When Innate Immunity Hurts: Implications for Medical Device Failure

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Learning Targets

• Explain innate immunity/inflammatory response
• Relate phagocytosis to the inflammatory response
• Explain how the inflammatory response is regulated
Immunity

Outside

Physical & Chemical Barriers (skin & mucus membranes)

Inside
Barriers to infection

- Epithelial layers produce protective substances
  - Acidic pH
  - Enzymes
  - Antimicrobial peptides
    - Psoriasin

- Why does our skin secrete psoriasin?
Immunity

Outside

Physical & Chemical Barriers (skin & mucus membranes)

Inside

Innate Immunity
• First line of defense
• Non-specific
• No memory
• Same response to repeat infection

Adaptive Immunity
• Max response in days
• Specific
• Memory
• More rapid response to repeat infection
Pathogen Recognition

- **PAMPs** – Pathogen-Associated Molecular Patterns
- **PRRs** – Pattern Recognition Receptors

- **Inflammation** is triggered when innate immune cells detect infection or tissue injury

Inflammatory Response

1. Tissue damage and bacteria cause resident sentinel cells to release chemoattractants and vasoactive factors that trigger a local increase in blood flow and capillary permeability.

2. Permeable capillaries allow an influx of fluid (exudate) and cells.

3. Neutrophils and other phagocytes migrate to site of inflammation (chemotaxis).


Figure 5-17
Kuby Immunology, Seventh Edition
© 2013 W. H. Freeman and Company
Phagocytosis
Phagocytosis

- Bacteria or Foreign object (splinter)
- PAMP/PRR -or- C3b (complement protein)
- Opsonization

Inflammatory cell membrane (neutrophils and macrophages)

Phagocytosis Video 1

Phagocytosis Video 2

https://www.youtube.com/watch?v=Z_mXDvZQ6dU

www.BetaGlucans.info
Inflammatory Response

Pathogens invade tissues

Cells injured

Activate molecules in plasma, mast cells, macrophages

Vasodilation

Increased capillary permeability

Phagocytes migrate to region

Increased phagocytosis

Antibodies pass from blood into inflamed area

Bring Phagocytes, nutrients, antibodies

Redness

Increased temperature

Fever

Edema

Pain

Release IL-1

Systemic response
Inflammation-Related Diseases

- Atherosclerosis
- Rheumatoid arthritis
- COPD
- Sepsis
- Asthma
- Allergy
- Diabetes
- Transplant rejection
- Cancer

Medical Device Failure
Implant rejection

http://www.ucdenver.edu/academics/colleges/medicalschool/departments/immunology/faculty/Pages/SAlper.aspx
Discussion Question

• What do you think causes diseases associated with inflammation?
Issues with Innate Immunity

- Restenosis
- Cracked pacemaker lead insulation
- Post-surgical complications of cardiopulmonary bypass
- Bioprosthetic valve calcification

Wiederman et al, Ann Thorac Surg 2010
Biocompatibility

“The condition of being compatible with living tissue or a living system by not being toxic or injurious and not causing immunological rejection”
Regulation of the inflammatory response

- Under homeostatic conditions, response to foreign stimuli closely regulated
- Inhibitory immune cell surface receptors
- Immunoreceptor Tyrosine Inhibitory Motif (ITIM) protein family
  - Signal Regulatory Protein Alpha (SIRPα)

Decreased Immune Response
CD47

- Expressed in virtually all cells
- CD47-SIRPα interaction inhibits immune response
- Over-expressed in most cancer cells

Slee JB et al. Polymers 2014
Questions?
The use of CD47 as an anti-inflammatory agent on medical polymers

Pacemaker leads, glucose sensors, cardiopulmonary bypass tubing, hemodialysis tubing, & LVAD tubing
Does CD47 prevent *in vitro* cell attachment?
**In vitro assay**

**Attachment Assay**

THP-1 = human monocyte-derived macrophage cell line

3 day incubation

Wash with PBS
Fix cells
Stain with DAPI
Count adhered Cells

Modified vs Control Surfaces
THP-1 Attachment Assay

A.

Unmodified  Recombinant  Peptide

DIC

DAPI

B.

Adhered Cells/200X

field

Unmodified  Recombinant  Peptide
Does CD47 prevent *ex vivo* blood cell attachment?
Chandler Loop Assay

A. Unmodified

B. Recombinant

Adhered Cells/200X field

Unmodified

Recombinant

Peptide

Slee JB et al. J. Vis. Exp. 2014
The use of CD47 as an anti-inflammatory agent on vascular stents

Steel stents, orthopedic implants, dental implants
Vascular Stents

http://en.wikipedia.org/wiki/Cardiology

Restenosis

http://www.yoursurgery.com/ProcedureDetails.cfm?BR=5&Proc=33
Does CD47 prevent \textit{in vivo} cell attachment?
CD47 Prevents Cell Attachment *In Vivo*

- **Bare Metal Stent**
  - 2,000X
  - 10,000X

- **CD47 stent**
  - 2,000X
  - 10,000X

Slee JB et al. In Prep
CD47 Prevents Restenosis *In Vivo*

CD47 decreases restenosis measures by almost 30%

*Slee JB et al. In Prep*
Summary

• Pathogens and foreign objects trigger an inflammatory response in the body.
• Innate Immunity is the first way the body deals with eliminating pathogens and foreign objects from the body.
• CD47 is a marker of “self” to immune cells.
• CD47 can be used on medical devices/implantable materials to prevent the inflammatory response.
Thank You!
Questions?

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