

Inate Immunity: A Review Article

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Abstract: *Innate immunity has been described as the first line of defence against infection/infectious agent. This review looked at various aspect of this important mechanism that serves to protect us against the relentless invasion by microbes.*

1. Innate Immunity

This is the first line of defence against microbial invasion includes physical and chemical barriers, humoral factors, phagocytic cells and a group of pattern- recognition receptors that identify micro-organisms- associated molecular patterns expressed on invading micro-organisms.

Human beings are exposed to millions of potential micro-organisms daily through contact, ingestion and inhalation. Our ability to avoid infection depends in part on the adaptive immune system which remembers previous encounters with specific micro-organism and destroys them when there is an attack again. The adaptive immune response are slow to develop on first exposure to a new micro-organism as specific clones of B and T cells have to become activated and expand; this can take a week or more than before the response are effective.

Single bacteria with a doubling time of one hour can produce getting to twenty (20) million progeny a full inflated infection per day. For this purpose, during the first critical hours and days of exposure to a new micro-organism we rely on our innate immune system to protect us from infection.

Innate immune responses are not specific to a particular micro- organism in a way that the adaptive immune responses behave. They depend on a group of proteins and phagocytic cells that recognize conserved features of micro-organisms and become rapidly activated to help destroy invaders. Whereas the adaptive immune system arose in growth less than five hundred (500) million years ago and is confined to vertebrates, innate immune responses have been found among both vertebrates and invertebrates, at the same time in plants and the necessary mechanisms that regulate them are conserved, the innate immune responses in vertebrates are also required to activate adaptive immune responses.

In vertebrates, skin and other epithelial surfaces including those lining the lung and gut provide a physical barrier between the inside of the body and the outside world. The pathway between neighbouring cells prevents easy entry by potentials micro- organisms. The interior epithelial surfaces are covered with a mucus layer that protects these surfaces against microbial, mechanical and chemical insult; many amphibians and fish also have a mucus layer covering their skin. The slimy mucus coating is made primarily of secreted mucin and other glycoproteins and it physically helps

prevent pathogens from adhering to the epithelium. It also facilitates their clearance by beating cilia on the epithelial cells.

Epithelial defences against microbial invasion. A cross section through the wall of the human small intestine showing three villi goblet cells secreting mucus are stained magenta. The protective mucus layer covers the exposed surfaces of the villi.

The mucus layer also contains substances that kill micro-organisms or inhibit their growth. Among the most abundant of these are antimicrobial peptides called defensins, which are found in all animals and plants. They are generally short (12-50) amino acids, positively charged and have hydrophobic or amphipathic domains in their folded structure. They made up of diverse family with a broad spectrum of antimicrobial activity, including the ability to kill or inactivate Gram- negative and Gram- positive bacteria, fungi (including yeasts), parasites (including protozoa and nematodes) and including enveloped viruses like HIV. Defensins are also the most abundant protein type in Neutrophils which use to kill phagocytosed micro-organisms.

It is still uncertain how defensins kill micro-organisms. One possibility is that they use their hydrophobic or amphipathic domains to insert into the membrane of their victims, thereby disrupting membrane integrity. Some of their selectivity for micro-organisms over host cells may come from their preference for membranes that do not contain cholesterol. After disrupting the membrane of the micro-organisms, the positively- charged peptides may also interact with various negatively- charged targets within the microbe including DNA. Because of the relatively non specific nature of the interaction between defensins and the microbes they kill, it is difficult for the microbes to require resistance to the defensins, in principle defensins might be useful as therapeutic agents to combat infection, it can be alone or in combination with traditional drugs (Murphy 2017).

The white blood cells involved in innate immunity are as follows and they have different functions:

- 1) Monocytes (which develop into macrophages)
- 2) Neutrophils
- 3) Eosinophils
- 4) Basophils
- 5) Natural killer cells

These cells also participate in innate immunity:

- 1) Mast cells
- 2) The complement system
- 3) Cytokines

2. Monocytes and Macrophages

Macrophages develop from a type of white blood cell called monocytes. Monocytes become macrophages when they move from the blood stream to the tissues. Monocytes move to the tissues when infection occurs over a period of about 8 hours, monocytes enlarge greatly and produce granules within themselves becoming macrophages. The granules are filled with enzymes and other substances that help kill and digest bacteria and other foreign cells. Macrophages stay in the tissues; they ingest bacteria, foreign cells and dead cells. (The processes of a cell ingesting are called phagocytes.) Macrophages secrete substances that attract other white blood cells to the site of the infection; they also help T cells recognize an intruder and thus also participate in acquired immunity.

