

Surgery

SIRS (Systemic Inflammatory Response Syndrome)

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SIRS

- Definition of SIRS/MOF etc
- Causes
- Why is it important?
- Mortality of SIRS/Sepsis
- Cell and organism response to stress
- Players (Molecules, Cells)
- Clinical Stages
- Treatment

Definition

The Systemic Inflammatory Response Syndrome

- Final common pathway of many insults
- High Mortality

Definition - ACCP/SCCM (1992)

Presence of two or more of the variables below

Variable	Abnormality
Temperature	Less than 36 Centigrade More than 38 Centigrade
Pulse Rate	More than 90
Resp Rate	More than 20 pCO_2 less than 4.3 kPa
White Cells	Less than 4 More than 12 or More than 10% immature forms

More definitions

- Infection
- Sepsis
- Severe Sepsis
- Septic Shock

Infection - Sepsis

Infection

Inflammatory response to the presence of microbes or invasion of normally sterile tissue by microbes

Sepsis

SIRS due to a microbial origin

Severe Sepsis - Septic Shock

Severe Sepsis

Sepsis with organ dysfunction, hypoperfusion or hypotension

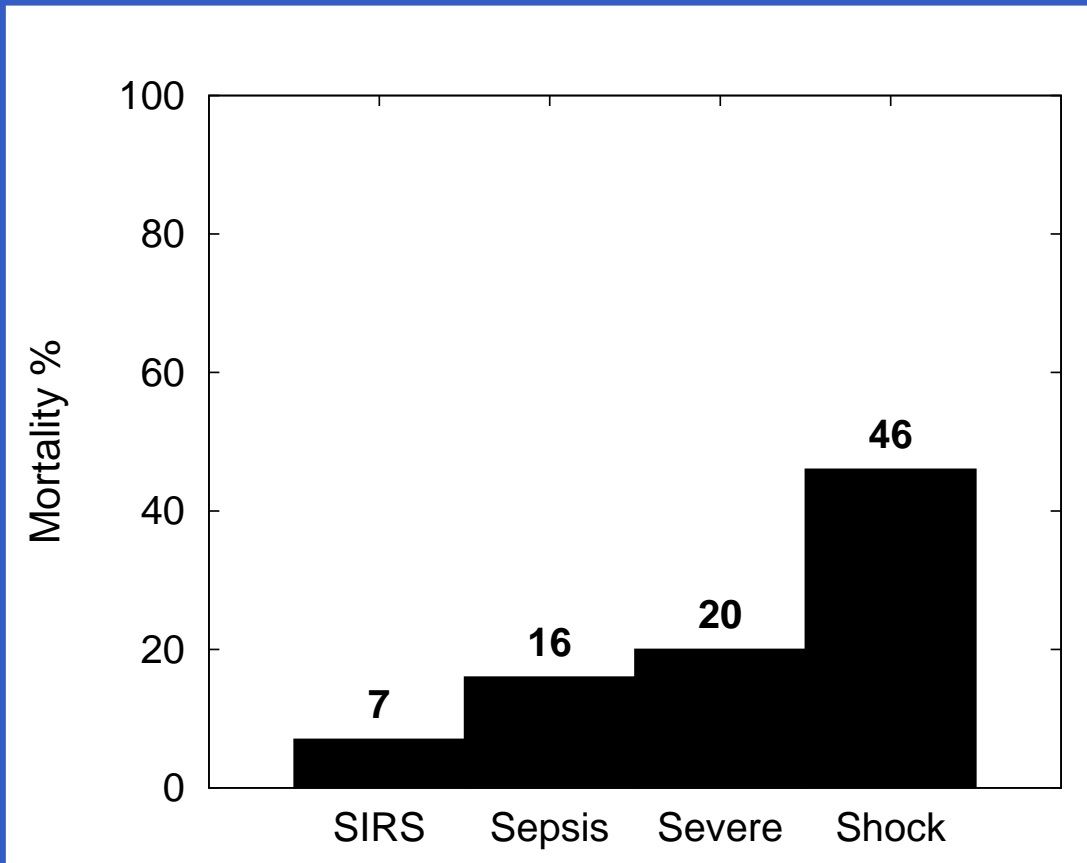
Septic Shock

Severe Sepsis with hypotension despite adequate fluid resuscitation

Causes of SIRS

- Infection
- Trauma
- Burns
- Pancreatitis
- Sepsis
- Ischaemia-Reperfusion
- Hypovolemic or Haemorrhagic shock

Mortality in SIRS/Sepsis



- Stepwise increase in mortality

Rangel Frausto et al JAMA. 1995 273:117-23

Why is it important

- Advances in care of surgical patient are not sufficient to date
- Modulation of SIRS possible direction

Advances in Care of Surgical patient

- Pre op preparation; Rapid Transportation, Paramedical Care, ATLS vs Scoop and Run
- Better Surgery; Minimally Invasive, Damage Control, Planned re-op, Volume and Outcome data
- Better Anaesthesia
- Prediction of outcome; Scoring Systems, Genotypic Markers
- Critical care; ICU specialist, Organ systems support

Modulation of SIRS?

