EARLY INFLAMMATORY RESPONSES TO VASCULAR DEVICES

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INTERACTIONS IN PIS

SURFACE

BLOOD — FLOW

PATIENT

SURGEON — DEVICE

VIRCHOW'S TRIAD
POSTIMPLANTATION SYNDROME - PIS

INFLAMMATORY RESPONSE FOLLOWING ENDOVASCULAR REPAIR OF AN AORTIC ANEURYSM – EVAR

CLINICAL INDICATIONS:
- FEVER: >38°C
- LEUKOCYTES: >12,000/µL, >10,000/µL, >9,800/µL
- CRP: >10mg/L

- RELEASE OF INFLAMMATORY MEDIATORS
- ENDOTHELIAL DYSFUNCTION
- GRAFT MATERIAL: WOVEN DACRON, ePTFE, NITINOL
- ENDOVASCULAR SURGICAL/DEPLOYMENT TECHNIQUE
- CO-MORBIDITIES
EARLY AND LATE RESPONSES IN BLOOD/TISSUE/MATERIAL INTERACTIONS

Fig. 1. Interactions controlling the success or failure of vascular grafts.
DISEASED ABDOMINAL AORTIC ANEURYSM

ATHEROSCLEROSIS

CELL TYPES:

ENDOTHELIUM
NEUTROPHILS
MACROPHAGES
DENDRITIC CELLS
MAST CELLS
T and B LYMPHOCYTES
STEM/PROGENITOR CELLS
PLATELETS

MARKERS:

IL-1, IL-6, TNF-α, CRP
IL-8, FGF, IL-10,
MMPs, TIMPs
Proteases
INF-γ, IL-2
PF-4, β-TG
ENDOVASCULAR DEVICES
DEPLOYMENT INDUCED EFFECTS

MARKED ALTERATIONS IN BLOOD FLOW
TURBULENCE, STASIS

FOCAL THROMBOSIS – PROVISIONAL MATRIX
PRIMARY AND SECONDARY COAGULATION
PLATELET ADHESION, AGGREGATION, AND
ACTIVATION
INFLAMMATORY CELL ADHESION AND ACTIVATION

ENDOTHELIAL DENUDATION, DYSFUNCTION

ATHEROSCLEROTIC PLAQUE DISRUPTION

INCOMPLETE DEPLOYMENT OF ENDOVASCULAR DEVICE
THROMBOSIS

SURGICAL INJURY

ENDOTHELIAL INJURY
  • DEPLOYMENT– EXTENT
  • EXTENT OF ATHEROSCLEROSIS
  • PLAQUE VULNERABILITY

FLOW DISTURBANCE
  • TURBULENCE, STASIS

COAGULATION – PRIMARY, SECONDARY

PLATELET ADHERENCE, AGGREGATION

PROVISIONAL MATRIX - THROMBUS
THROMBUS – PROVISIONAL MATRIX

ACUTE PHASE RESPONSE

FIBRIN NETWORK CONTAINING:

- COAGULATION PRODUCTS
- PLATELET PRODUCTS
- CELLULAR PRODUCTS

“A SLOW RELEASE MATRIX” FOR:

- CHEMOKINES
- CHEMOTACTIC AGENTS
- PROTEASES
- INHIBITORS
- CYTOKINES
- GROWTH FACTORS
- ROS
EARLY CELLULAR ADHESION TO VASCULAR MATERIALS

EFFECT OF IMPLANT SURFACE CHEMISTRY UPON ARTERIAL THROMBOSIS
C.L. VAN KAMPEN AND D.F. GIBBONS.
JOURNAL OF BIOMEDICAL MATERIALS RESEARCH, VOL. 13, 517-541 (1979)