Neutrophils: The most common type of white blood cells in the blood stream, are among the first immune cells to defend against infection. They are phagocytes, which ingest bacteria and other foreign cells. Neutrophils contain granules that release enzymes to help kill and digest these cells. Neutrophils circulate in the bloodstream and must be signalled to leave the blood stream and enter tissues. The signal often comes from the bacteria themselves, from complement proteins or from damaged tissue all of which produce substances that attract Neutrophils to an infected area. (The process of using substances to attract cells to a particular site is called chemotaxis). Neutrophils also release substances that produce fibers in the surrounding tissue. These fibers will trap bacteria, thus keeping them from spreading and making them easier to destroy.

Eosinophils: can ingest bacteria, but they also target foreign cells that are too large to ingest. Eosinophils contain granules that release enzymes and other toxic substances when foreign cells are encountered. These substances make holes in the target cell's membranes. Eosinophils circulate in the bloodstream. Nevertheless, they are less active against bacteria than Neutrophils and macrophages. One of their main functions is to attach to thus help immobilize and kill parasites. Eosinophils may help destroy cancer cells. They also produce substances involved in inflammation and allergic reactions. People with allergic, parasitic infections or asthma often have more eosinophils in the bloodstream than people with less numbers of eosinophils in their blood.

Basophils: They don't ingest foreign cells; they contain granules filled with histamine a substance involved in allergic reactions. When basophils encounter allergens (antigens that cause allergic reactions), they release histamine. Histamine increases blood flow to damaged tissues, resulting in swelling and inflammation. They also produce substances that attract Neutrophils and eosinophils to an infected area.

Natural Killer Cells: They are called "natural" killers because they are ready to kill immediately after they formation. Natural killer cells recognize and attach to infected cells or cancer cells, then release enzymes and other substances that damage the outer membranes of these cells. They are important in the initial defense against viral infections. Natural killer cells also produce cytokines that regulate some of the functions of T cells, B cells and macrophages.

Mast Cells: They are present in the tissues. Their function resembles that of basophils in the blood. When they encounter an allergen, they release histamine and other substances involved inflammatory and allergic reactions.

Cytokines: They are the messengers of the immune system. White blood cells and certain other cells of the immune system produce cytokines when an antigen is detected.

There are many different cytokines, which affect different parts of the immune system:

- 1) Some cytokines stimulate activity. They stimulate certain white blood cells to become more effective killers and to attract other white blood cells to infected area.
- 2) Other cytokines inhibit activity, helping end an immune response.
- 3) Some cytokines, called interferons, interfere with the reproduction (replication) of viruses; they also participated in acquired immunity (Nguyen 2008).

The Complement System

This is an essential component of humoral innate immunity comprised of a collection of plasma proteins activated by microbes, which mediates microbial destruction and inflammation. Complement activation can occur in three (3) pathways: classical, alternative and lectin. In the classical pathway the complement component C1 detects IgM, IgG1 or IgG3 bound to the surface of a microbe. C1 is made up of C1q, C1r and C1s subunits that form multimeric complexes, which bind IgM or IgG attach to microbial surfaces. C1r and C1s are serine proteases. Activated C1s produces a C3 convertase (C4b2b) that made up of C4b and C2b bound to the microbial surface. The C3 convertase cleaves C3, producing C3b, which covalently binds to C4b2b, producing C5 convertase. The C5 convertase then activates the late steps of complement activation leading to assembly of the membrane attack complex (MAC) and subsequent cytolysis. The alternative pathway is initiated by small amounts of C3b, which are spontaneously generated in the plasma. C3b that remains unbound to a cell surface are rapidly undergo and inactivated. The C3b attach to a microbe becomes a binding site for factor B. The bound factor B is then cleaved by factor D, producing factor Bb that covalently binds to C3b, forming the alternative pathway C3 convertase which activates the late steps of complement activation similar to the classical pathway. The lectin pathway is activated by MBL or ficolins binding to microbial surfaces. MBL then binds to MBL-associated serine proteases (MASPs)-1, -2 and -3. MASP-2 cleaves C4 and C2 to activate the complement cascade similar to the classical pathway.