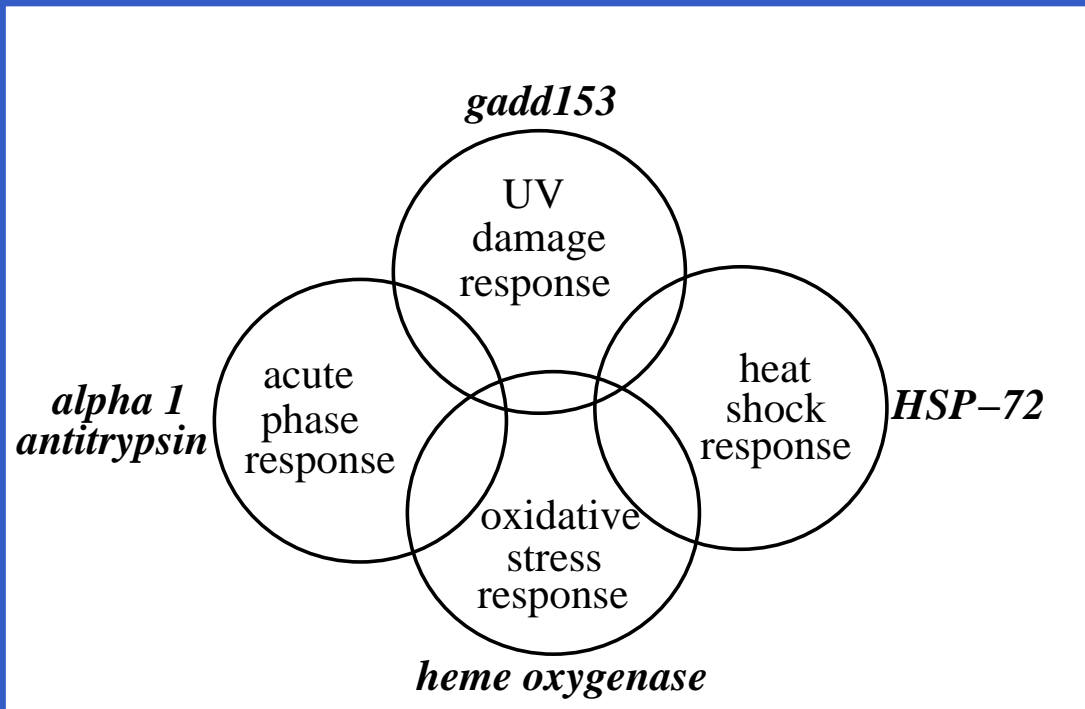
Holy Grail

- Activated Protein C
- Enteral feeding
- Immuno-nutrition

Review of the Basics

- Cellular response to stress
- Organism response to stress
- Special cells
- Special molecules

Cellular response to stress



Critical Care Med 22(6):901-3, June 1994

- Heat Shock
- UV damage
- Oxidative damage
- Acute phase

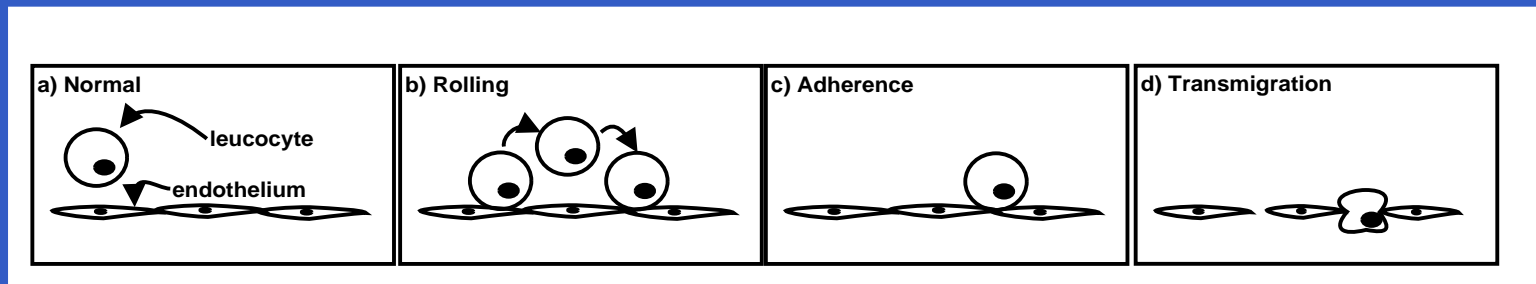
Organism response to stress

- Special cells
 - Leucocyte
 - Endothelial cell
- Special molecules
 - Inflammatory Mediators
 - Cytokines (pro, anti and mixed effect)

