Immunology in the Trauma Patient

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- I have no disclosures as it pertains to this presentation
Basic Immunology

- ‘Danger Theory’
  - Immune system recognizes not just nonself (e.g., bacteria, fungi, transplanted organ, etc) but any threat to homeostasis
  - Immune response is triggered by endogenous cellular alarm signals from distressed or injured cells
Basic Immunology

- **Adaptive immunity**
  - Antigen-specific immune response
  - Antigen must be processed and recognized
  - Creates immune cells specifically designed to attack the antigen
  - Memory

- **Innate immunity**
  - Nonspecific defense mechanisms that come into play immediately or within hours of an antigen’s appearance
  - Activated by chemical properties of the antigen

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Basic Immunology

- **Innate Immune System**
  - Highly sensitive organ of perception
  - Mobile immune cells responsible for evoking inflammatory and adaptive immune response
    - Neutrophils, macrophages, dendritic cells, etc
  - Somatic cells
    - Epithelial cells, fibroblasts, smooth muscle cells, etc
Basic Immunology

- **Pattern recognition receptors continuously survey the extra- and intracellular compartments**
  - Toll like receptors (TLRs), nod-like receptors (NLRs), C-type lectin receptors (CLR), retinoic-acid-protein 1 (RIG-1)-like receptors

**Basic Immunology**

- **PAMP: pathogen-associated molecular pattern**
  - Evolutionarily conserved structures expressed by foreign invaders such as bacteria, fungi, viruses
Basic Immunology

- DAMP: damage-associated molecular pattern
  - Intracellularly sequestered molecules that remain unrecognized by the immune system under normal condition
  - Cellular stress or tissue injury allows exposure on surface, actively secreted, passively released from dying cells
  - ATP, HMGB-1, matricryptins, cold-inducible RNA-binding protein, histones and mitochondrial DNA
Basic Immunology

Activation of Innate Immune System ➔ Inflammation

- Provides protection to the host
  - Killing invading pathogens
  - Removing damaged/dead cells
  - Repairing destroyed tissue via wound healing
  - Balancing metabolic irregularities and inducing a supportive adaptive immune response

Inflammatory response to infection protects host from infection

Inflammatory response to tissue injury promotes tissue repair
Shock, Extensive/Extended Surgical Intervention

- Innate immune response unbalanced
  - Dysregulated cascade systems
    - Coagulopathy
    - Complementopathy
  - Reprogrammed, rapidly suppressed immunological function
    - Decreased expression of HLA-DR in macrophages
  - ‘Cytokine storm’ can lead to alterations in Na⁺-K⁺ ATPases resulting in electrophysiological membrane dysfunction
Neutrophils after Severe Trauma

- Genetic storm with functional reprioritization of leukocytes
- Usually results in balanced pro-inflammatory/anti-inflammatory protective effects
- Pro-inflammatory (SIRS)
  - Chemotaxis, cytokine release (IL-6, IL-1Ra, IL-8, IL-10), generation of ROS, phagocytosis, formation of neutrophil extracellular traps (NETS) and bacterial killing
- Anti-inflammatory (previously referred to as CARS)
  - M1 to M2 phenotype
Persistent Inflammation-Immunosuppression Catabolism Syndrome (PICS)

- Ongoing protein catabolism
- Innate and adaptive immunosuppressive features
  - Reduced generation of cytokines
  - Loss of monocyte-macrophage function
  - Persistently increased number of MDSCs
  - Reduction in # and function of effector T cells
- Poor wound healing
- Infections
- High mortality rate
**Additional Factors that Compromise Immune Function**

- Nosocomial infections
- Immunocompromising comorbidities
- Unfavorable epigenetic or microbiome perturbations
- Programmed cell death can be disturbed
- Lymphocytes and crypt intestinal epithelial cells driven to apoptosis
  - Inability to normalize posttraumatic lymphopenia is associated with a poor outcome
- **Excessive immune, coagulopathy and ROS responses lead to endotheliopathy and dysfunction of cellular barriers**
  - More DAMPs and PAMPs
  - Amplifies a vicious cycle of tissue injury and damaging immunological processes

*Huber-Lang, et al.* Nature Immunology 19:327; 2018
Endothelial Glycocalyx (EG)

- Thick (0.2-3.0μm) negatively charged CHO-rich layer coating the vascular endothelium
- PGs provide structural support and GAGS attach
  - PGs: syndecans/glypicans
  - GAGS: heparan sulfate, chondroitin sulfate, hyaluronan
- Syndecans are major constituent ensuring endothelial integrity
- Cell adhesion molecules (ICAMS/selectins) are major glycoproteins

Glycocalyx Function

- Physical barrier between blood and vessel wall
- Maintains fluidity by modulating interactions of endothelium with blood cells and proteins
Glycocalyx Function

- Regulates cell adhesion and vascular permeability
- Creates a high intravascular colloid-osmotic gradient
- Acts as a mechano-transducer by sensing shear stress and inducing endothelial release of NO

EG Response to Trauma

- Shedding of EG components occurs in response to
  - Ischemia/hypoxia
  - Reactive oxygen species
  - Inflammation/sepsis
  - Trauma-related sympatho-adrenal activation
- Levels of syndecan-1 on admission correlate with extent of tissue damage, ↑ vascular permeability and mortality
Glycocalyx Response to Trauma

- Loss of HSPG exposes ICAM and selectins that promote WBC and platelet adhesion
- Adhesion induces further release of cytokines, proteases, heparanase that worsens EG degradation and increases permeability

Glycocalyx Response to Trauma

- Free HS acts as a DAMP and likely contributes to autoheparinization
- Components of glycocalyx contribute to propagation of sterile inflammation but concurrently also contribute to immunosuppression
Hemorrhagic Shock and EG

- **Endothelial glycocalyx injured by hemorrhagic shock is partially restored by plasma but not by LR (mice)**
- **Plasma transfusion decreased syndecan 1 and factor VIII levels (humans)**
- **Plasma first resuscitation trial (PRCT) hopes to show that plasma given first will:**
  - Attenuate acute traumatic coagulopathy
  - Improve metabolic recovery
  - Decrease blood component transfusion
  - Reduce incidence of acute lung injury and MOF
  - Decrease mortality at 24 h or 28 days
    - Moore EE, et al. Shock 41(suppl 1):35; 2014

Summary

- **Immune response following trauma is complex, interconnected and redundant**
- **Inflammatory response to tissue injury promotes tissue repair**
- **An unbalanced response can lead to dysregulated complement or coagulation cascades, cytokine storm, and immunosuppression**
- **Patients with severe injury are at risk for MOF or PICS**
Summary

▪ Endothelial glycocalyx is being realized as increasingly important in the response to injury
▪ Our understanding of resuscitation is again changing as increasing evidence suggests plasma should be given first as it may exert a beneficial effect on the glycocalyx

Thank you!