In addition to their role in microbial lysis, complement components also serve as opsonins. Complement-coated microbes can be phagocytosed with complement receptors on phagocytes. Complement receptor type 1 (CR1) is a high affinity receptor for the C3b and C4b fragments of complement and mediates the internalization of C3b- and C4b-coated particles. CR1 on erythrocytes also mediates the clearance of immune complexes from the circulation. The complement type 2 receptor (CR2) is expressed on B cells and follicular dendritic cells and binds proteolytic fragments of C3, including C3d, C3dg and iC3b. CR2 (also known as CD21) augments humoral immune responses by enhancing B cell activation by antigen and by promoting trapping of antigen-antibody complexes in germinal centers. Enhanced B cell activation through CR2 is another way in which the innate immune system influences subsequent adaptive immune responses. In addition to this CR2 is also the receptor for Epstein-Barr virus. Complement receptor 3 (CR3) is composed of CD18 and CD11b and is expressed in PMNs and monocytes/macrophages. CR3 binds to iC3b bound to the surface of microbes leading to phagocytosis and destruction of the micro-organism. The activation of complement through the alternative pathway can greatly enhance monocyte-generated TNF- α evoked by gram-positive bacteria such as group B streptococcus.

Deficiencies of components of the complement system lead to a wide variety of diseases. Deficiencies of early components of the complement pathway are associated with invasive bacterial infections due to encapsulated organisms. In addition to this lack of early components of the complement pathway are associated with rheumatic disorders, including a lupus-like syndrome that may be due to impaired immune complex clearance, impaired clearance of apoptotic cells and loss of complement-dependent B cell tolerance. Deficiency of factor 1 is also associated with increased incidence of invasive infection with encapsulated bacteria including glomerulonephritis and autoimmune disease. Deficiency of C1-INH protein and function either hereditary or acquired leads to angioedema. C1-INH hinders C1, Factors X1a and X11a, kallikrein and thus, dysregulation of these cascades leads to generation of vasoactive products that result in angioedema. Deficiencies of late components of complement, including C5 through C9 including factors B, D and properdin result in susceptibility to meningococcal infections. Deficiency of factor H function is associated with membranoproliferative glomerulonephritis, haemolytic-uremic syndrome and age-related molecular degeneration. Deficiency of MBL is associated with increased susceptibility to bacterial infections in infancy and in individuals with conditions such as cystic fibrosis (Nesargikar PN 2012).

Complement activation targets micro-organisms for phagocytosis or lysis:

The complement system consists of about twenty (20) interacting soluble proteins that are mainly made by the liver and circulate in the blood and extracellular fluid. Most of them are inactive until they are triggered by an infection. They were originally identified by the ability to amplify and complement the action of antibodies; some components of complement are also pattern recognition receptors that can

be activated directly by micro-organism-associated immunostimulants.

The early complement components are activated first. There are three (3) sets of these complement belonging to three distinct pathways of complement activation- the classical pathway, the lectin pathway and the alternative pathway. The early components of all the three pathways act locally to activate C3, which is the pivotal component of complement. Individuals with a deficiency in C3 are subject to repeated bacterial infections. The early components and C3 are all proenzymes which are activated sequentially by proteolytic cleavage. The cleavage of each proenzyme in the series activates the next component to generate a serine protease, which cleaves the next proenzyme in the series and it will continue. Since each activated enzyme cleaves many molecules of the next proenzyme in the chain, the activation of the early components consists of an amplifying proteolytic cascade.

The principal stages in complement activation by the classical, lectin and alternative pathways in all the three pathways, the reactions of complement activation usually take place on the surface of an invading microbe, such as a bacterium C1-C9.

Many of these cleaves liberate a biologically active small peptide fragment and a membrane-binding larger fragment. The binding of the large fragment to a cell membrane, usually the surface of micro-organism helps to carry out the next reaction in the sequence. In this way complement activation is confined largely to the particular cell surface where it began. The larger fragment of C3, called C3b binds covalently to the surface of the pathogen. Once in place it is not only acts as a protease to catalyze the subsequent steps in the complement cascade, it is also recognized by specific receptors on phagocytic cells that enhance the ability of these cells to phagocytose the micro-organism. The smaller fragment of C3 (called C3a), as well as fragments of C4 and C5 act independently as diffusible signals to promote an inflammatory response by recruiting phagocytes and lymphocytes to the site of infection.

