Immunology
Innate Immune System

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1 Overview

- Innate immune response
  - Fast
  - Germline encoded
  - Limited specificity
  - Contains the infection
  - Activates the adaptive immune response
- The innate immune system senses
  - Foreign molecules
  - Host proteins modified by muicrobial enzymes
  - Changes caused by infections
  - Missing or stressed self
- The innate immune system relies on four main types of receptors
  - Complement system
  - Fc receptors
  - Natural Killer cells receptors
  - Pattern recognition receptors
    - Toll-like receptors
      - TLR involved in bacterial PAMPs recognition
        (i) TLR2/1 and 2/6: Lipoprotein,
        (ii) TLR4: Lipopolysaccharide,
        (iii) TLR5: Flagelline,
        (iv) TLR9: CpG DNA
      - TLR involved in viral and parasitic PAMPs recognition
        (i) TLR2/1 and 2/6: Lipoprotein,
        (ii) TLR3: double-stranded RNA
        (iii) TLR7 and 8: single-stranded RNA
        (iv) TLR9: CpG DNA

- The four key mechanisms that are involved in innate immune responses to microorganisms:
    1. Phagocytosis
    2. Intracellular killing
    3. Cell recruitment
    4. Antigen presentation

2 Complement system

- Responds immediately and binds to molecular components of pathogens, particularly those that are already coated with antibodies
- Successive complement proteins become activated in a sequential manner through:
    - Cleavage (splitting), and/or
    - Structural changes leading to a series of enzymatic cascade events that result in pathogen desctruction
- Derives its name from the fact that it is complementary to the antibody response of adaptive immunity.
- Effector functions
    1. Opsonisation
    2. Leukocyte activation
    3. Cell lysis: Membrane attack complex
- Classical Pathway
    - Triggered by binding of C1q to Fc portions of Immunoglobulin G (IgG) and IgM
    - CH2 domain of Fc of IgG3 ¿ 1 ¿ 2
    - CH3 domain of IgM
- Lectin Pathway
    - Mannose-binding lectin interacting with carbohydrate patterns
    - Ficolins interacting with acetyl patterns
    - Shares activation proteins with the classical pathway
    - C4b2a
- Alternative pathway
    - Constitutively active
    - C3bBb
    - C3b amplification
    - C3b is capable of cleaving C5

3 Microbiota

- **Microbiota** or commensal bacterial colonizes the majority of healthy epithelial tissues to keep pathogens under control.
  - These species can produce antimicrobial molecules or trigger their production by the epithelial cells.
  - Microbiota homeostasis can be disturbed by different environmental factors or host genetics which leads to dysbiosis and can influence host inflammatory responses.
- Functions of the innate immune system
  - **Function 1**: Immediate, non-specific host defences
  - **Function 2**: Initiates appropriate adaptive responses
- Mucosal epithelium
  - **Neutrophil**
    - Polymorphonuclear leukocyte
    - Not in mucosal tissue
    - Firs recruited by inflammation
  - **Macrophage** and **Dendritic cell**
    - Monuclear phagocytosis
    - Patrol mucosal tissue
    - Normally recruited after neutrophils
- Cytokines produced by macrophage:
  - Interleukin 1
    - Vascular activation
    - Local tissue destruction
    - Increase access of immune cells
    - Systemic effect: fever
  - Tumour Necrosis Factor α
    - Vascular permeability
    - Increase access of immune cells
    - Systemic effect: fever
  - Interleukin 6
    - Lymphocytes activation
    - Stimulates antibody production
    - Systemic effect: fever
  - Interleukin 8
    - Chemotactic factor
    - Immune cells recruitment

- The intestinal microbiota
  - Humans have 10^{14} intestinal bacteria
  - Provide nutrients and block pathogens
  - Many immune disorders connected to microbiota disruption
- Disruption of the microbiota leads to
  - Poorer responses to cancer treatment,
  - Type 1 diabetes,
  - Autoimmunity,
  - Susceptibility to infection
- Germ-free animals are shown to have
  - Smaller lymphoid structures,
  - Fewer dendritic cells and macrophages,
  - Fewer B cells and Th17 lymphocytes
- The signals from the microbiota result to an enhanced immune response by the innate immune system.
- The commensal bacteria benefit from a nutritionally rich and protected habitat in the human GI tract, while they in turn benefit the host by making indigestible nutrients available to the body.
- Some beneficial bacteria help restrict the access of pathogenic microorganisms to the gut tissue b building a protective biofilm.
- The benefits of human microbe symbiosis can be extended to human mental health
  - The bidirectional communication between the resident microbes of the GI tract and the brain plays a key role in maintaining brain health.
  - The GI microbiota influences human behavior and may affect the pathophysiology of mental illnesses.
  - The study of germ-free animals shows that brain development is abnormal when the gut microbiome is missing.
  - The gut microbiome influences the inflammatory reactions within the brain by modulating the activation of microglial cells and affecting myelination and neurogenesis in adult brains.
  - Apart from the ENS, the vagus nerve is instrumental for the flow of information from the gut to the brain.

