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BIOCOMPATIBILITY:
LOCAL AND SYSTEMIC EFFECTS

M. Spector, Ph.D

BIOMATERIALS-TISSUE INTERACTIONS

BIOMATERIAL
- Strength
- Modulus of Elasticity
- Fracture mechanics
- Wear
- Metal corrosion
- Polymer degradation

TISSUE
- Protein Adsorption
- Particles
- Cell Response
- Ion Release
- ECM proteins
- Cytokines
- Eicosanoids
- Enzymes

Length Scale
10nm 100nm 1µm 10 µm 100 µm 1mm

Time Scale
1 sec 1 day 10 days 100 days

Tissue Remodeling
Cell-cell interactions
Bone
BIOMATERIALS-TISSUE INTERACTIONS:
Tissue Response to Implant Breakdown

**IMPLANT**
- Fracture
- Wear
- Metal Corrosion
- Polymer Degradation

**TISSUE RESPONSE**
- Fibroblast
- Degradation: Fibrous Tissue (Cell Contraction?)
- Macrophage
- Osteoclast
- Degradation Products/Ions

**RESPONSE TO IMPLANTS:**
WOUND HEALING

- Injury
  - Mild
  - Resolution
- Moderate/Severe
  - Vascularized Tissue (Inflammation)
  - Non-vascular
  - No Healing

- Reparative (Healing) Process
  - Repair (Scar)
  - Regeneration
RESPONSE TO IMPLANTS:
WOUND HEALING

Injury

Mild
Resolution

Moderate/Severe
Vascularized Tissue
(Inflammation)

Non-vascularized Tissue

Resolution (Inflammation)

No Healing

Reparative (Healing)
Process

Repair (Scar)
Regeneration

4 Tissue Categories
Connective Tissue
Epithelium
Nerve
Muscle
CT: Bone
Mu: Skeletal Muscle
Ep: Epidermis
Art: Articular Cartilage
CT: Articular Cartilage
CT: Dermis, Ligament
Mu: Skeletal Muscle
Mu: Skeletal Cardiac Muscle
RESPONSE TO IMPLANTS: WOUND HEALING

Injury

Regeneration
Tissue of Labile and Stable Cells
Framework* Intact
Regeneration

Repair
Tissue of Permanent Cells
Framework Destroyed
Scar

* “Stroma”

RESPONSE TO IMPLANTS: WOUND HEALING

Surgical Implantation

Acute Inflammation
Vascular Response
Clotting
Phagocytosis
Neovascularization
New Collagen Synthesis

Inc. time
Granulation Tissue

Tissue of Labile and Stable Cells
Framework Intact
Regen.
Scarring
(incorp.
of implant)
Chronic Inflammation

Tissue of Permanent Cells
Framework Destroyed
Implant Movement
Scarring
(fibrous encapsulation; synovium)

Chronic Inflammation
I. Metchnikoff

First identified “macrophages” and “microphages” (polymorphonuclear neutrophils, PMNs) in an organism around a foreign body.
In 1923 a piece of glass was removed from a patient's back; it had been there for a year. It was surrounded by a minimal amount of fibrous tissue, lined by a glistening synovial sac, containing a few drops of clear yellow fluid.

Photo removed due to copyright restrictions.

Diagrams removed due to copyright restrictions.
Synovium:
Macrophage-like (Type A) and Fibroblast-like (Type B) Cells

Photo removed due to copyright restrictions.

Tissue response to a cylindrical implant of polysulfone in lapine skeletal muscle, 2 yrs. post-op

Fibrous tissue

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Skeletal muscle
Polyethylene implant, 6 mos. post-op

Polyethylene

Photo removed due to copyright restrictions.

