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Relevance of Innate Immunity in Pathogenesis of Periodontitis -A review

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I. INTRODUCTION

- Immunity is derived from a Latin word IMMUNIS meaning "to make safe''
- Immune response involves recognizing the pathogen or other foreign material and mounting a reaction against it to eliminate it.
- It is the body's defense against disease causing organisms, malfunctioning cells, and foreign particles
- Disorders of the immune system can result in diseases
- All multicellular organisms possess intrinsic mechanisms for defending themselves against microbial infections
- These defense mechanisms are called as INNATE IMMUNITY as they are already present
- They are also called as NATURAL IMMUNITY or NATIVE IMMUNITY

How innate immunity and adaptive immunity are interconnected …

- Innate immunity , in addition to providing early defence against microbes also instructs the adaptive immunity to respond to different microbes .
- Adaptive immune response uses mechanisms of innate immunity to eradicate infections

How is it different from adaptive immunity …

- Innate immunity recognizes and responds to microbes but not against nonmicrobial substances
- It may also be triggered by damaged host cells
- In ADAPTIVE IMMUNITY , it must be stimulated by the microbes , and acts against nonmicrobial antigens also .

How does innate immune system recognize microbes …

- Components of Innate immunity recognize structures shared by various classes of microbes and not present on host cells
  - Phagocytes express receptors for LPS bacterial lipopolysacharides also called as ENDOTOXIN , which is present in cell wall of bacterial species
  - Terminal Mannose residues are also typical of bacteria
  - Phagocytes also recognize double stranded RNA found in viruses but not in mammalian cells
  - Phagocytes recognize unmethylated CpG oligonucleotides , common in microbial DNA butnot in mammalian DNA

- Microbial molecules which are targets of innate immunity are called as "pathogen-associated molecular patterns" , as they are shared by microbes of same type
- Receptors of innate immunity which recognize these shared structures are called as "pattern recognition receptors"

- Components of Innate immunity are evolved to recognize the structures of microbes necessary for its survival and infectivity :
  - By this feature , even microbe which has mutated , or which is not expressing the targets of innate immune response recognition , still cannot evade innate immune response
  - This is unlike adaptive immune response , where antigens can undergo mutation and may not be recognized by lymphocytes

- Innate immune system can also recognize molecules which are released from stressed or necrotic cells :
  - Such molecules come under the group of "damage-associated molecular patterns"

- Innate immune system receptors are encoded in the germline and not produced by somatic recombination of genes :

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- This is in contrast with the adaptive immune system , where the receptors (antibodies and T cell receptors) are produced by random recombination of genes ,
- The recombination can produce different receptors but does not have a predetermined specificity

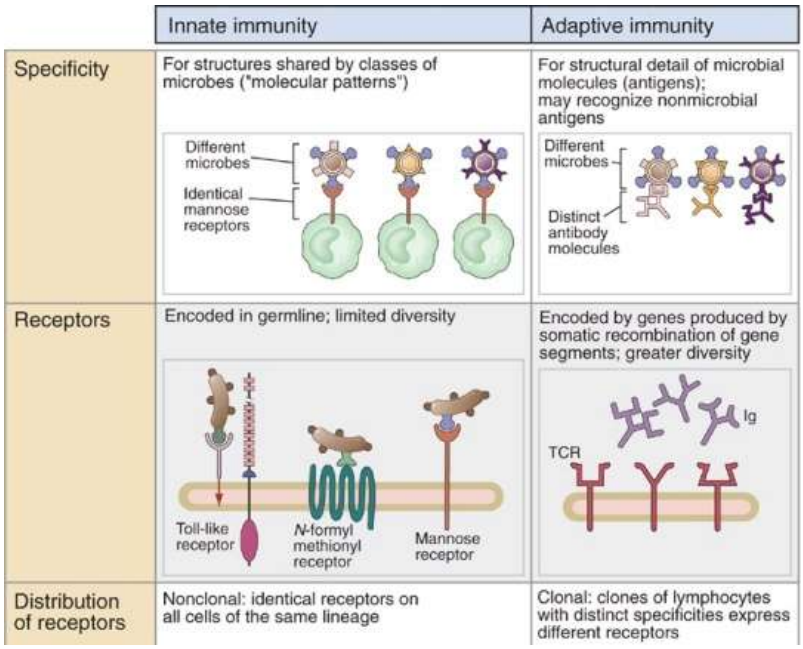
- Innate immunity does not attack the host :
- This is due to the inherent specificity of innate immunity for microbial structures
- Mammalian cells also express regulatory molecules which prevent innate immune reactions

- Innate immune systems respond in same way to repeated attacks with the same microbes , but adaptive immune system responds more efficiently to each attack
- This is because innate immune response does not show any memory

- The principal types of reactions for innate immune system is INFLAMMATION and ANTI-VIRAL DEFENSE :
- Inflammation is due to recruitment and activation of leukocytes
- Antiviral activity is due to action of Natural killer cells (NK CELLS) and cytokines and interferons.

Based on these features , innate and adaptive immunity can be differentiated as …

	INNATE	ADAPTIVE
Specificity	Specific for structures common for microbes	Specific for structures of antigens
Receptors	Limited diversity of receptors ,and are encoded in the germline	Greater diversity of receptors , and are encoded by genes
Distribution of receptors	Nonclonal distribution : identical receptors on all cells	Clonal distribution : clones of lymphocytes with distinct specificities express different receptors



What are the Receptors of Innate Immunity for microbes …

- The receptors are present on the cells which react against microbes

- Several classes of receptors are present for different types of microbial products

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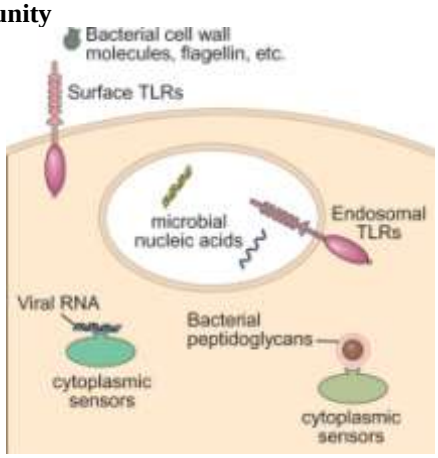
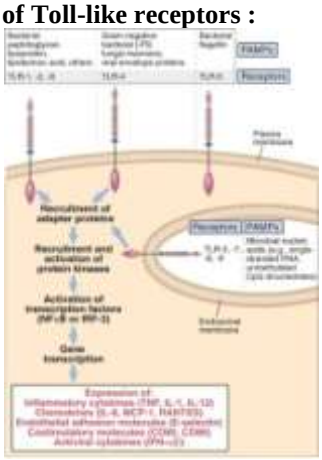
Cellular locations for receptors of innate immunity