Role of the Leucocyte

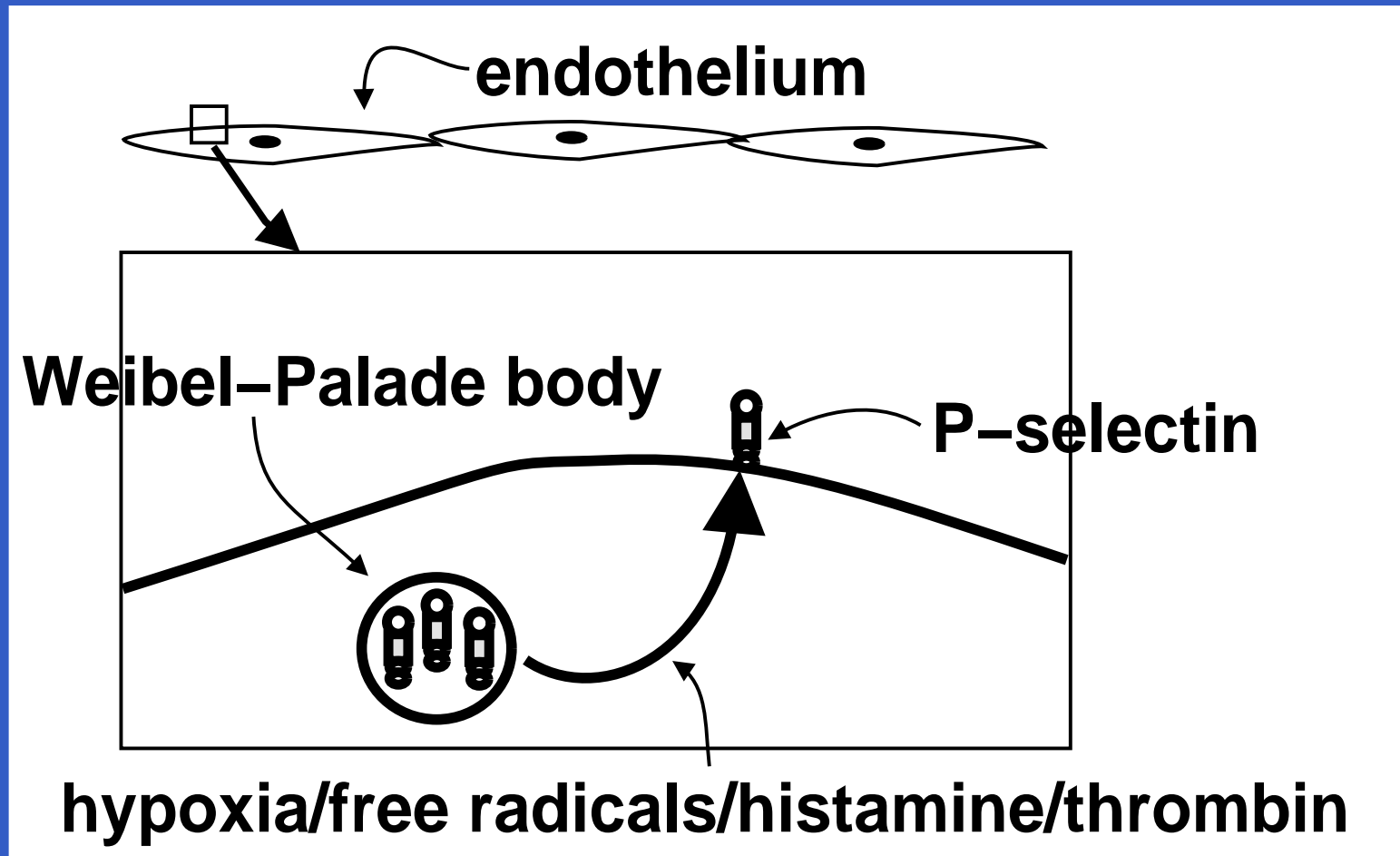
- Leucocyte endothelial interactions
- Reactive Oxygen Species
- Release of Active Agents
- Physical Occlusion of capilleries