The classical pathway is activated by IgG or IgM antibody molecules attached to the surface of microbes. Mannan-binding lectin, the protein that initiates the second pathway of complement activation, this is a serum protein that forms clusters of six carbohydrate-binding heads around a central collagen-like stalk. This group binds specifically to mannose and fucose residues in bacterial cell walls that have the correct spacing and orientation to match up perfectly with the six carbohydrate-binding sites, providing an excellent example of a pattern recognition receptor. These initial binding events in the classical and lectin pathways cause the recruitment and activation of the early complement components. The alternative pathway, C3 is spontaneously activated at low levels and the resulting C3b covalently attaches to both host cells and micro-organisms. Host cells produce a series of proteins that prevent the complement reaction from going further on their cell surfaces. Because micro-organisms lack these proteins, they are singled out for destruction. Activation of the classical or lectin pathways

also activates the alternative pathway through a positive feedback loop amplifying their effects.

Membrane- immobilized C3b, gotten by any of the three pathways triggers a further cascade of reactions that leads to the assembly of the late components to form membrane attack complexes. These complexes assemble in the micro-organism membrane near the site of C3 activation and have a characteristic appearance in negatively stained electron micrographs where they are seen to form aqueous pores through the membrane. For this reason they disturb the structure of the bilayer in their vicinity, they make the membrane leaky and in some cases cause the microbial cell to lyses much as the defensins mentioned earlier.

Assembly of the late complement components to form a membrane attack complex, when C3b is produced by any of the three activation pathways it is immobilized on a membrane, where it causes the cleavage of the first of the late components, C5 to produce more electron micrographs of negatively stained complement lesions in the plasma membrane of a red blood cell. The self amplifying, inflammatory and destructive properties of the complement cascade make it essential that key activated components be rapidly inactivated after they are generated to ensure that the attack does not spread to nearby host cells. Deactivation is achieved in at least two ways. First specific inhibitor proteins in the blood or on the surface of host cells terminate the cascade either by binding or cleaving certain components once they have been activated by proteolytic cleavage. Secondly, many of the activated components in the cascade are unstable; unless they bind immediately to either an appropriate component in the cascade or to a nearby membrane and they become rapidly inactive (Lewis LA 2014).

Phagocytic cells engulf and destroy micro-organisms:

In all animals, invertebrate as well as vertebrate, the recognition of a microbial invader is usually quickly followed by engulfment by phagocytic cell. Plants however, lack this type of innate immune response. Invertebrates, macrophages reside in tissues throughout the body and are especially abundant in areas where infections are likely to arise, including the lungs and gut. They are also present in large numbers in connective tissues, the liver and the spleen. These long- lived cells patrol the tissues of the body and are among the first cells to encounter invading microbes. The second major family of phagocytic cells in vertebrates are Neutrophils and are short- live cells which are abundant in blood but not present in normal healthy tissues. They are rapidly recruited to sites of infection both by activated macrophages and by molecules such as formylmethionine-containing peptides released by the microbes themselves.

Microphages and Neutrophils display a variety of cell-surface receptors that enable them to recognize and engulf micro-organisms. These include pattern recognition receptors such as Toll-like receptors (TLRs). In addition, they have cell-surface receptors for the Fc portion of antibodies produced by the adaptive immune system, as well as the C3b component of complement. Ligand binding to any of these receptors induces actin polymerization at the site of micro-organism attachment cause the phagocyte's

plasma membrane to surround the micro-organism and engulf it in a large membrane- enclosed phagosome.

Once the micro-organism has been phagocytosed, the macrophage or neutrophil unleashes an impressive armory of weapons to kill it. The phagosome is acidified and fuses with lysosomes, which contain lysozyme and acid hydrolases that can degrade bacterial cell walls and proteins. The lysosomes also contain defensins, which make up about 15% of the total protein in Neutrophils. In addition, the phagocytes assemble an NADPH oxidase complex on the phagosomal membrane that catalyzes the production of a series of highly toxic oxygen- derived compounds, including superoxide (O₂), hydrochlorite (HOCl), the active ingredient in bleach, hydrogen peroxide, hydroxyl radicals and nitric oxide (NO). The production of these toxic compounds is accompanied by a transient increase in oxygen consumption by the cells called respiratory burst. Whereas microphages will gradually survive this killing and continue to go round tissues for other micro-organisms, Neutrophils usually die. Dead and dying Neutrophils are a great component of the pus cells that forms in acutely infected wounds. The characteristic greenish tint of pus cells is due to abundance in Neutrophils of the copper- containing enzyme myeloperoxidase, which is one of the components of active in the respiratory burst. If a micro-organism is too large to be successfully phagocytosed (if it is a large parasite eg such as nematode), a group of microphages eg Neutrophils or eosinophils will gather around the invader. They will secrete their defensins and other lysosomal products by exocytosis and will also release the toxic products of the respiratory burst. This concentrated discharge is generally sufficient to destroy the micro-organism, eosinophils attacking a schistosome larva. Large parasites, such as worms cannot be ingested by phagocytes. When the worm is coated with antibody or complement, eosinophils and other white blood cells can recognize and attack it.