What are the TOLL LIKE RECEPTORS …

- It is homologous with Drosophila protein called Toll .
- They are specific for different components of microbes
  - TLR-2 is essential for responses to several bacterial lipoglycans
  - TLR-3 ,TLR-7 and TLR-8 for viral nucleic acids
  - TLR-4 for bacterial lipopolysacharide or endotoxins
  - TLR-5 for a component of bacterial flagella called as flagellin
  - TLR-9 for unmethylated CpG oligonucleotides
- When the TLR's are engaged , signals are generated which activate transcription factors and stimulate expression of cytokines , enzymes and proteins involved in antimicrobial functions

Functions of Toll-like receptors :



Where are Toll Like Receptors present …

- Some are present on the cell surface : they recognize products of extracellular microbes
- Some are present in the endosomes , which ingest the microbes

What are the other receptors of Innate Immunity …

- Cell surface receptor recognizes peptides that begin with N-formyl methionine , which is present in bacterial proteins
- Receptor for terminal Mannose residues is involved in phagocytosis of bacteria
- Cytoplasmic receptors recognize viral nucleic acids or bacterial peptides
- Other cytoplasmic receptors recognize components of dead cells, uric and DNA
- Some receptors associate with a multi-protein complex called the INFLAMMASOME , which transmits signals that activate an enzyme and cleaves precursor of cytokine interleukin-1 to generate interleukin-1 in active form

With regard to inflammasome , what are autoinflammatory syndromes ?

- Certain mutations in the genes,can lead to gain in function and affect the inflammasome and lead to these rare diseases
- The clinical manifestations are a result of excessive interleukin-1 production
- Interleukin-1 antagonists are highly effective therapies

What are the components of Innate immunity …

- The innate immunity consists of :
  - Epithelial barriers
  - Cells in circulation and tissues
  - Plasma proteins

How the epithelial barriers take part in innate immunity …

- Common portals of entry for microbes are :
  - Skin
  - Gastrointestinal tract
  - Respiratory tract
- All three entry portals are lined by continuous epithelia, which physically interfere with entry of microbes .
- Epithelia contain a type of lymphocyte called intraepithelial lymphocytes, which belong to T cell lineage , but express antigen receptors .
- Some of these T cells express receptors composed of γ and δ chains not α and β T cell receptors
- These recognize microbial lipids and other structures shared b microbes of the same type

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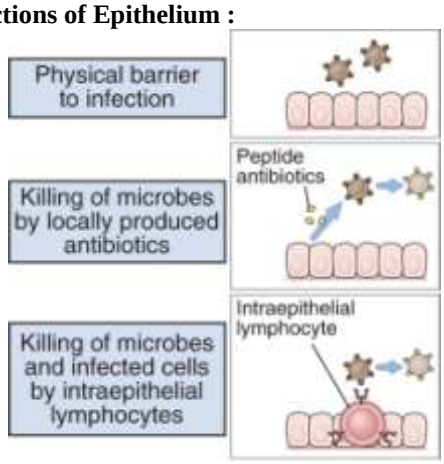
Functions of Epithelium :



- So , to summarize the functions of epithelia in innate immunity :
  - Physical barrier to infection
  - Killing of microbes by locally produced antibiotics
  - Killing of microbes and infected cells by intraepithelial lymphocytes

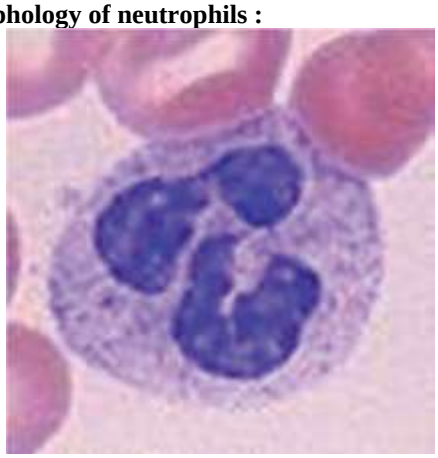
How the phagocytes take part in innate immunity …

- Two types of circulating phagocytes are neutrophils and monocytes
- They are respond to site of infection , and recognize and ingest microbes for intracellular killing

What is the role of Neutrophils in innate immunity …

- They are the most abundant leukocytes in the blood
- Also called as polymorphonuclear leukocytes

Morphology of neutrophils :



- The normal count is about 4000-10000 per µl of blood
- But, in response to infections, the production of neutrophils from the bone marrow increases rapidly, and their number may rise to 20,000 per µL of blood.
- The production of neutrophils is stimulated by cytokines, known as colony-stimulating factors, that are secreted by many cell types in response to infections and act on bone marrow stem cells to stimulate proliferation and maturation of neutrophil precursors.
- Neutrophils are the first cell type to respond to most infections, particularly bacterial and fungal infections.
- They ingest microbes in the circulation, and they rapidly enter extravascular tissues at sites of infection, where they also ingest microbes and die after a few hours

A more detailed presentation of neutrophils will be given later ….

What is the role of Monocytes in Innate immunity …

- Monocytes are less abundant than neutrophils, numbering 500 to 1000 per µL of blood
- They ingest microbes in the blood and in tissues.
- Unlike neutrophils, monocytes that enter extravascular tissues survive in these sites for long periods
- In the tissues, these monocytes differentiate into cells called **macrophages**.
- Blood monocytes and tissue macrophages are two stages of the same cell lineage, which often is called the mononuclear phagocyte system.
- Resident macrophages are found in connective tissues and in every organ in the body, where they serve the same function as that of mononuclear phagocytes.