Leucocyte-Endothelial Interactions

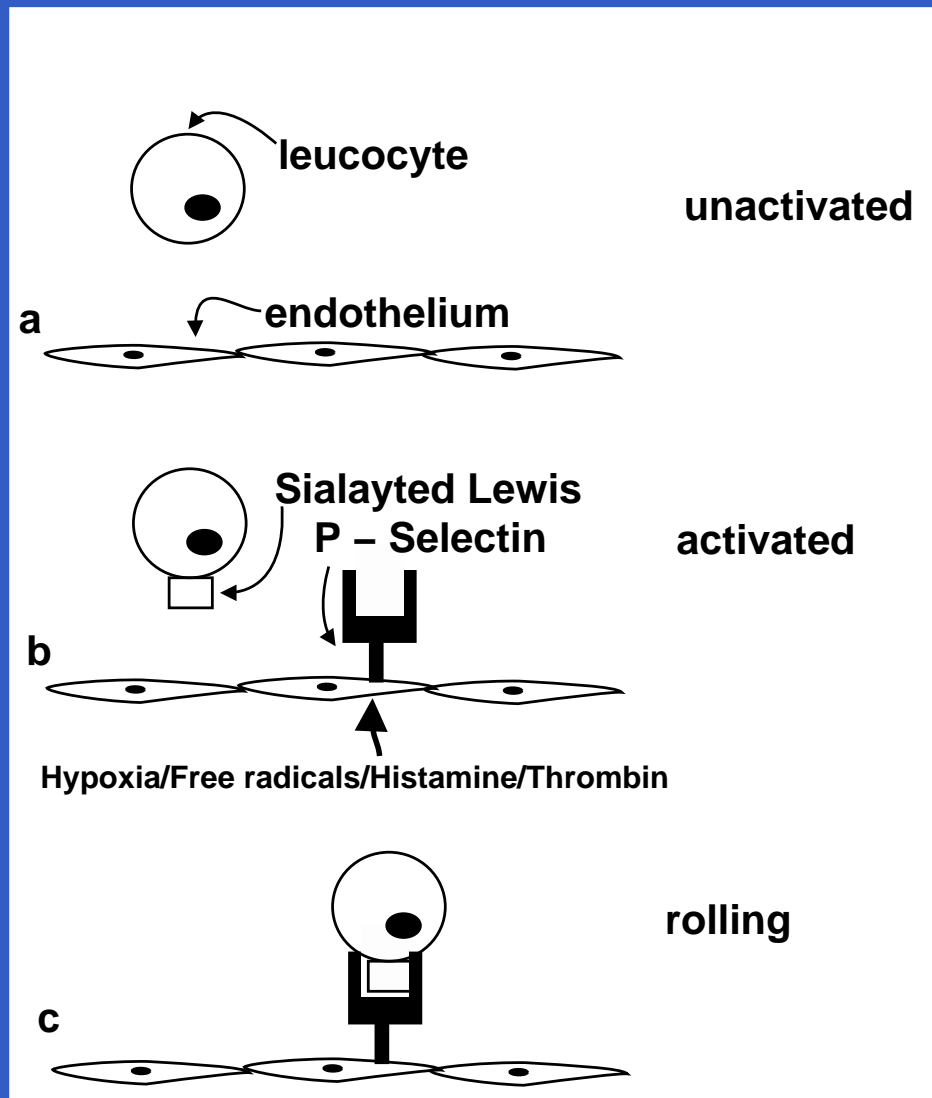


- Rolling
- Adherence
- Transmigration

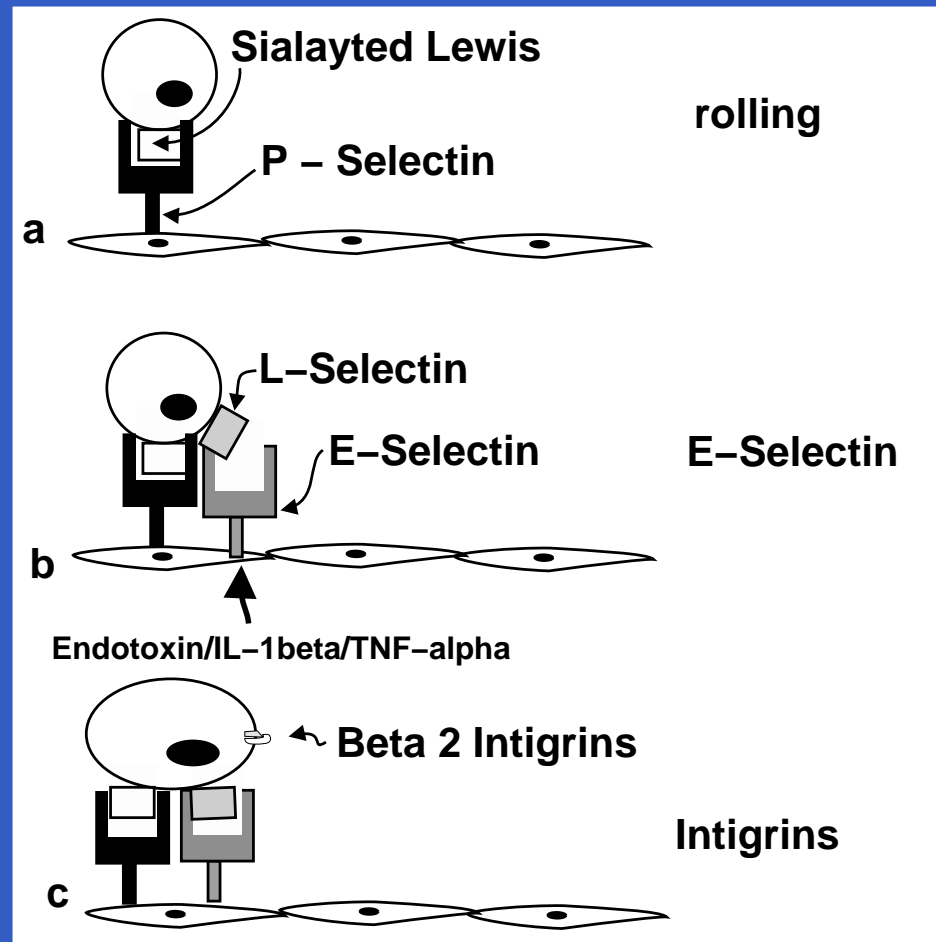
Rolling - P-selectin



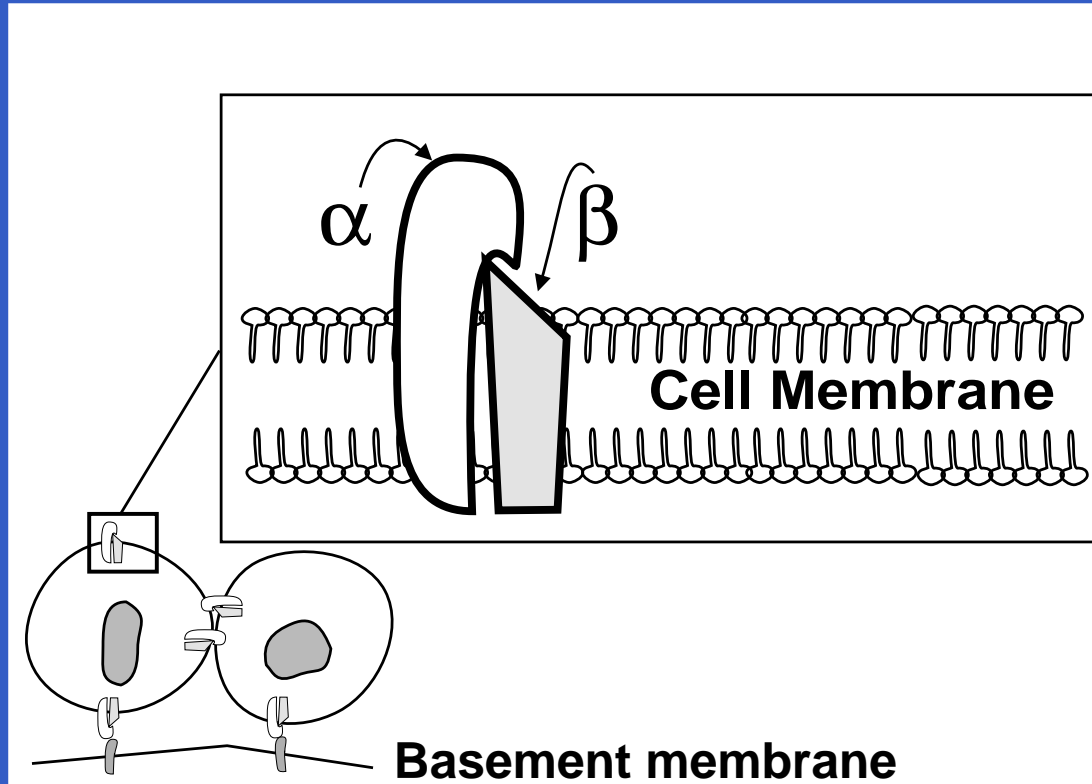
Rolling



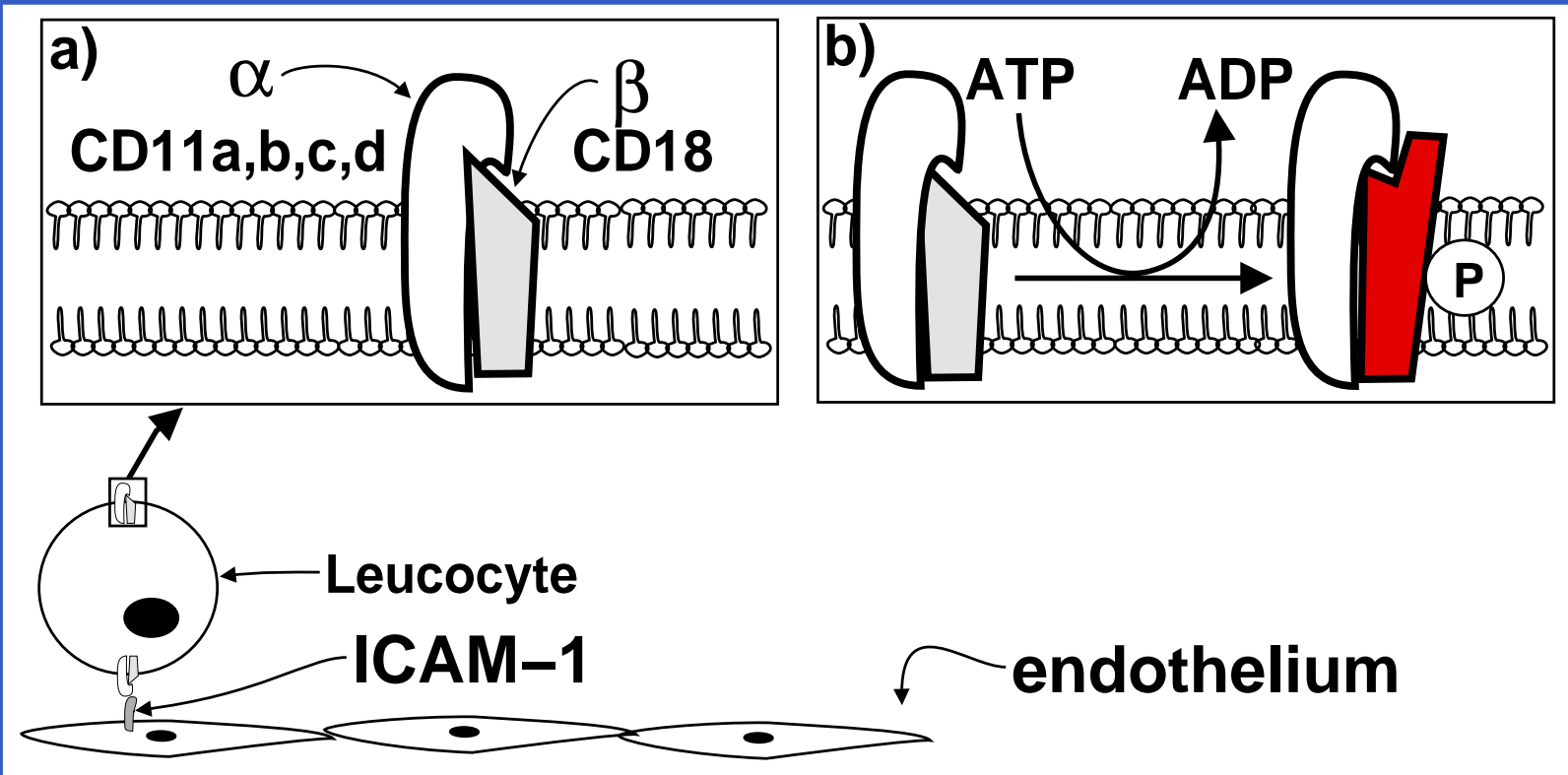
Adherence



Integrins



Beta2 - Integrins



Transmigration

- Integrin to ICAM-1 binding
 - Block by Ig against CD11/CD18
 - Block by Ig against ICAM-1
- Integrin to VCAM-1 binding
- L and E Selectins do not play a role
- Leucocyte extends pseudopodia and migrates into interstitium

Role of the Leucocyte - Reactive Oxygen Species

- Leucocyte endothelial interactions
- Reactive Oxygen Species
- Release of Active Agents
- Physical Occlusion of capilleries

Reactive Oxygen Species