Many micro-organisms have developed strategies that allow them to avoid being ingested by phagocytes. Some Gram-positive bacteria coat themselves with a very thick, slimy polysaccharide coat, or capsule that is not recognized by complement or any phagocyte receptor. Other micro-organisms are phagocytosed but avoid being killed; as we saw earlier, *Mycobacterium tuberculosis* prevents the maturation of the phagosome and thereby survives. Some micro-organisms escape the phagosome completely and yet others secrete enzymes that detoxify the products of the respiratory burst. For such cunning micro-organisms these first lines of defense are insufficient to clear the infection and adaptive immune responses are required to accommodate them (Stoermer 2011).

Activated macrophages recruit additional phagocytic cells to sites of infection

When micro-organism invades a tissue, it almost and elicits an inflammatory response. This response is characterized by pain, redness, heat and swelling at the site of infection, all caused by changes in local blood vessels. The blood vessels enlarge and become permeable to fluid and proteins, leading to local swelling and an accumulation of blood proteins that aid in defense, including the components of the complement cascade. At the same time, the endothelial cells lining the

local blood vessels are stimulated to express cell adhesion proteins that facilitate the attachment and extravasion of white blood cells, including Neutrophils, lymphocytes and monocytes (the precursors of macrophages).

The inflammatory response is mediated by a variety of signalling molecules such as prostaglandins and protein (peptide), all of which contribute to the inflammatory response. The proteolytic release of complement fragments also contribute. Some of the cytokins produced by activated macrophages are chemoattractants (known as chemokines). Some of these attract Neutrophils, which are the first cells recruited in large numbers to the site of the new infection. Others will attract monocytes and dendritic cells. The dendritic cells pick up antigens from the invading micro-organisms and carry them to nearby lymph nodes, where they present the antigens to lymphocytes to arrange the forces of the adaptive immune system. Other cytokins incites fever, a rise in body temperature. On the other hand fever helps the immune system in the fight against infection, since most bacterial and viral micro-organisms grow better at lower temperatures, whereas adaptive immune responses are more potent at higher temperatures.

Some proinflammatory signalling molecules stimulate endothelial cells to express proteins that incite blood clotting in local small vessels. By infecting the vessels and cutting off blood flow, this response can help prevent the micro-organism from entering the blood stream and spreading the infection to other parts of the body.

The same inflammatory responses which are so effective at controlling local infections, can have catastrophic consequences when they occur in a disseminated infection in the blood stream, a condition called sepsis. The systemic release of proinflammatory signalling molecules into the blood causes dilation of blood vessels, loss of plasma volume and widespread blood clotting which an often fatal condition is known as septic shock. Inappropriate or determined inflammatory responses are also associated with some chronic conditions such as asthma.

Inflammation of the airways in chronic asthma restricts breathing. Light micrograph of a section through the bronchus of a patient who died of asthma. There is almost total obstruction of the airways by a mucus plug. The mucus plug is dense inflammatory.

Just as with phagocytosis some micro-organisms have developed mechanisms either to prevent the inflammatory response or, in some places take advantage of it to spread the infection for example many viruses encode potent cytokine antagonists that block aspects of the inflammatory response. Some of these are simply modified forms of cytokine receptors, encoded by genes acquired by the viral genome from the host. They bind the cytokins with high affinity and block their activity. Some bacteria such as Salmonella induce an inflammatory response in the gut at the initial site of infection, thereby recruiting macrophages and Neutrophils that they then invade. By this the bacteria hitch a ride to other tissues in the body (DeFranco AL 2007).

