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Phagocytic Cells: Mechanisms of Bacterial Killing and Tissue Injury

Tuesday, February 12, 2008
9:00 AM

- Phagocytic Cells
  - Lymphocytes - 30% of WBC - Viral defenses - mostly nucleus, slighlty larger than RBC
  - Granulocytes - 70% of WBC - bacterial defenses
    - Neutrophils - 60% - multi lobed nucleus, granules
    - Eosinophils - 3% - parasites, allergic asthma
    - Basophils - 1% - blue in slides b/c of basic granules
    - Monocytes - 6% - big, kidney bean shaped nucleus
    - Moncytes --> Macrophages in tissue
  - Kupffer cells in liver sinusoids
  - Spleen has lots of WBCs too
- Neutrophils and Macrophages
  - Functions
    - Ingest foreign material
    - Kill bacteria and other microbes
    - Degrade necrotic tissue and foreign antigens
    - If there for too long, can cause tissue damage
  - Neutrophil Recruitment
    - Tissue injury leads to inflammatory mediator and chemoattractant release
    - Inflammatory mediators make endothelium more sticky and permeable for cells to pass through (localization and migration)
    - Chemoattractants set up gradient that recruits neutrophils to site (localization)
    - Neutrophils can phagocytose, produce oxidants, release lysosomal granules
      - NADPH oxidase activation via min electron transport system
      - Lysosomal granule fusion: degranulation
    - Most chemoattractants work via GPCR or Tyrosine Kinase signal transduction
  - Opsonization and Phagocytosis
    - Fc receptors for antibody
    - Complement receptors: C3b binding
    - Other receptors: receptors for collectins (mannose binding protein)
    - Neutrophil has receptors for opsonins that bind and then form phagosome --> phagolysosome
    - Once bacterium is in, NADPH oxidase makes H_2O_2 from O_2 via O_2^- (superoxide anion)
      - w/o NADPH oxidase --> chronic granulomatous disease of childhood
      - Respiratory increase due to NADPH oxidase activity seen
    - Elastase/collegenase break down bacteria
    - Myeloperoxide converts H_2O_2 to HOCl (bleach)
    - NO synthase: makes NO radical from Arg --> vasodilation, intracellular cytotoxic agent, neurotransmitter; can be converted to make OH radicals or peroxynitrates
- Targets of Neutrophil Products
  - Targets of Oxidants
    - Unsaturated lipids: LOOH
    - Proteins: sulfhydryls, methionine, tyrosine
    - Nucleic acids
  - Degranulation
    - Bactericidal proteins
    - Proteases
      - Serine proteases (elastase)
      - Metalloproteinases (collegnase, gelatinase)

        - Acid hydrolases
    - Oxidants/Proteases must be in balance w/ Antioxidants/Antiproteases
    - Protective mechansims
        - Specific enzymes
            - Superoxide dismutase: takes superoxide anion and makes hydrogen peroxide
            - Catalase: converts hydrogen peroxide to water and oxygen
            - Glutathione peroxidase: takes peroxides and makes water, oxidized glutathione, and lipid-OH from LOOH
        - Non-specific scavengers
            - Vitamin E
            - Vitamin C
            - β-carotene
        - Anti-proteases
            - α-1-antiprotease (anti-trypsin) - in liver
                - Plasma protein
                - Binds proteases including elastase
                - Inactivated by oxidants
                    - HOCl or metalloproteinases
            - α-2-macroglobulin
                - Plasma protein
                - Binds proteases
            - TIMPs
                - Tissue inhibitors of metalloproteinases
                - Cell derived