Porous Coated Co-Cr Tibial Component (retrieved 1 yr. post-op)

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RESPONSE TO IMPLANTS:
WOUND HEALING

- Surgical Implantation
  - Vascular Response
  - Clotting
  - Phagocytosis
  - Neovascularization
  - New Collagen Synthesis

- Tissue of Labile and Stable Cells
- Tissue of Permanent Cells

- Framework
  - Intact
  - Destroyed
  - Regen. (incorp. of implant)

- Implant Movement

- Scar* (fibrous encapsulation; synovium)

- Chronic Inflammation

* Including contraction

MACROPHAGES ON SURFACES
- Macrophages are attracted to surfaces (dead space)
- Fuse to form MFBGC
- More MFBGCs on irregular surface

Clotting
Phagocytosis
Neovascularization
New Collagen Synthesis

Tissue of Labile and Stable Cells
Tissue of Permanent Cells

Framework
Intact
Regen. (incorp. of implant)
Chronic Inflammation

Multinucleated Foreign Body Giant Cell

Inc. time
FIBROBLAST BEHAVIOR IN FIBROUS TISSUE AROUND IMPLANTS

- Proliferation and increased matrix synthesis of fibroblasts leads to an increase in the thickness and density of the scar tissue.
- Fibroblast contraction results in scar contracture.

BREAST IMPLANTS
Capsular Contracture

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Photograph shows Grade IV capsular contracture in the right breast of a 29-year-old woman seven years after subglandular (on top of the muscle and under the breast glands) placement of 560cc silicone gel-filled breast implants.
**BREAST IMPLANTS**

**Capsular Contracture**

**What is Capsular Contracture?**
Scar tissue that forms around the implant which causes the breasts to harden (similar to what a contracted muscle feels like) as the naturally forming scar tissue around the implant tightens and squeezes it. While capsular contracture is an unpredictable complication, it is also the most common complication of breast augmentation.

**How can Capsular Contracture be prevented?**
Textured implants help deter contracture because of their rough surface which is intended to discourage a hard capsule from forming. Under the muscle (sub-pectoral or 'partial sub-muscular') placement of the implant reduces risk of capsular contracture by an average of 8 - 10%. Whereas over the muscle (in front of the muscle or 'sub-mammary') has 10 - 25% or more chance of capsule contracture.

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**CAUSE OF CAPSULAR CONTRACTION**

Myofibroblasts, and the regulatory protein TGF-β, were found in the contracted capsules around silicone breast implants but not in non-contracted capsules. Mature skin scar tissue did not contain TGF-β or myofibroblasts.

How can Capsular Contracture be prevented?  
Massage and or compression. This is usually only done with smooth implants and may be suggested for a period between a few weeks to as long as you have your implants. Do not massage bruises!

The "no-touch" technique. This method includes meticulously rewashing surgical gloves before handling any instrument and implants. Only the head surgeon touches the implant, using a unique Teflon cutting board and immediately inserting the implant underneath the muscle. All of these measures help ensure that no foreign substance attach themselves to the implant, which could inflame the surrounding tissue and cause complications such as capsular contracture.

α-smooth muscle actin-fusion peptide (SMA-FP) inhibits the tension exerted by lung fibroblasts on silicone substrates. After washing our of the FP, cells contract again.

Chondrocytes (P2 Canine) in a Type I Collagen-GAG Matrix: Contraction

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40 min B Kinner
Human Articular Chondrocytes in Monolayer Culture
IH - Green: α-smooth muscle actin; Orange: type II collagen

Chondrocytes express the gene for α-smooth muscle actin and this enables them to contract

B. Kinner, et al. JOR 2001;19:233

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MUSCULOSKELETAL CELLS THAT CAN EXPRESS α-SMOOTH MUSCLE ACTIN AND CAN CONTRACT

• Articular chondrocyte
• Osteoblast
• Meniscus fibroblast and fibrochondrocyte
• Intervertebral disc fibroblast and fibrochondrocyte
• Ligament fibroblast
• Tendon fibroblast
• Synovial cell
• Mesenchymal stem cell


POSSIBLE ROLES FOR α-SMOOTH MUSCLE ACTIN-ENABLED CONTRACTION

Musculoskeletal Connective Tissue Cells
• Tissue engineering Contracture of scaffolds
• Healing Closure of wounds (skin wounds and bone fractures)
• Disease processes Contracture (Dupuytren’s)
• Tissue formation and remodeling Modeling of ECM architecture (e.g., crimp in ligament/tendon?)
**IMPLANT MATERIALS/BIOMATERIALS**