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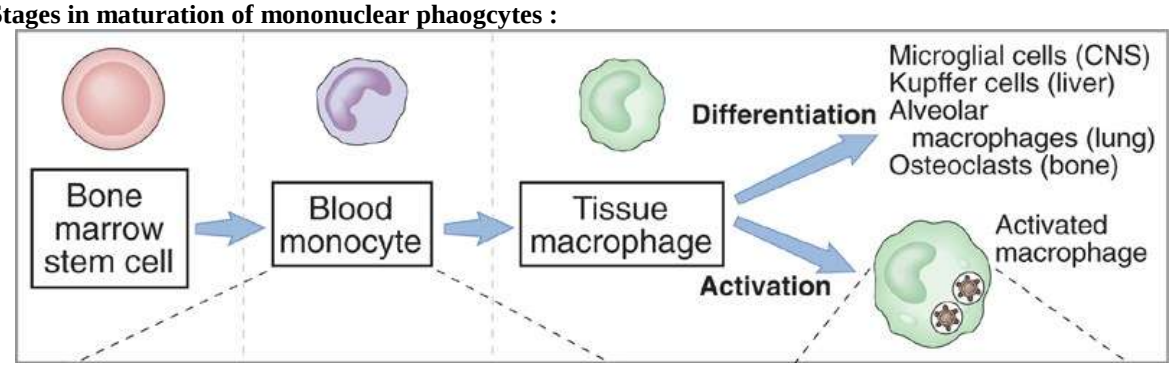
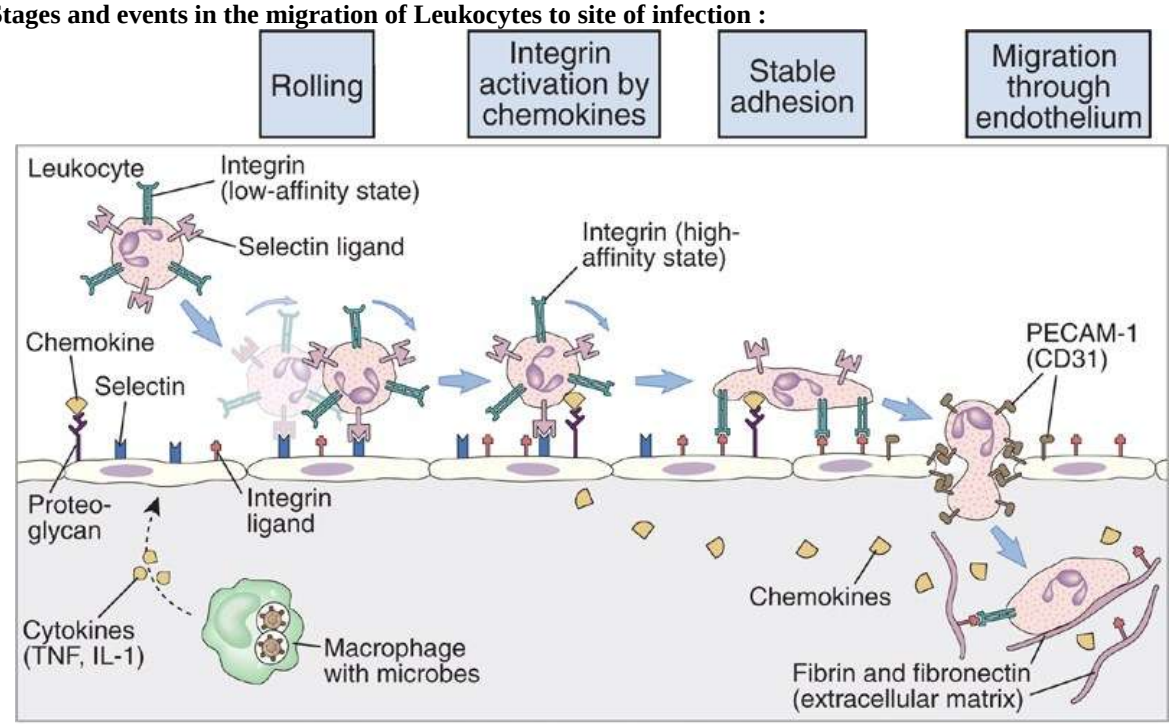
Stages in maturation of mononuclear phaogcytes :



So , the features of Neutrophils and monocytes …

- Neutrophils and monocytes migrate to extravascular sites of infection by binding to endothelial adhesion molecules and in response to chemoattractants that are produced on encounter with microbes.:
  - The accumulation of leukocytes at sites of infection, with concomitant vascular dilation and increased leakage of fluid and proteins in the tissue, is called **inflammation.** Inherited deficiencies in integrins and selectin ligands lead to defective leukocyte recruitment to sites of infection and increased susceptibility to infections.

Stages and events in the migration of Leukocytes to site of infection :



In this regard , what are leukocyte adhesion deficiencies …

- Inherited deficiencies in integrins and selectin ligands lead to defective leukocyte recruitment to sites of infection and increased susceptibility to infections.
- These disorders are called leukocyte adhesion deficiencies.

Other features of Neutrophils and Macrophages …

- **Neutrophils and macrophages use several types of receptors to recognize microbes in the blood and extravascular tissues and to initiate responses that function to destroy the microbes :**
  - These receptors are the TLRs and receptors for formyl methionine peptides, and receptors for

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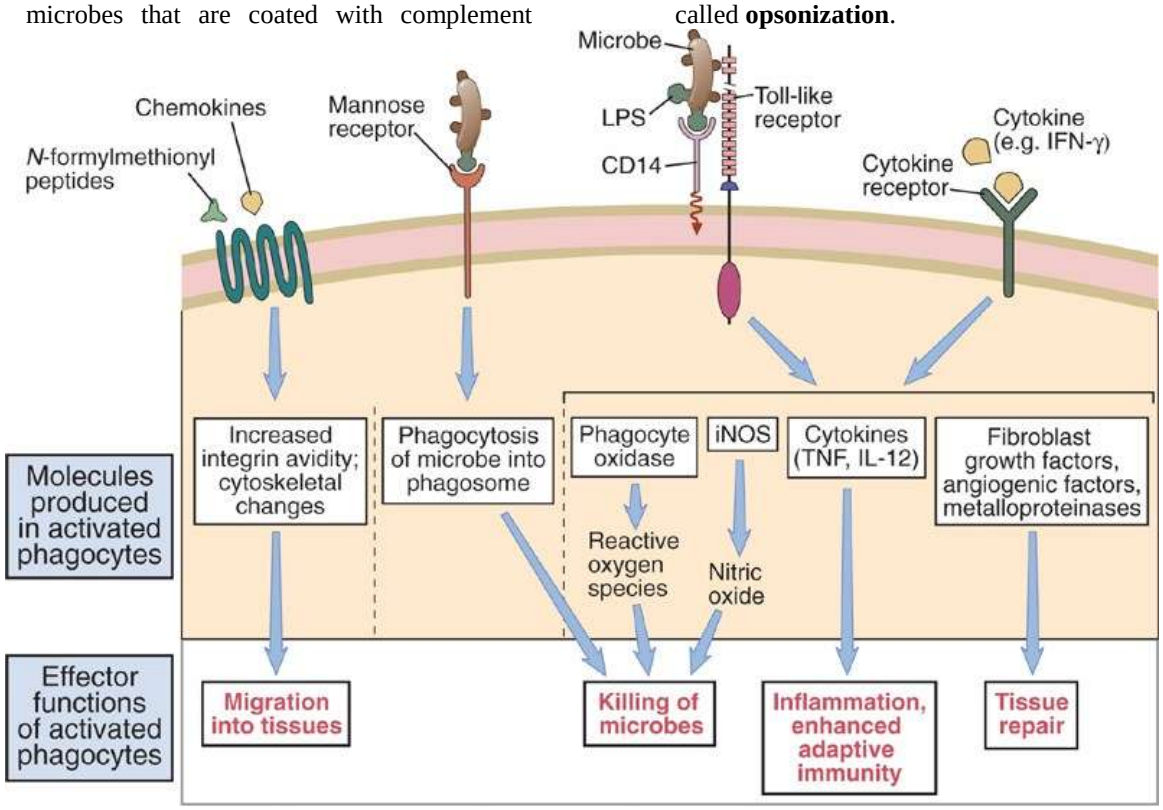
cytokines, mainly IFN-γ and chemokines, mannose receptors and scavenger receptors.

