (Or-Guil et al. 2018; Park et al. 2018).

4.4 Conclusion

In the book chapter, authors have tried to put lights on the interaction between microbial pathogenesis and host immune response. The microbial interaction with immune response elements has raised many questions towards scientific community due to their well-organized system. Science has many scientific solutions to overcome antibiotic resistance through interrupting microbial pathogenicity routes but still some hidden mechanisms are unknown which have to be discovered. Various unknown mechanism are present contributing to the microbial pathogenicity and host response towards the infection, hence, new approaches has to approve for prevention and control.

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