**TISSUE RESPONSE**

**Soft Tissue (that does not regenerate)**

- Fibrous capsule (scar)
  
  Synovium: fibrous tissue interspersed with macrophages
  
  Wound healing response of repair (scar formation) coupled with macrophage accretion at the “dead space” - chronic inflammation

**Bone**

- Tissue integration and tissue bonding

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**TISSUE INTEGRATION**

**TISSUE BONDING**

- Tissue Integration (Osseointegration)
  
  Apposition of tissue (bone) to the implant (contact of bone with the surface but not necessarily bonding)
  
  Regeneration of tissue up to the surface of the implant

- Tissue Bonding (Bone Bonding)
  
  Chemical bonding of tissue (viz., bone) to the surface
  
  Protein adsorption and cell adhesion
  
  Biomaterials: calcium phosphates and titanium (?)
Why are there no macrophages on the surface of the implant?

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Plasma-Sprayed Hydroxyapatite Coating

Photos removed due to copyright restrictions.

Photos removed due to copyright restrictions.

Plasma-sprayed HA coating on a canine femoral stem, 6 mos. post-opc
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Photos removed due to copyright restrictions.
J. Charnley, 1979

Photos removed due to copyright restrictions.

Titanium Wear Debris

Co-Cr Particles

Photos removed due to copyright restrictions.
Macrophage response to motion and particles

Unstable prosthesis

Particles → Motion → Bone resorption (Osteolysis)

Enzymes

PGE₂

IL-1

Macrophage (15-25µm)

Chemoattractants

Osteoblasts

Osteoclasts

Bone resorption

Osteoclast precursor cells

Polyethylene wear particles

H. McKellop, 1994 Hip Society

The number of particles generated by a hip prosthesis

7 x 10¹¹ particles/yr.

700,000 particles/step
NUMBER OF INHALED PARTICLES

Avg. particle burden of urban atmosphere:
10\(^5\) particles/liter

Respired volume in man = 1 liter/min.
Therefore, 10\(^5\) particles are inhaled/min.

10\% of the inhaled particles are deposited in the lungs.
Therefore, 10\(^4\) particles are deposited in the lungs per min.
5 \times 10^9\) particles/yr.

RESPONSE TO PARTICLES

- Type of material
- Size
  - mm, \(\mu\)m, nm
- Location
  - Joint fluid
  - Peri-prosthetic tissues
  - Synovium
  - Lymphatic system
- Number
RESPONSE TO PARTICLES

• Size
  – mm  No adverse response.
  – µm  Able to be phagocytosed by macrophages; macrophages release molecules that stimulate bone resorption.
  – nm  Sub-micrometer (nanoparticles) interfere with function of cell organelles; enter into the nucleus and interfere with genetic functions.
The total of 15 cemented and uncemented total hip replacement prostheses.

\[76\% < 0.5\mu m\]
\[92\% < 1.0 \mu m\]


The total of 3 total knee replacement prostheses.

\[43\% < 0.5\mu m\]
\[72\% < 1.0 \mu m\]

PARTICLE SIZE

- A large percentage of polyethylene particles in periprosthetic tissues are of nanometer size
  - less than 200 nm
- These nanometer size particles would go through the filters often used to capture particles from joint fluid
  - 200 nm diameter pores in the filter

ISOLATION OF PARTICLES FROM JOINT FLUID

Characteristics of Polyethylene Wear Particles Isolated from Synovial Fluid After Mobile-Bearing and Posterior-Stabilized Total Knee Arthroplasties

Yukihide Minoda,1 Akio Kobayashi,1,2 Hiroyoshi Iwaki,3 Masatsugu Miyaguchi,1 Yoshinori Kadoya,1 Hirotsugu Ohashi,1 Kunio Takaoka1

solutions were filtered through a 0.2-μm pore nylon filter
NANOPARTICLE TOXICITY

• Particles from prostheses have become smaller (from micrometer to nanometer).
• Introduction of nanotechnology into medicine (i.e., engineered nanoparticles for various applications) has raised questions about the biological response to nanoparticles.
• Several federal agencies (NIH, EPA) are looking into this issue.
• 2 major causes of death are cancer and heart disease; there are indications that nanoparticles can adversely contribute to these processes.