- Receptors for products of complement activation and for antibodies avidly bind microbes that are coated with complement proteins and function in ingestion of microbes and in the activation of the phagocytes.
- The process of coating microbes for efficient recognition by phagocytes is called **opsonization**.



- **Neutrophils and macrophages ingest (phagocytose) microbes and destroy the ingested microbes in intracellular vesicles:**
- Phagocytosis is a process that begins with membrane receptors binding to the microbe, followed by extension of the phagocyte plasma membrane around the microbe.
- The membrane then closes up and pinches off, and the microbe is internalized in a membrane-bound vesicle, called a phagosome.
- The phagosomes fuse with lysosomes to form phagolysosomes. At the same time as the microbe is being bound by the phagocyte's receptors and ingested, the receptors deliver signals that activate several enzymes in the phagolysosomes.
- One of these enzymes, called phagocyte oxidase, converts molecular oxygen into superoxide anion and free radicals. These substances are called reactive oxygen species (ROS), and they are toxic to the ingested microbes.
- A second enzyme, called inducible nitric oxide synthase, catalyzes the conversion of arginine to nitric oxide (NO), also a microbicidal substance.
- The third set of enzymes are lysosomal proteases, which break down microbial proteins.
- All of these microbicidal substances are produced mainly within lysosomes and phagolysosomes, where they act on the ingested microbes but do not damage the phagocytes.
- In some instances, the same enzymes and ROS may be liberated into the extracellular space and may injure host tissues.
- This is the reason why inflammation, usually a protective host response to infections, may cause tissue injury as well.

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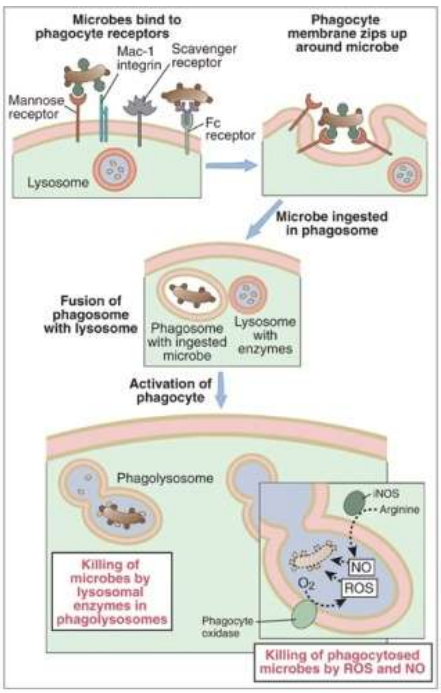


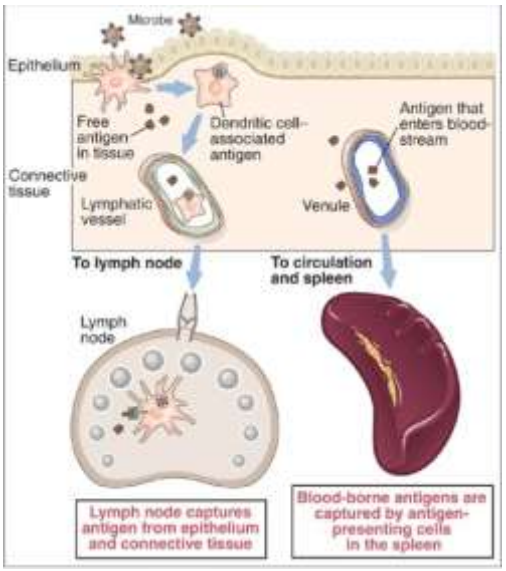
In this regard, what is Chronic granulomatous disease …

- Inherited deficiency of the phagocyte oxidase enzyme is the cause of an immunodeficiency disease called chronic granulomatous disease.
- In this disorder, phagocytes are unable to eradicate intracellular microbes, and the host tries to contain the infection by calling in more macrophages and lymphocytes, resulting in collections of cells around the microbes that are called granulomas

What is the role of Dendritic Cells in Innate Immunity …

- Dendritic cells respond to microbes by producing cytokines that recruit leukocytes and initiate adaptive immune responses.
- Dendritic cells constitute an important bridge between innate and adaptive immunity.

- **Protein antigens of microbes that enter the body are captured mainly by dendritic cells and concentrated in the peripheral lymphoid organs, where immune responses are initiated**
- The epithelia and subepithelial tissues contain a network of dendritic cells.
- The same cells are present in the T cell-rich areas of peripheral lymphoid organs and, in smaller numbers, in most other organs
- In the skin, the epidermal dendritic cells are called Langerhans cells.
- Epithelial dendritic cells are said to be "immature," because they are inefficient at stimulating T lymphocytes.
- These immature dendritic cells express membrane receptors that bind microbes, such as receptors for terminal mannose residues on glycoproteins,
- Dendritic cells use these receptors to capture and endocytose microbial antigens.
- Some soluble microbial antigens may enter dendritic cells by pinocytosis.



So , what is pinocytosis …

Pinocytosis or cell-drinking or bulk-phase pinocytosis or non-specific, non-absorptive pinocytosis or fluid endocytosis is a form of endocytosis

Small particles are brought into the cell, forming an invagination, and then they are suspended within small vesicles called as pinocytotic vesicles that subsequently fuse with lysosomes to hydrolyze, or to break down, the particles.