• Canines
• 30 seconds to 2 weeks
• In situ perfusion fixation under physiological pressure
• Light microscopic evaluation
• Scanning Electron Microscopy evaluation
Fig. 3. Optical micrograph of the thrombus deposit on the surface of Glu(OH):Leu-1:1 after 10 min of implantation. Massive platelet-leukocyte pillars (plp) extend up from the surface of the implant (i) into the vessel lumen (v). Fibrin (f) and entrapped red blood cells fill the spaces between pillars. Original magnification = 100×.
Fig. 4. Scanning electron micrograph of the surface of a platelet–leukocyte pillar present on the surface of Glu(OH):Leu-1:1 after 10 min of implantation. A leukocyte (l) is shown on a background of aggregated platelets (p). The particular surface morphology of the leukocyte shown is characteristic of polymorphonuclear leukocytes, which predominated corresponding histological sections. Bar = 2 \mu m.
Fig. 7. Scanning electron micrograph of the surface of Glu(ONa):Leu-1:1 after 15 min of implantation showing close-up view between pillars. Numerous leukocytes (l) are adhered directly to the implant surface (i). The leukocytes demonstrate pseudopod extension and various stages of spreading on the implant surface. Bar = 10 μm.
Fig. 10. Scanning electron micrograph of endothelial cells (e) covering the thrombus surface on Glu(ONa):Leu-1:1 after 1 week of implantation. Endothelial cell borders (b) are readily discernible and the underlying thrombus (t) is visible in small gaps between some endothelial cells. Bar = 10 µm.
ENDOTHELIALIZATION OF VASCULAR PROSTHESES – EARLY CELL ADHESION

METABOLISM AND ULTRASTRUCTURE OF THE ARTERIAL WALL IN ATHEROSCLEROSIS, ABEL L. ROBERTSON, JR., CLEVELAND CLINIC QUARTERLY, VOL. 32, 99-117 (1965)

• Barr Body identification within the nucleus of cross-transfused adherent female cells on Dacron vascular grafts in male canines

ORIGIN OF ARTERIAL PROSTHESIS LINING FROM CIRCULATING BLOOD CELLS, JR MACKENZIE, M HACKEET, C. TOPUZLU, DJ TIBBS, ARCHIVES OF SURGERY, VOL. 97, DEC., 879-885 (1968)

• Monocyte tagging with carbon particles
• 1 week – mononuclear (stem) cell adhesion
• 4 weeks – “endothelial” patches
• 16 weeks – “mature” endothelium
Fig. 1. Origin of pseudointimal cells coating vascular prosthesis. Dogs received total body irradiation preceding exchange transfusion with blood from opposite sex and replacement of a segment of abdominal aorta with a dacron prosthesis. The origin of the pseudointimal cells up to 40 days following transplantation was determined by their chromosomal characteristics. In both male and female hosts, the majority of intimacyes originated from blood cells.
CHALLENGES IN PIS DIAGNOSIS

PIS (TRANSIENT) VS SIRS (CHRONIC)
• NON-INFECTIOUS VS INFECTIOUS (SEPSIS)

STANDARDIZED DIAGNOSTIC CRITERIA
• RAPID – POC – POINT OF CARE

BIOMARKERS – ACCURATE, SELECTIVE, SPECIFIC
• CRP – C-REACTION PROTEIN, LIVER
• PCT – PROCALCITONIN, LUNG AND INTESTINE CELLS
  • SEPSIS MARKER
• sCD25 – SOLUBLE IL-2 RECEPTOR ALPHA CHAIN
  • T-CELL ACTIVATION
• sCD14 – LPS RECEPTOR FRAGMENT
  • MONOCYTES, MACROPHAGES
• OTHERS IN DEVELOPMENT

OVERLAP BETWEEN COAGULATION, THROMBOSIS, AND INFLAMMATION
Hemostasis & Thrombosis

PRO-THROMBOTIC

FAVOR THROMBOSIS

Extrinsic coagulation sequence

Exposure of membrane-bound tissue factor

Platelet adhesion: Held together by fibrinogen

vWF

Collagen

INHIBIT THROMBOSIS

ANTI-THROMBOTIC

Inactivates thrombin, factors Xa, IXa

Proteolysis of factors Va and VIIIa

Active protein C → Protein C

Inhibit platelet aggregation

PGI₂, NO and adenosine diphosphatase

Antithrombin III

Thrombin

Thrombomodulin

Endothelium

Heparin-like molecule
Blood Surface Interactions

Thrombin

Contact Phase

ARTIFICIAL SURFACE

VESSSEL WALL

Intrinsic
Extrinsic
Phospholipid
ADP
TxA2
PF4
βTG
Plasmin
Thrombinogen
Activated Protein C
Protein C
T:AT III
Plasminogen
Plasminogen Activator
Fibrinogen
Fibrin
FDP
Plasminogen
Prothrombin
Activated Protein C
Plasminogen
Plasmin
Plasma Protease Inhibitors
PGI2
vWF
Heparin