Natural Killer Cells Induce Virus- Infected Cells to kill themselves

Another way that the interferons help vertebrates defend themselves against viruses is by stimulating both innate and adaptive cellular immune responses. This is how interferons enhance the expression of class 1 MHC proteins, which present viral antigens to cytotoxic T lymphocytes. Here we look at how interferons enhance the activity of natural killer cells (NK cells), which are part of the innate immune system like cytotoxic T cells, NK cells destroy virus- infected cells by inducing the infected cell to kill itself by undergoing Apoptosis. Not like T cells, however natural killer (NK) cells do not express antigen- specific receptors. How then can virus-infected cells be distinguished from uninfected cells?

Natural killer (NK) cells monitor the level of class 1 MHC proteins, which are expressed on the surface of most vertebrate cells. The presence of high levels of these proteins inhibits the killing activity of NK cells, so that the NK cells selectively kill cells expressing low levels, including both virally-infected cells and some cancer cells. Many viruses have developed mechanisms of inhibit the expression of class 1 MHC molecules on the surface of the cells they infect, in order to avoid detection by cytotoxic T lymphocytes. Adenovirus and HIV for example encode proteins that block class 1 MHC gene transcription. Herpes simplex virus and cytomegalovirus block the peptide translocators in the ER membrane that transport proteasome-derived peptides from the cytosol into the lumen of the ER; such peptides are required for newly made class 1 MHC proteins to assemble in the ER membrane and be carried through the Golgi apparatus to the cell surface. Cytomegalovirus causes the retrotranslocation of class 1 MHC proteins from the ER membrane into the cytosol, where they are rapidly destroyed by proteasomes. Proteins encoded by still other viruses prevent the delivery of assembled class 1 MHC proteins from the ER to the Golgi apparatus or from the Golgi apparatus to the plasma membrane. By evading recognition by cytotoxic T cells by these however, a virus incurs the great anger of NK cells. The local production of IFN- α and IFN- β activates the killing activity of NK cells and also increases the expression of class 1MHC proteins in uninfected cells. The cells infected with virus that blocks class 1MHC expression are thereby exposed and become the victims of the activated NK cells. Thus, it is difficult or impossible for viruses to hide from both the innate and adaptive immune systems simultaneously.

A natural killer (NK) cell attacking a cancer cell, the NK cell is the smaller cell on the left. This scanning electron micrograph was taken shortly after the NK cell attached, but before it induced the cancer cell to kill itself.

Both NK cells and cytotoxic T lymphocytes kill infected target cells by inducing them to undergo apoptosis before the virus has had a chance to replicate. It is not surprising that many viruses have acquired mechanisms to inhibit apoptosis, particularly early infection. Apoptosis depends on an intracellular proteolytic cascade, which the cytotoxic cell can trigger either through the activation of a cell-surface

death receptors or by injecting a proteolytic enzyme into the target cell. Viral proteins can interfere with nearly every step in these pathways. In some cases however, viruses encode proteins that act late in their replication cycle to induce apoptosis in the host cell thereby releasing progeny virus that can infect neighbouring cells.

The competition between micro-organisms and host defences is remarkably balanced. At present humans seem to be gaining a slight advantage, using public sanitation measures, vaccines and drugs to aid the efforts of our innate and adaptive immune systems. However, infectious and parasitic diseases are still the leading cause of death worldwide and new epidemics such as AIDS continue to emerge. The rapid evolution of micro-organisms and the almost infinite variety of ways that they can invade the human body and evade immune responses will prevent us from ever succeeding the battle completely (Bertaina A 2018)

3. Summary

The innate immune responses are the first line of defense against invading micro-organisms. They are also required to initiate specific adaptive immune responses. Innate immune responses depend on the body's ability to recognize conserved features of micro-organisms that are not present in the uninfected host. These include many types of molecules on microbial surfaces and the double-stranded RNA of some viruses. Many of these micro-organism-specific molecules are recognized by toll-like receptor proteins, which are found in plants and in vertebrate and vertebrate animals. In vertebrates, microbial surface molecules also activate complement, a group of blood proteins that act together to disrupt the membrane of the micro-organism, to target micro-organisms for phagocytosis by microphages and Neutrophils and to produce an inflammatory response. The phagocytic cells use a combination of degenerative enzymes, antimicrobial peptides and reactive oxygen species to kill the invading micro-organisms. In addition, they release signalling molecules that activate an inflammatory response and begin to put the forces of the adaptive immune system. Cells infected with viruses produce interferons, which induce a series of cell responses to inhibit viral replication and activate the killing of activities of natural killer cells and cytotoxic T lymphocytes.

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