4 Antigen processing - MCH Class I and Class II

- Innate immune responses are maintained in part by professional antigen presenting cells (APCs):
  - Dendritic cells,
  - Monocytes/macrophages,
  - B cells
- The different routes in which various antigen peptides (epitopes) can be processed and presented to a cell.
  1. A pathogen or extracellular antigen is phagocytized by an antigen-presenting cell (dendritic cell) and placed into a vesicle. Ingested pathogens are digested by lysosomes to extract their antigens.
  2. The antigens bind with MHC proteins that enter the vesicle.
  3. The MHC proteins, now carrying antigens, are released from the vesible and travel to the outer surface of the cell membrane.
  4. The dendritic cell is now presenting antigens, which will activate T cells that bind with the MHC proteins.
- Class II versus Class I
  - Human Leukocyte Antigen II
    - Expressed by specialised antigen presenting cells but expression can be induced on some other cell types.
    - Composed of α chain plus β chain heterodimer
    - Presents antigenic peptides to CD4 helper cells
    - Has a peptide groove that can accommodate peptides of variable lengths, around 10-20 amino acids
    - Peptides are derived from uptake and processing of exogenous antigen, for example bacterial protein
    - Can present intracellular antigens
  - Human Leukocyte Antigen I
    - Expressed by all nucleated cells (all cells, except red blood cells)
    - Composed of a single 'heavy' chain plus β-2-microglobulin
    - Presents antigenic peptides to CD8 cytotoxic cells
    - Has a peptide groove with rather constrained peptide binding, accommodating peptides around 8-10 amino acids
    - Peptides are derived from endogenously transcribed antigens for example viral or tumour antigens
    - Can present exogenous peptides

5 Natural Killer Cells

- Natural killer cell in a nutshell
  - Natural killer cells belong to group I Innate Lymphocytes (ILCs)
  - Responsible for a prompt response to a large variety of pathogenic microorganisms
  - Effective killers of virally infected cells and control early signs of cancer
  - Prior activation are not required for their activation
  - **Function:** These immune cells can recognise and kill the cells of someone's body that had been infected with a pathogen. Natural killer cells can also recognise and destroy tumour cells.
  - **Disease** People who have deficient natural killer cells, usually because of an inherited immune disorder, may be more prone to certain viruses.
  - **Location**: Natural killer cells (transcription factor: E4BP4) are present in the block and can move into other tissues to find targets.
- Helper-like non-cytotoxic Innate Lymphocytes
  - There are three main groups of non-cytotoxic ILCs
    - The groups are based on the cytokines they produce and the transcription factors that regulate their development and function
    - Many ILCs seem to reside at the body surfaces where they play a critical role in regulating epithelial cell responses and maintaining homeostasis.
    - ILC1 (T-bet) $\rightarrow$ Interferon-γ and TNFα: Protect against infections and can be found in the intestinal epithelium
    - ILC2 (RORγt) $\rightarrow$ IL5, IL13, and IL9: Respond to epithelial-derived cytokines, e.g., IL25 and IL33, by proliferating and producing IL5 and IL13
    - ILC3 (GATA3) $\rightarrow$ IL17 and IL22: Support lymphoid tissue development, help mucosal response via IL22, and support anti-bacterial defence via IFNγ
- Natural killer cells
  - NK cell development primarily occurs within the bone marrow
  - Bone marrow ablation associated with dramatic defects in NK cell homeostasis and function
  - Third major lymphocyte subset: represent approximately 10-15% of the peripheral-blood lymphocytes in humans
  - Potent lytic cells and cytokine producers
  - Part of the innate immune system so pivotal before the adaptive immunity develops
  - Act quickly as they do not need pre-sensitisation
  - Their activity is further boosted by cytokines, such as: IFNα, IFNβ, IFNγ, TNFα, IL-12 and IL18

- Main effector function
  - Killing of target cells
  - Secretion of pro-inflammatory cytokines
- Main effector mechanisms
  - Use of stored cytotoxic proteins such as perforin and granzyme
  - Induce apoptosis through FASL and TRAIL
  - Secrete cytokines such as IFNγ and TNFα
- Inhibitory NK receptors
  - Recognise MHC class I molecules
  - Binding of MHC class I to the receptor leads to an inhibitory signal preventing the NK cell from killing a healthy cell
  - Inhibitory receptors carry distinct motifs called Immunoreceptor Tyrosine-based inhibitory motif (ITIM)
  - ITIM motifs recruit inhibitory tyrosine phosphatases SHP-1 and SHP-2 which leads to inhibition of signalling
- Activating NK receptors
  - Recognise either MHC class I or non-MHC class I molecules
  - Binding of an activating receptor in the absence of inhibitory signals leads to NK activation and cytotoxic activity
  - Some activating receptors can overcome inhibitory signals (NKG2D)
- Two cell death pathways
  - Perforin-dependent
    - NK carry 'lytic' or cytotoxic granules which are released when it interacts closely (forms a close synapse) and actively with a target cell
    - The main content of granules are perforin and several kinds of granzymes
    - Granzymes are serine proteases (enzymes) that cause DNA breakage and fragmentation
  - Death receptor-dependent