Activated Protein C
Activated Protein C
Protein C
AT III
Fig. 5. Optical micrograph of the thrombus deposit on Glu(OH):Leu-1:1 after 15 min of implantation. Platelet-rich areas (p) are generally distinct from fibrin and red blood cell areas (f). Polymorphonuclear leukocytes (l) are the predominant cell type. Original magnification = 400×.
Macrophage and Lymphocyte Derived Cytokines

<table>
<thead>
<tr>
<th>Macrophage</th>
<th>Lymphocyte</th>
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<tbody>
<tr>
<td>IL-1ra</td>
<td>TNF-α</td>
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<tr>
<td>TGF-β</td>
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<tr>
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Anti Inflammation
Pro Wound Healing
CELL TYPE at the MICROSPHERE/TISSUE INTERFACE vs. IMPLANTATION TIME

TYPE OF CELLS (%)

IMPLANTATION TIME (DAYS)
The obvious we see eventually,
The completely apparent takes longer.

Edward R. Murrow
MYOFIBROBLASTS

• A NEW PLAYER IN THE FOREIGN BODY REACTION AND HEALING RESPONSE TO BIOMATERIALS

• SCAFFOLD AND FIBROUS CAPSULE CONTRACTION THROUGH SMA

• RESPONSIVE TO SUBSTRATE MECHANICAL RESISTANCE

• PERSISTENT FOR THE DURATION OF THE RESORPTION PROCESS
Macrophages as master conductors…

- Classically activated (M1):
  - inflammatory, microbicidal, and tumor destructive
- Alternatively activated (M2)
  - M2a: growth stimulation, tissue repair, collagen formation
  - M2b: Pro- and anti-inflammatory function. Regulatory
  - M2c: Debris scavenging, pro-healing function

David M. Mosser et al., Nature Immunology, 2008, 8, 958-969.
IN VIVO MACROPHAGE ADHESION, APOPTOSIS, AND FUSION
Origin and plasticity

Epithelial-mesenchymal transition
Circulating bone marrow derived fibrocytes
Tissue-derived stem cells

Differentiation

Fibroblast
Myofibroblast

Proliferation

Maintenance and regulation of extracellular matrix
Wound healing
Regulation of interstitial fluid volume and pressure

Dysregulation of differentiation and function

Diseases of diminished or excess extracellular matrix deposition

Lung
Emphysema
Interstitial lung diseases
Asthma
COPD
Obliterative bronchiolitis

Skin
Scleroderma
Hypertrophic scars
Keloids
Lipodermatosclerosis
Dupuytren's contracture

Bones & joints
Rheumatoid arthritis
Osteoarthritis

Circulatory system
Atherosclerosis
Cardiac fibrosis
Pulmonary hypertension

Others/multiple systems
Epithelial derived tumours
Renal fibrosis
Liver sclerosis
Diabetes
Crohns disease
Peritoneal adhesions
Pleural adhesions
Aging
Ocular fibrosis
Neural adhesions/fibrosis
Myelofibrosis
Stroke-induced brain scarring/tendinitis
Fig. 2. Distinct mechanisms contribute to pathological tissue remodeling during highly polarized type 1 and type 2 responses. Sustained type 1 responses (IFN-γ and IL-17A) lead to substantial tissue damage. The injury, in turn, activates TGF-β, which suppresses the inflammatory response while activating extracellular matrix production by myofibroblasts that contribute to fibrosis. During a polarized type 2 response, IL-13 serves as an important driver of fibrosis, with the IL-13 decoy receptor (IL-13Rα2) and IL-10 exhibiting negative regulatory activity. Effective tissue regeneration is typically associated with less polarized immune responses.
Fig. 3. Integrated perspective of potential activation phenotypes and metabolic pathways in wound macrophages.
Figure 1. The inflammatory response at tissue/material interfaces.