- How they cause damage
- Where they come from

Reactive Oxygen Species - How they damage

- Paritally empty outer shell (reactive++)
- DNA nicking
- Lipid membrane peroxidation
- Protein crosslinking and degredation
- Attraction of inflammatory cells
- Activation of inflammatory cells
- Promotion of leucocyte-endothelial interaction

Reactive Oxygen Species - Parenchymal cells



- Last short period
- Dependent on supply of Hypoxanthine

Reactive Oxygen Specis - Leucocyte



- NADPH Oxidase membrane bound
- Production unlimited provided oxygen available
- Myeloperoxidase stored in granules

Role of the Leucocyte - Release of Active Agents

- Leucocyte endothelial interactions
- Reactive Oxygen Species
- Release of Active Agents
- Physical Occlusion of capilleries

Leucocyte - Active Agents

- LTB₄ (Potent chemoattractant, adhesion, transmigration)
- TNF- α (Pro inflammatory cytokine)
- Elastase, Collagenase, Gelatinase (Hole in BM, interstitial matrix, transmigration)

Organism response to stress - Inflammatory Mediators

- Special cells
 - Leucocyte
 - Endothelial cell
- Special molecules
 - Reactive Oxygen Species
 - Inflammatory Mediators
 - Cytokines (pro, anti and mixed effect)

Inflammatory Mediators - PAF

PAF

- PAF
- LTB4
- C5
- Thrombin
- Membrane phospholipid, platelets
- Hypoxia stimulates Leucocyte PAF release
- Leucocyte PAF receptor
 - Increased expression CD11/CD18
 - Generation of oxygen free radicals
 - Release of lactoferrin, myeloperoxidase

Inflammatory Mediators - LTB4

LTB4 (SRS-A)