What is the role of Dendritic cells (continued) …

- At the same time, microbes stimulate innate immune reactions by binding to Toll-like receptors (TLRs) and other sensors of microbes in the dendritic cells, and in epithelial cells and resident macrophages in the tissue
- Results in production of inflammatory cytokines such as tumor necrosis factor (TNF) and interleukin-1 (IL-1).
- Activated dendritic cells lose their adhesiveness for epithelium and begin to express the surface receptor CCR7 which is

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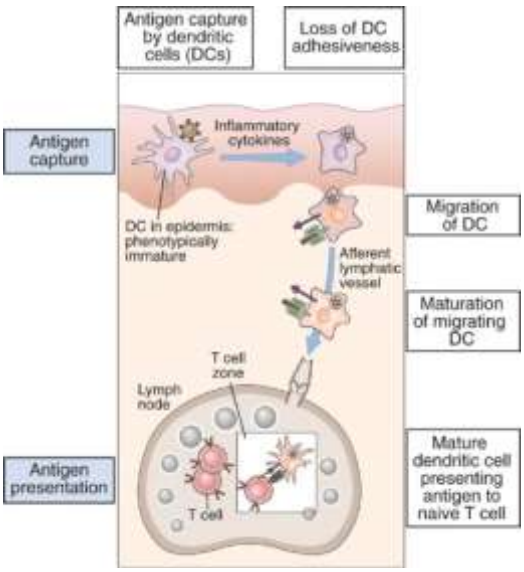
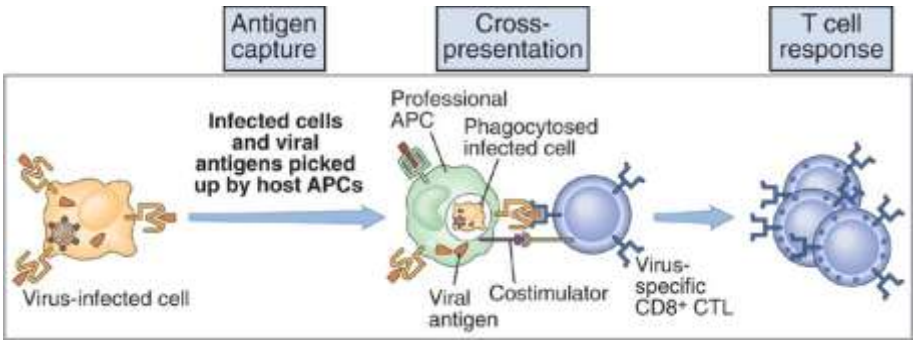
specific for chemoattracting cytokines (chemokines) produced in the T cell zones of lymph nodes.

- These chemokines direct the dendritic cells to exit the epithelium and migrate through lymphatic vessels to the lymph nodes draining that epithelium
- During the process of migration, the dendritic cells mature from cells designed to capture antigens into APCs capable of stimulating T lymphocytes.
- This maturation is reflected in increased synthesis and stable expression of MHC molecules, which display antigen to T cells.
- Soluble antigens in the lymph are picked up by dendritic cells that reside in the lymph nodes, and blood-borne antigens are handled in the same way by dendritic cells in the spleen.
- The net result of this sequence of events is that the protein antigens of microbes that enter the body are transported to and concentrated in the regions of lymph nodes where the antigens are most likely to encounter T lymphocytes.



- **Dendritic cells also are involved in initiating the responses of $CD8^+$ T lymphocytes to the antigens of intracellular microbes.**
  - Dendritic cells ingest virus infected cells and display the antigens present in the infected cells for recognition by $CD8^+$ T lymphocytes.
  - This process is called **cross-presentation** (or cross-priming),
  - In one cell type, the dendritic cells, can present the antigens of other cells, the infected cells, and prime (or activate) naive T lymphocytes specific for these antigens.
  - The dendritic cells that ingest infected cells may also present microbial antigens to $CD4^+$ helper T lymphocytes.



What are Natural Killer Cells …

- (NK) cells are a class of lymphocytes
- NK cells make up approximately 10% of the lymphocytes in the blood and peripheral lymphoid organs.
- These cells contain abundant cytoplasmic granules and express characteristic surface markers, but they do not express immunoglobulins and T cell receptors, the antigen receptors of B and T lymphocytes, respectively.

What is the role of Natural Killer Cells in Innate Immunity …

- Natural killer (NK) cellsrecognize infected and stressed cells and respond by killing these cells and by secreting themacrophage-activating cytokine IFN-γ

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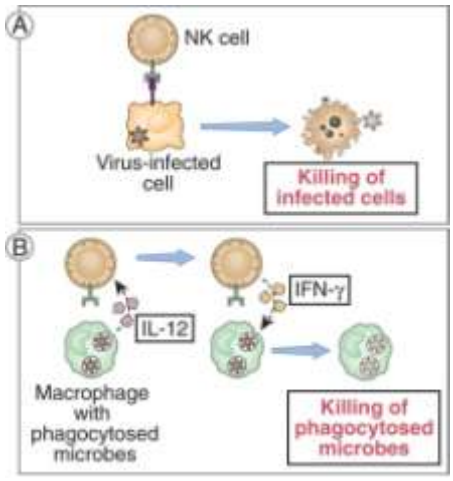


- Activation of NK cells triggers the discharge of proteins contained in the NK cells cytoplasmic granules toward the infected cells.
- These NK cell granule proteins include molecules that enter the infected cells and activate enzymes that induce apoptotic death.
- By killing infected host cells, NK cellsfunction to eliminate cellular reservoirs of infection and eradicate infections by obligate intracellular microbes, such as viruses.
- Activated NK cells also synthesize and secrete the cytokine IFN-γ. IFN-γ activates macrophages to become more effective at killing phagocytosed microbes.
- NK cells and macrophages function cooperatively to eliminate intracellular microbes:

- Macrophages ingest microbes and produce IL-12,

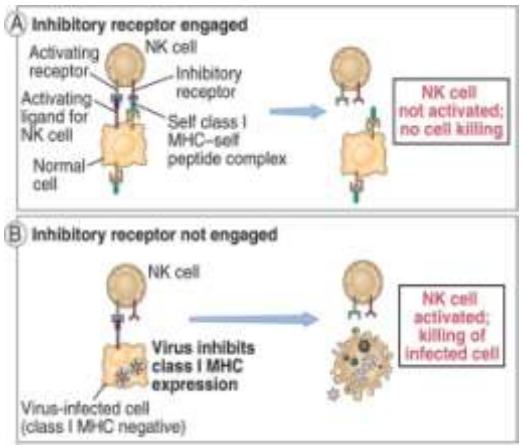
↓

- IL-12 activates NK cells to secrete IFN-γ,

↓

- IFN-γ in turn activates the macrophages to kill the ingested microbes.

