3	Outline of the Innate Immune System	- Mechanical barriers of the body include longitudinal flow of air or fluid protecting the skin, gut, movement of mucus by cilia for lung protection, and tears and nasal cilia for protection of eyes and oral cavity - Skin secretes waxy chemicals by lamellar bodies to protect bacterial entry into cell junctions - Gut has Paneth cells producing defensins which are highly positively charged molecules which can help form a pore in lipid membranes of pathogens - Lungs have goblet cells which produce mucus as a physical barrier - Tears have lysozymes which catalyzes the peptidoglycan and digests bacterial cell wall for protection - Complement system contributes to innate and adaptive immunity by opsonization, release of anaphylatoxins and MAC formation -- interacts with antibodies to mediate formation of MAC and production of convertases - Stranger danger model: stranger = pathogen, danger = mutated cells which NK cell can mediate killing - Immune cells can be derived from common myeloid progenitor or common lymphoid progenitor, lymphoid progenitors derive B cells, T cells, NK cells and ILCs from (CILP, common innate lymphoid progenitors) - Granulocytes include neutrophils, eosinophils and basophils where neutrophils are the most abundant in blood and migrated from the bone marrow from a chemotactic gradient of IL-8, whereas basophils and eosinophils are more prone for parasitic immunity - Mast cells causes degranulation by binding to IgE based on the Fc epsilon receptor - Dendritic cells capture antigen and present it to t cells in the lymph - Natural killer cells detect MHC presence and regulates cell health based on activation and inhibitory receptors, activation can be done by stress induced proteins and inhibition by cells expressing normal repertoire of MHC molecules - Macrophages are tissue resident forms of monocytes which recruits cells and kills cells via phagocytosis, macrophage action · Cytokine and chemokine release leads to blood flow, increased vascular diameter and adhesion increase · Prostaglandins stimulate pain, blood flow induces redness and heat, swelling · Effect can impair functions and clotting can block spread of pathogen from the wound - NK cells and ILCs are considered innate immune cells but are generated from a lymphoid progenitor - Eosinophils and basophils are examples of innate cells that have PAMPs but will not phagocytose
4	The complement system	- Alternative: spontaneous C3 tickover, C3b binds to factor B, cleaved by factor D forming C3bBb stabilized by factor P (properdin), C3a anaphylatoxin - Lectin: ficolin or mbl binding to pathogen mannose, triggers binding to C4, cleaved by MASP2 to C4b, C4a release as anaphylatoxin, C4b binds C2 cleaved by MASP 2 forming C4b2a - Classical: IgM IgG binding C1q domain activation, C1r activates C1s as serine proteases cleaving C4 into C4b, C4a release as anaphylatoxin, C4b binds C2 cleaved by serine protease forming C4b2a - C3 convertases cleave C3 to produce C5 convertase by attachment of C3b, making C3bBbC3b, or C4b2aC3b, which cleaves C5 - C5a release is anaphylatoxin which can trigger chemotaxis and inflamation-- aid phagocytosis - C5b recruitment of C6, 7, 8, 9 forms MAC
5	Regulation of complement	- CR1, 3, 4 acts with C3b (CR1) or iC3b (CR3,4) for phagocytosis - CR1 clears complement complexes in the spleen and liver by phagocytic cells - C3b breakdown initiated by MCP/CR1 and Factor I, first producing iC3b, releasing C3f, then further cleavage, leaves C3dg on the cell surface - CR2, expressed on B cells, interacts with C3dg (a breakdown product of C3b) which activates B cells during BCR interaction --> CR2 also a receptor for EBV binding which can cause swelling of lymph nodes when B cells are infected via entry through this receptor - **Anaphylatoxins C3a C5a induces TNFa and histamine release by mast cells, causing leakage of blood vessels and migration of leukocytes, but also aids phagocytosis because binding of C3b is not sufficient** - Regulation can be done by · C1 INH, serpin, which inhibits MASP and Serine proteases in lectin and classical pathway forming C3 convertase · C3 convertase inhibition: DAF, CR1, MCP: C4b2a · C3 convertase inhibition: DAF, CR1: C3bBb · C5 convertase inhibition: Factor I, H CR1: C5 convertase (cleaved by factor I) · *note that C3 convertase breakdown can be further broken down by MCP, CR1 and factor I to produce C3dg, and factor I contributes to C3 convertase breakdown although not directly, but will degrade the disocciated complexes. Factor I deficiency will contribute to C3 depletion in the altnerative pathway · C7 inhibition: protein S binding preventing insertion of MAC pore into membrane · C8 inhibition: CD59 inhibits pore formation of MAC