Lecture 2 – Induced innate immune responses

Objectives:

- Understand key differences in innate versus adaptive immunity
    - Cells, timing, memory
- Understand early events in activation of innate immune cells
- How chemokines are involved in recruitment of cells to sites of inflammation
- Adhesion molecules, extravasation of leucocytes
- Actions of pro-inflammatory cytokines

Summaries:

- Physical and chemical barriers
    - Mechanical
        - Epithelial cells joined by tight junctions
        - Flow of air or liquid (exhalation/flushing [urination + tears]), cilial beating (nose + lungs)
    - Chemical
        - Low pH, fatty acids, enzymes (pepsin, DNase) + pulmonary surfactants
    - Microbiological
        - Normal microbiota → compete for space, nutrition and resources
- Pathway of infection
    - **Inflammatory inducers** (bacterial LPS, ATP, urate crystals) → **Sensor cells** (macrophages, neutrophils, DCs) → **Mediators** (cytokines + cytotoxicity) → Target tissues (produce antimicrobial proteins, antiviral proteins + killing of virally infected cells)
- Immune cell lines
    - Originates from the haematopoietic stem cell (HSC) → two cell lines → common myeloid (→ innate blood cells) and lymphoid (→ T and B cells) progenitors
- Types of immune cells
    - *Macrophages:* Phagocytose, degrade, present antigens to T and B cells
    - *Dendritic Cells:* key antigen presenting cells; has both MHC class I and II; only cell able to activate naïve T cells; rarer than macrophages; produce lots of cytokines and soluble mediators
    - *Neutrophils:* large numbers found in the blood and at sites of infections; produces defensins
    - *Eosinophils:* essential in parasitic attack, also utilising IgE
    - *Basophils:* important in allergic and anti-parasitic defence
    - *Mast cells:* mediate hypersensitivity reactions
- Comparing the innate and adaptive immunity
    - *Innate immunity* → no time lag (immediate), not hugely antigen specific, no memory
    - *Adaptive immunity* → lag period, antigen specific, develops memory
- Viral infection
    - Initially viral load is keep from growing by innate factors → production of IFN-a + b, TNF-a and IL-12 and NK-cell mediated killing of virally infected cells
    - Then after ~5 days the adaptive immune response is activated → T cell mediated killing of cells
- Macrophage activation by pathogens
    - PAMPs → PRRs → activated macrophage to engulf the pathogen + process + present → release cytokines and chemokines to attract other innate cells
    - Phagocyte digestion of pathogens
        - Binding of PAMP to PRR → aggregation of surface receptors → intracellular cascade → endocytosis into an endosome → fusion with lysosome → phago-/endo-lysosome → oxidative species and cytotoxic agents → degrade → present
    - Cytokines secreted by macrophages
        - *IL-1:* activates endothelium; tissue destruction; Systemically → fever (innate response to kill bacteria) and production of IL-6
        - I*nflammasome* production
        - *TNFa*: potent cytokine; activates endothelium for IgG, complement, cellular access; activate adaptive and innate cells; systemically → fever, mobilise metabolites and causes shock/sepsis
        - *IL-6:* activates lymphocytes; stimulate antibody production; Systemically → fever and acute-phase protein production
        - *CXCL8:* chemokine; chemotactic factor (attracts neutrophils, basophils and T cells)
        - *IL-12:* activates NK cells; differentiation of CD4 T cells → Th1 cells

    - Macrophage activation → co-stimulation of T cells
        - Constant presentation of antigens (self or otherwise) to the surface
        - Infection, but DCs not active
            - Presents to naïve T cell → not enough co-stimulation → minimal response
                - Pathogens block DC activation to prevent adequate T cell activation
        - Infection, and DCs are active
            - Present to naïve T cell → interactions of CD80/86 with CD28 → activation
- Dendritic cell maturation
    - Activated by pathogen in the periphery → endocytose, process + present → move to LN to T cells
- Innate response influences the adaptive immune response generated
    - **Viruses + bacteria** → DC → IL-12 → NK cell → IFNg → CD4 + IL-12 + IFNg → Th1 → IL-1, IFNg, TNFb
    - **Other pathogens** → DC → NK → IL-4 → CD4 + IL-4 → Th2 → IL-4, IL-13, IL-5
- Chemokines
    - Chemoattractant cytokines attract cells to the site of inflammation via concentration gradients
        - Small molecules that bind G-protein couple surface receptors
    - One chemokine receptor can receive many chemokine ligands → made and act on many cells → different cell types have different effector changes after binding
    - *HIV and chemokines* → co-evolution, thus, HIV has harnessed the CCR5 (chemokine receptor usually binding chemokine 1alpha) and CXR4 (usually binds SDF-1) to access CD4 T cells
- Phagocyte extravasation
    - Cytokines and chemokines released activate endothelium and attract leukocytes (neutrophils), respectively
        - Tissues are made leaky, loosen tight junctions, and upregulate certain ligands and receptors
    - Activated endothelium expresses selectin receptor and integrin ligand
        - Tether → Roll → Activate → Arrest → Move
    - Adhesion molecules
        - On endothelium: P- and E-selectins, ICAM-1
        - On innate leukocytes: LFA-1 (integrin)
- Pro-inflammatory cytokines
    - IL-1b, IL-6, TNF-a → activates complement opsonisation, phagocytosis, viral resistance, increased antigen processing, activate adaptive immune response; Systemic infection
    - Interferons (class I IFN (a and b) and IFNg)
        - Critical in antiviral immunity
            - Resistance to viral replication in all cells, increase MHC class I (endogenous; CD8+), activate macrophages and DCs, activate NKs → kill infected cells
- Innate immune system response to infection immediately
    - Innate immune system
        - Pre-formed, not antigen specific, BUT broadly specific effectors
        - Immediate but no memory formation
        - Germline receptors
            - Use patterns to generate receptors → recognise PAMPs and DAMPs from self cells
    - Adaptive immune system
        - Always activated
        - Activated from Day 2 → takes time for clonal expansion, etc.
            - Lag period
        - Highly antigen specific (one unique antigen recognised/receptor/cell) and will develop memory
            - Recombined germline → adaptive receptor production