- **The activation of NK cells is determined by a balance between engagement of activating and inhibitory receptors**
- The activating receptors recognize cell surface molecules that commonly are expressed on stressed cells, including those infected with viruses and intracellular bacteria.
- Other activating receptors are DNA damage and malignant transformation
- Another activating receptors of NK cells is called NKG2D and it recognizes molecules that resemble class I major histocompatibility complex (MHC) proteins and is expressed in response to many types of cellular stress.
- Another activating receptor is specific for IgG antibodies bound to cells.
- The recognition of antibody-coated cells results in killing of these cells, a phenomenon called **antibody-dependent cellular cytotoxicity (ADCC).**
- Activating receptors on NK cells have signaling subunits that contain **immunoreceptor tyrosine-based activation motifs (ITAMs)** in their cytoplasmic tails.
- ITAMs, which also are present in subunits of lymphocyte antigen receptors, become phosphorylated on tyrosine residues when the receptors bind their ligands.
- The phosphorylated ITAMs bind and promote the activation of cytoplasmic protein tyrosine kinases,
- These enzymes phosphorylate, and activate, other substrates eventually leading to cytotoxic granule exocytosis and production of IFN-γ.



- The inhibitory receptors of NK cells are specific for self class I MHC molecules, which are expressed on all healthy nucleated

cells and function to block signaling by activating receptors.
- The host uses CTLs to recognize MHC-displayed viral antigens, viruses shut off MHC expression, and NK cells have evolved to respond to the absence of MHC molecules.

What are the other classes of Lymphocytes that take part in Innate immunity …
- Several types of lymphocytes that have some features of T and B lymphocytes also function in the early defense against microbes and may be considered as part of the innate immune system.
- They have limited diversity.
- As mentioned earlier, **γδ T cells** are present in epithelia.
- **NK-T cells,** some of which express surface molecules typically found on NK cells, are present in epithelia and lymphoid organs.
- They recognize microbial lipids bound to a class I MHC-related molecule called CD1.
- **B-1 cells** are a population of B lymphocytes that are found mostly in the peritoneal cavity and mucosal tissues, where they produce antibodies in response to microbes and microbial toxins that pass through the walls of the intestine.
- Most of the circulating IgM antibodies found in the blood of normal individuals, called **natural antibodies**, are the products of B-1 cells, are specific for carbohydrates that are present in the cell walls of many bacteria.
- Another type of B lymphocyte, called **marginal zone B cells,** is present at the edges of lymphoid follicles in the spleen and other organs and also is involved in rapid antibody responses to blood-borne polysaccharide-rich microbes.
- Thus , these populations of lymphocytes make responses that are characteristic of adaptive immunity such as antibody production but have features of innate immunity such as rapid responses and limited diversity of antigen recognition

What is the role of the Complement system in Innate Immunity …
- The complement system is a collection of circulating and membrane-associated proteins that are important in defense against microbes.
- Many complement proteins are proteolytic enzymes, and complement activation involves the sequential activation of these enzymes, sometimes called an enzymatic cascade.
- The complement cascade may be activated by any of three pathways.
- The **alternative pathway** is triggered when some complement proteins are activated on microbial surfaces and cannot be controlled, because complement regulatory proteins are not present on microbes (but are present on host cells). This pathway is a component of innate immunity.
- The**classical pathway** is triggered after antibodies bind to microbes or other antigens and is thus a component of the humoral arm of adaptive immunity.
- The **lectin pathway** is activated when a plasma protein, mannose-binding lectin, binds to terminal mannose residues on the surface glycoproteins of microbes.
- This lectin activates proteins of the classical pathway, but because it is initiated by a microbial product, in the absence of antibody, it is a component of innate immunity.
- Activated complement proteins function as proteolytic enzymes to cleave other complement proteins.
- The central component of complement is a plasma protein called C3, which is cleaved by enzymes generated in the early steps.
- The major proteolytic fragment of C3, called C3b, becomes covalently attached to microbes and is able to activate downstream complement proteins on the microbial surface.
- The three pathways of complement activation differ in how they are initiated, but they share the late steps and perform the same effector functions.

What are the functions of Complement system in host defense …
- First, C3b coats microbes and promotes the binding of these microbes to phagocytes, by virtue of receptors for C3b that are expressed on the phagocytes. Microbes that are opsonized with complement proteins are rapidly ingested and destroyed by phagocytes.
- Second, some proteolytic fragments of complement proteins, especially C5a and C3a, are chemoattractants for phagocytes, and they promote leukocyte recruitment **(inflammation)** at the site of complement activation.
- Third, complement activation leads to the formation of a polymeric protein complex that inserts into the microbial cell membrane, disturbing the permeability barrier and

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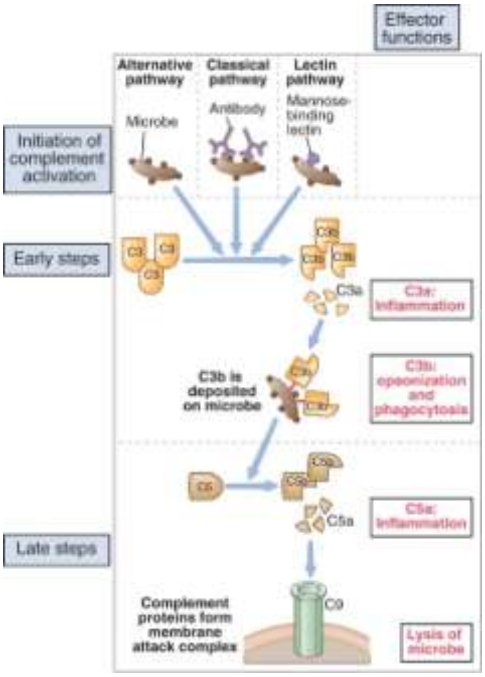
causing either osmotic lysis or apoptotic death of the microbe.



What is the role of Cytokines in Innate Immunity …

- Cytokines are soluble proteins that mediate immune and inflammatory reactions and are responsible for communications between leukocytes and between leukocytes and other cells.
- Most cytokines are called **interleukins,** implying that these molecules are produced by leukocytes and act on leukocytes
- The principal sources of cytokines are dendritic cells and macrophages activated by recognition of microbes.
- Binding of bacterial components or of viral molecules to TLRs of dendritic cells and macrophages is a powerful stimulus for cytokine secretion by the cells.
- Cytokines are secreted in small amounts in response to an external stimulus and bind to high-affinity receptors on target cells.
- Most cytokines act on the cells that produce them (autocrine actions) or on adjacent cells (paracrine actions).
- In innate immune reactions against infections, many dendritic cells and macrophages may be activated that lead to production of large amounts of cytokines ,and these cytokines can be active distant from their site of secretion (endocrine actions).