- PAF
 - LTB4
 - C5
 - Thrombin
- Metabolite of Arachidonic Acid
 - Lipo-oxygenase pathway
 - Chemoattractant
 - Increased adhesion/transmigration
 - Promotes leucocyte to release;
 - Oxygen radicals
 - Proteolytic enzymes

Organism response to stress - Cytokines

- Special cells
 - Leucocyte
 - Endothelial cell
- Special molecules
 - Reactive Oxygen Species
 - Inflammatory Mediators
 - Cytokines (pro, anti and mixed effect)

Cytokines - Pro Inflammatory - IL-1

Pro Inflammatory

- Pro-Inflammatory
 - Anti-Inflammatory
 - Mixed
- IL-1
 - IL-2
 - IL-6
 - IL-8
 - TNF- α

IL-1

- One of main mediators (with TNF- α) of septic shock
- Effects blocked by IL-1ra

Cytokines - Pro Inflammatory - IL-2

Pro Inflammatory

- Pro-Inflammatory
 - IL-1
 - IL-2
- Anti-Inflammatory
 - IL-6
- Mixed
 - IL-8
 - TNF- α

IL-2

- T-cell
- Activation of T, B and NK cells
- Tried in Melanoma and Renal Cell Carcinoma (Vascular Leak Syndrome)