“Nano's Troubled Waters:”

“Latest toxic warning shows nanoparticles cause brain damage in aquatic species and highlights need for a moratorium on the release of new nanomaterials.

• A new study revealing that engineered carbon molecules cause brain damage in fish is one more brick in the wall of evidence suggesting that manufactured nanoparticles are harmful to the environment and to health.
• How many warnings do government regulators require before they take action to ensure that uses of nanoparticles are safe before workers in production facilities are harmed and before consumers are further exposed? ”
RESPONSE TO PARTICLES

- **Type of material**
- **Size**
  - mm, μm, nm
- **Location**
  - Joint fluid
  - Peri-prosthetic tissues
  - Synovium
  - Lymphatic system
- **Number**

LYMPHATIC SYSTEM

- Filters out organisms and particles.
- The lymphatic vessels are present wherever there are blood vessels.
- More than 100 tiny, oval structures (called lymph nodes).
  - scattered all along the lymph vessels.
  - filter out particles
- Particles that pass through the lymph node enter into the blood circulation.
Lymphadenopathy

Photos removed due to copyright restrictions.

SMALL PARTICLE DISEASE: LYMPHADENOPATHY

- Enlargement of the node.
- Particles drained from tissue by the lymphatic system are phagocytosed by macrophages in the nodes.
- No adverse clinical sequelae yet noted, but can confound differential diagnosis of other diseases.
- Concern about the clinical sequelae of nanoparticles that gain access to the vascular system.

LOCAL AND SYSTEMIC RESPONSES SMALL PARTICLE DISEASE

- **Local Component**
  Particle induced focal destruction of tissue around the implant

- **Systemic Component**
  Lymphadenopathy
BIOLOGICAL RESPONSE TO METAL DEBRIS

• Immune responses

PATIENT CONCERNS ABOUT METAL DEBRIS

Am I allergic to my metal implant?
IMMUNE RESPONSE TO METAL IONS

- "Metal allergy" has been incriminated as the cause of failure in certain patients.
- However, results obtained to date are not definitive.

METAL SENSITIVITY IN PATIENTS

- 10-15% of population have dermal sensitivity to metal (14% to Ni)
- Metal ions bind to proteins to form immunogenic complexes
- Metals known as sensitizers:
  - Ni > Co and Cr >>> Ti and V
- 60% of pts. with failed TJRs were metal sensitive vs. 25% with well-functioning implants
  - Did metal sensitivity cause failure or did the failed implant cause metal sensitivity?

Hallab, Merritt, Jacobs, JBJS 83-A:428 (2001)
METAL SENSITIVITY IN PATIENTS

• “May exist as an extreme complication in only a few highly susceptible patients (< 1%), or it may be a more common subtle contributor to implant failure.”

• “It is likely that cases involving implant-related metal sensitivity have been underreported because of the difficulty of diagnosis.”

• Patients who have displayed sensitivity to metal jewelry are at higher risk.

Hallab, Merritt, Jacobs, JBJS 83-A:428 (2001)

CELL RESPONSE TO METAL PARTICLES

• Macrophages in vitro
• Particles of Ti alloy not toxic; Co-Cr highly toxic
• Ti induced more release of PGE₂ than Co-Cr
• Exp. to Ti increased the release of PGE₂, IL-1, TNF, and IL-6; exp. to Co-Cr decreased release of PGE₂ and IL-6 and had little effect on IL-1 and TNF
• “release of Ti....worse than....Co-Cr”

CELL RESPONSE TO METAL PARTICLES

- Bovine articular chondrocytes
- Co was toxic to cells at all conc.
- At high conc. Cr, Ti, and Ti alloy were toxic
- At high conc. all metals decreased enzyme activity
- PGE$_2$ increased with conc., except for Ti alloy


BIOLOGICAL RESPONSE TO METAL PARTICLES AND IONS

Summary

- Metal particles and ions are released from TJR prostheses; the amounts can be reduced by careful design and manufacturing
- Cellular response to metal particles has some of the same elements as the response to particles of other materials
- No indication yet that metal particles and ions are responsible for profound adverse responses