What are the functions of Cytokines …

- TNF, IL-1, and chemokines are the principal cytokines involved in recruiting blood neutrophils and monocytes to sites of infection. At high concentrations, TNF promotes thrombus formation on the endothelium and reduces blood pressure by a combination of reduced myocardial contractility and vascular dilatation and leakiness.
- **Septic Shock :** Severe gram-negative bacterial infections sometimes lead to a lethal clinical syndrome called **septic shock.**
  - It is characterized by low blood pressure , disseminated intravascular coagulation, and metabolic disturbances.
  - The early manifestations of septic shock are caused by very high levels of TNF, which is produced in response to the bacteria.
- Dendritic cells and macrophages also produce IL-12 in response to LPS and other microbial molecules. The role of IL-12 in activating NK cells leads to macrophage activation, has been mentioned previously.
- NK cells produce IFN-γ, whose function as a macrophage-activating cytokine .As IFN-γ is produced by T cells also, it is considered a cytokine of both innate immunity and adaptive immunity.
- In viral infections, dendritic cells, macrophages, and other infected cells produce cytokines called type I interferons, which inhibit viral replication and prevent spread of the infection to uninfected cells. A type I IFN called IFN-α is used clinically to treat chronic viral hepatitis.

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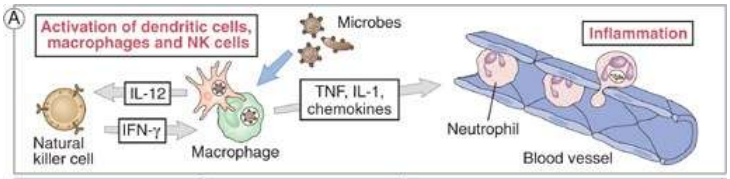

B

Cytokine	Principal cell source(s)	Principal cellular targets and biologic effects
Tumor necrosis factor (TNF)	Macrophages, T cells	Endothelial cells: activation (inflammation, coagulation) Neutrophils: activation Hypothalamus: fever Liver: synthesis of acute phase proteins Muscle, fat: catabolism (cachexia) Many cell types: apoptosis
Interleukin (IL-1)	Macrophages, endothelial cells, some epithelial cells	Endothelial cells: activation (inflammation, coagulation) Hypothalamus: fever Liver: synthesis of acute phase proteins T cells: T_H17 differentiation
Chemokines	Macrophages, dendritic cells, endothelial cells, T lymphocytes, fibroblasts, platelets	Leukocytes: Increased integrin affinity, chemotaxis, activation
Interleukin-12 (IL-12)	Dendritic cells, macrophages,	NK cells and T cells: IFN-γ production, increased cytotoxic activity T cells: T_H1 differentiation
Interferon-γ (IFN-γ)	NK cells, T lymphocytes	Activation of macrophages Stimulation of some antibody responses
Type I IFNs (IFN-α, IFN-β)	IFN-α: dendritic cells, macrophages IFN-β: fibroblasts	All cells: anti-viral state, increased class I MHC expression NK cells: activation
Interleukin-10 (IL-10)	Macrophages, dendritic cells, T cells	Macrophages, dendritic cells: inhibition of IL-12 production, reduced expression of costimulators and class II MHC molecules
Interleukin-6 (IL-6)	Macrophages, endothelial cells, T cells	Liver: synthesis of acute phase proteins B cells: proliferation of antibody-producing cells T cells: T_H17 differentiation
Interleukin-15 (IL-15)	Macrophages, others	NK cells: proliferation T cells: proliferation
Interleukin-18 (IL-18)	Macrophages	NK cells and T cells: IFN-γ production
TGF-β	Many cell types	Inhibition of inflammation T cells: differentiation of T_H17, regulatory T cells

What are the other plasma proteins of Innate Immunity …

- Several circulating proteins in addition to complement proteins are involved in defense against infections.
- Plasma mannose-binding lectin (MBL) is a protein that recognizes microbial carbohydrates and can coat microbes for phagocytosis or activate the complement cascade by the lectin pathway
- MBL belongs to the collectin family of proteins, contain a carbohydrate-binding (lectin) domain.
- Surfactant proteins in the lung also belong to the collectin family and protect the airways from infection.
- C-reactive protein (CRP) binds to phosphorylcholine on microbes and coats the microbes for phagocytosis by macrophages, which express a receptor for CRP.
- The circulating levels of many of these plasma proteins increase rapidly after infection. This protective response is called the **acute phase response** to infection

So , when the components of Innate immunity are so effective ,
How do Microbes evade Innate Immunity …

- Pathogenic microbes have evolved to resist the mechanisms of innate immunity and are still able to enter and colonize their hosts.
- Some intracellular bacteria resist destruction inside phagocytes.
- Listeria monocytogenes produces a protein that enables it to escape from phagocytic vesicles and enter the cytoplasm of infected cells, where it is no longer susceptible to reactive oxygen species and nitric oxide (which are produced mainly in phagolysosomes).
- The cell walls of mycobacteria contain a lipid that inhibits fusion of vesicles containing ingested bacteria with lysosomes.
- Other microbes have cell walls that are resistant to the actions of complement proteins.

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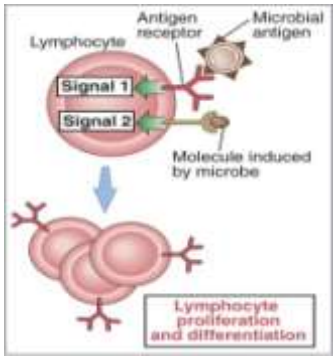
Mechanism of immune evasion	Organism (example)	Mechanism
Resistance to phagocytosis	Pneumococci	Capsular polysaccharide inhibits phagocytosis
Resistance to reactive oxygen species in phagocytes	Staphylococci	Production of catalase, which breaks down reactive oxygen intermediates
Resistance to complement activation (alternative pathway)	*Neisseria meningitidis*	Sialic acid expression inhibits C3 and C5 convertases
	Streptococci	M protein blocks C3 binding to organism, and C3b binding to complement receptors
Resistance to antimicrobial peptide antibiotics	*Pseudomonas*	Synthesis of modified LPS that resists action of peptide antibiotics

As mentioned previously,
How does Innate Immunity stimulate the Adaptive Immunity …

- **Innate immune responses generate molecules that function as "second signals," together with antigens, to activate T and B lymphocytes.**
  - Antigen-specific lymphocytes requires two signals: Antigen itself is "signal 1," and microbes, innate immune responses to microbes, and host cells damaged by microbes all may provide "signal 2".
  - This requirement for microbe-dependent second signals ensures that lymphocytes respond to infectious agents and not to harmless, noninfectious substances.
  - In experimental situations or for vaccination, adaptive immune responses may be induced by antigens without microbes.
  - In all such cases, the antigens have to be administered with substances, called **adjuvants,** that elicit the same innate immune reactions as microbes do.
  - In fact, many potent adjuvants are the products of microbes.