Cytokines - Anti Inflammatory - IL-10

Anti Inflammatory

- Pro-Inflammatory
 - IL-4
- Anti-Inflammatory
 - IL-10
- Mixed
 - IL-13

IL-10

- IL-10 has been shown to protect mice from the effects of endotoxic shock

Cytokines - Mixed Effect

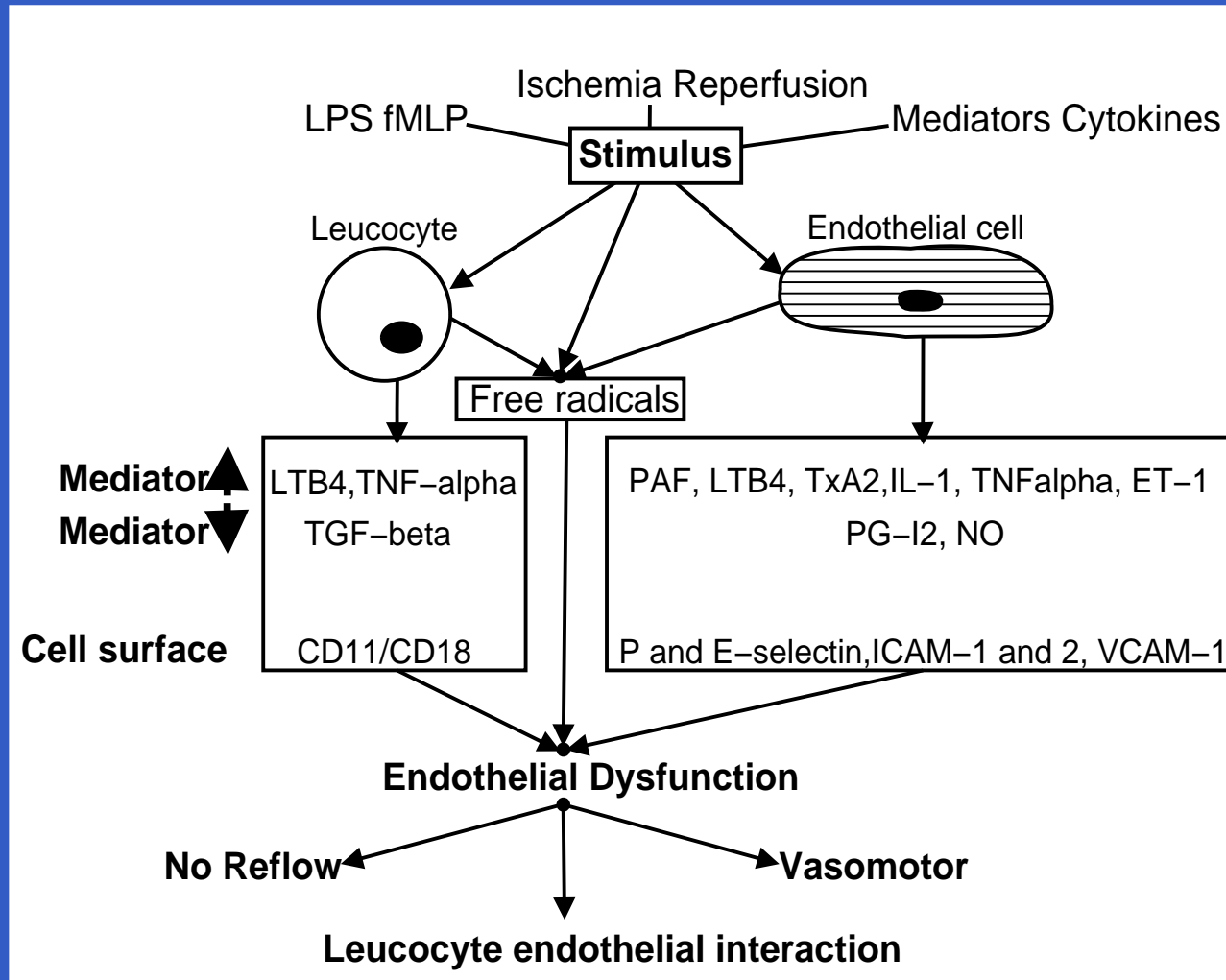
Anti TGF- β

- Pro-Inflammatory
 - Anti-Inflammatory
 - Mixed
- Decreased productions monokines and lymphokines
 - Reduced IL-1, IL-6 and TNF- α

Pro TGF- β

- Chemo-attractant

Final Common Pathway



SIRS - Clinical Stages

Clinical Stages 1 – 3

1. Local response
2. Spill over of cytokines into the circulation, but balance maintained
3. Massive proinflammatory swing;
 - Vasodilatation
 - Leaky capilleries
 - Myocardial dysfunction

Monitoring SIRS

Sepsis Markers

- WCC
- CRP
- Pro-calcitonin
- IL-6
- IL-10
- Endotoxin
- Protein-C

Role is unclear

Treatment of SIRS

Specific SIRS treatment

- Treat cause, remove source
- Support in ICU
- **Specific SIRS treatment**
- Enteral feeding
- Immuno-nutrition (Glutamine, omega-3, nucleotide rich)
- rAPC (Xirgis)
- G-CSF
- Anti-inflammatory Cytokines

SIRS and enteral feeding

- Increased nutritional needs
- Gastro-intestinal Blood barrier
- Alterations in normal gut flora
- Blunt catabolic response
- Bolster immune defences

2-fold decrease in infectious complications in patients fed enterally instead of parenterally

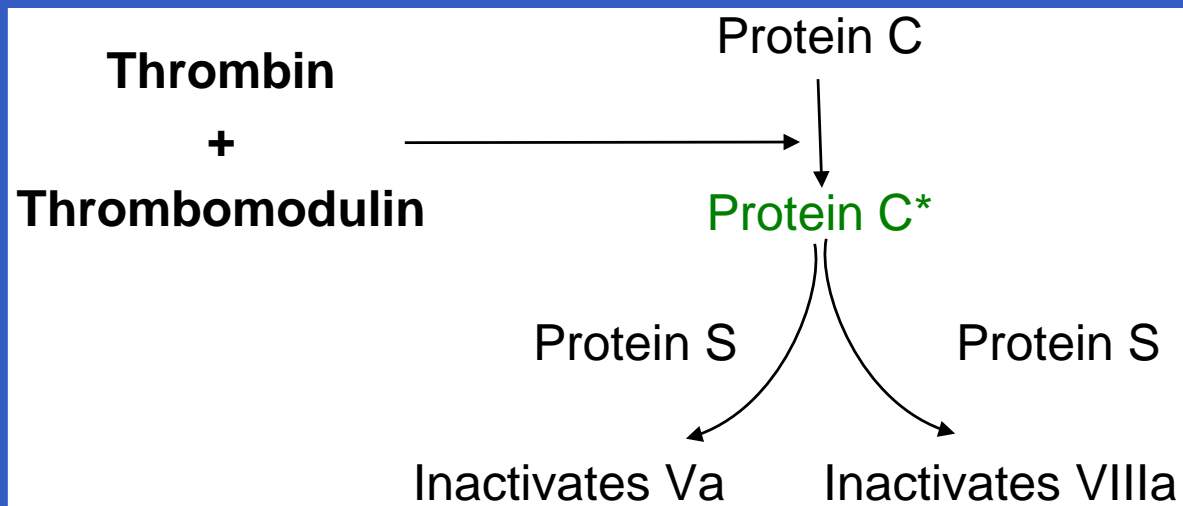
Ann Surg 216:172–183, 1992

Glutamine

- Glutamine in demand in inflammation
- Enterocytes need glutamine
- (Parenteral) Improves Nitrogen Balance
- (Parenteral) Reduces hospital Stay
- 30% studies show clinical benefit

Role of additional glutamine is probably beneficial but small

Activated Protein C - What it does



- Natural anticoagulant

- Protein C deficiency
- Protein S deficiency
- APC resistance
- Factor V Leiden

Sepsis

- Clotting
- D-Dimers
- FDP
- Protein C consumption

Activated Protein C - PROWESS RCT

- Recombinant human activated protein C *Drotrecogin alfa*
- 634 patients received drug, 637 received placebo

Group	Mortality (28 d)
Protein C	26.5 %
Placebo	33.9 %

Cost to save one life is about 160,000 Euro

Thanks

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Questions please