- Microbes (or IFN-γ produced by NK cells in response to microbes) stimulate dendritic cells and macrophages to produce two types of second signals that can activate T lymphocytes
  - First, the dendritic cells and macrophages express surface molecules called **costimulators,** which bind to receptors on naive T cells and function together with antigen recognition to activate the T cells.
  - Second, the dendritic cells and macrophages secrete the cytokine IL-12, which stimulates the differentiation of naive T cells into the effector cells of cell-mediated adaptive immunity.
- Blood-borne microbes activate the complement system by the alternative pathway.
  - One of the proteins produced during complement activation, called C3d, becomes covalently attached to the microbe.
  - B cells recognize the C3d bound to the microbe by a receptor for C3d.
  - The combination of antigen recognition and C3d recognition initiates the process of B cell differentiation into antibody-secreting cells.
  - Thus, a complement product serves as the second signal for humoral immune responses.

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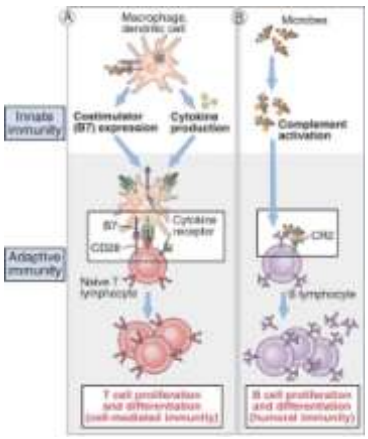

- Different types of microbes induce different innate immune responses, which then stimulate the types of adaptive immunity that are best able to combat different infectious pathogens.
  - Microbes that are encountered and ingested by dendritic cells or macrophages induce the second signals-that is, costimulators and IL-12-that stimulate T cell responses.
  - Blood-borne microbes activate the plasma complement system, which in turn stimulates B cell activation and antibody production.

II. CONCLUSION

- Oral infections, in particular gingival inflammation, originate from not just one but many microorganisms.
- The infection may result in chronic inflammation, which may lead to tissue destruction, as seen in chronic periodontitis.
- Although periodontal disease is caused by bacterial infection, the resulting tissue damage is due to the immune response.
- The first response triggered by bacterial infection is the innate immune response.
- Bacteria are taken up by macrophages, causing the macrophage to release cytokines.
- The cytokines cause the inflammation associated with periodontal disease.
- Cytokines cause the blood vessels to dilate and become permeable, leading to increased local blood flow, thus causing inflammation.
- The inflammation attracts neutrophils and more macrophages.
- Studies have shown that polymorphonuclear neutrophils (PMN) are the most abundant immune cells found in areas of periodontal disease.
- Interleukin-8 (IL-8) is a chemoattractant for neutrophils, therefore increased levels of IL-8 are found in gingival cells.
- The increase PMN and IL-8 are likely contributors to the inflammatory response
- The adaptive immune response is initiated by dendritic cells which act as antigen presenting cells (APC) to stimulate naive T cells.
- Porphyromonas gingivalis, one of the many bacteria involved in periodontal disease, is able to sensitize and activate dendritic cells .
- Once dendritic cells are activated and presenting bacterial peptide, they travel to the nearest lymph node in order to activate T cells.
- A major source of bone loss has been attributed to the presence of CD4+ T cells and the cytokines they secrete.
- Research has been conducted that associates periodontal disease with cardiovascular disease, premature births, and other problems.
- A possibility is that the cytokines and other inflammatory mediators, produced during periodontal disease could reach levels where they begin affecting the cardiovascular system and/or placental tissues.
- The mouth may serve as a "bacterial reservoir" for the lungs, possibly resulting in bacterial pneumonia.
- But, Research is currently being done to further substantiate the above mentioned associations.

In Conclusion, to summarize Innate Immunity …

- All multicellular organisms contain intrinsic mechanisms of defense against infections, which constitute innate immunity.
- The mechanisms of innate immunity respond to microbes and not to nonmicrobial substances. These are specific for structures present on various classes of microbes,and are mediated by receptors encoded in the germline, and are not enhanced by repeat exposures to microbes.
- TLRs, which are expressed on plasma membranes and in endosomes of many cell types, are a major class of innate immune system receptors that recognize different microbial products, including bacterial cell wall constituents and viral nucleic acids.
- The principal components of innate immunity are epithelia, phagocytes, dendritic cells, NK cells, cytokines, and plasma proteins, including the proteins of the complement system.
- Epithelia provide physical barriers against microbes, produce antibiotics, and contain lymphocytes that may prevent infections.
- The principal phagocytes, neutrophils and monocytes/macrophages, are recruited to sites

of infection, a process mediated by binding to endothelial adhesion molecules that are induced by the cytokines TNF and IL-1, and by responding to soluble chemoattractants, including chemokines, complement fragments, and bacterial peptides.

- Once at the site of infection, neutrophils and macrophages recognize microbes by several receptors, ingest the microbes for intracellular destruction, secrete cytokines, and respond in other ways that contribute to elimination of microbes and repair of infected tissues.
- NK cells kill host cells infected by intracellular microbes and produce the cytokine IFN-γ, which activates macrophages to kill phagocytosed microbes.
- The complement system is a family of proteins that are activated sequentially on encounter with some microbes and by antibodies (in the humoral arm of adaptive immunity). Complement proteins coat (opsonize) microbes for phagocytosis, stimulate inflammation, and lyse microbes.
- Cytokines of innate immunity function to stimulate inflammation (TNF, IL-1, chemokines), activate NK cells (IL-12), activate macrophages (IFN-γ), and prevent viral infections (type I IFNs).
- In addition to providing the early defense against infections, innate immune responses provide second signals for the activation of B and T lymphocytes.
- The requirement for these second signals makes sure that adaptive immunity is given by microbes (the natural inducers of innate immune reactions) and not by normal host.

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