Biocompatibility of Implantable Medical Devices

Lecture 13
Summary

• Biological response to implants
• Methods to reduce adverse effects
• Regulations governing medical devices
• Testing of implantable devices
Sequence of Response

1. Injury
2. Blood/Material Interactions
3. Provisional Matrix Formation
4. Acute/Chronic Inflammation
5. Granulation Tissue Formation
6. Foreign Body Reaction
7. Fibrosis/Fibrous Capsule Development
Injury

- Implantation of the device is likely to damage blood vessels in the vicinity
- Initially damaged blood vessels constrict (haemostasis) and clots can form
- Secondly the walls of surrounding blood vessels can dilate and become porous
- This lets out exudate containing inflammatory cells and factors.
Blood/Material Interactions

- Platelets and proteins like fibrin and fibronectin interact to form clots.
- These can coat the surface of the device as well as preventing further blood loss.
- Platelets release growth factors and other chemicals that attract inflammatory and immune cells to the injury.
Provisional Matrix Formation

- Proteins released due to injury to vascularised tissue form the matrix
- In a normal injury this forms the basis for the healing process
- For an implant this means almost immediate protein biofouling
- This can be a problem for a sensor
Acute Inflammation

• Inflammation is named for the redness, swelling, and temperature change
• This is caused by the flooding of the injury site with blood and exudate
• This also allows antibodies and immune cells to get to the site of the injury
• The first to arrive are neutrophils
Neutrophils

- Polymorphonuclear leukocytes/neutrophils - most abundant type of white blood cell
- Phagocytes are designed to detect and consume bacteria
- They also release products to attract and stimulate other immune cells to the injury
Phagocytosis

- Neutrophils engulf attackers
- Granules inside contain anti-bacterial agents
- Oxidation generates toxins
Neutrophil Chemotaxis

- Invading bacteria are “tagged” with antibodies
- Chemicals attract phagocytes
- Chemotaxis is movement up a chemical gradient
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Macrophages

- Monocytes are attracted to the wound site within a few hours/days of injury
- Growth factors present encourage them to mature into macrophages
- Much larger than neutrophils
- They consume pathogens and damaged tissue
Chronic Inflammation

- Inflammation should be a short term process or healthy tissue can be damaged
- Foreign bodies like medical implants can lead to unwanted chronic inflammation
- Chemical and physical properties of an implant are important considerations
- Movement of the implant can affect healing
Granulation Tissue

- Fibroblasts and endothelial cells proliferate at the implant site within a day or so.
- Together with immune cells they form granulation tissue, with red and granular appearance.
- This consists of a fibrous tissue matrix and new blood vessels.
Angiogenesis

• Fibroblasts and other cells in the granulation tissue require oxygenation

• Vascular endothelial cells at implant site form capillaries to supply blood

• This process is known as angiogenesis or neo-vascularisation
Foreign Body Reaction

- Phagocytes will not be able to engulf a typical implant due to size disparity
- Macrophages activated at the implant surface will produce corrosive enzymes
- They can also coalesce to form multi-nucleated foreign body giant cells
Fibrosis/Fibrous Tissue Formation

- Macrophages and FBGC may exist at the device surface for the lifetime of implant
- Beyond this the fibroblasts will gradually begin to produce a collagen matrix
- This fibrous tissue can eventually encapsulate the implant and seal it away
- This may not happen with porous materials
Impact on Implanted Devices

- Protein biofouling can lead to immediate reduction in sensor sensitivity
- Macrophages and FBGCs can release factors that degrade the implant
- Fibrous capsule formation can cut off a sensor from the environment
- Neo-vascularisation during granulation tissue stage could increase sensitivity
Implanted Drug Delivery System
Impact on Biosensor

Membrane biofouling

Electrode passivation

Membrane biodegradation

Electrical failure

Delamination of membranes

Enzyme degradation

Fibrous encapsulation

Capillary

Glucose molecules

Cells

Fig. 1. Schematic illustration of glucose molecules exiting a capillary and diffusing to a subcutaneously implanted needle-type glucose biosensor. In addition to normal component failure such as electrical failure, enzyme degradation, and membrane delamination, the sensor can fail from several physiologically related causes, such as membrane biodegradation, electrode passivation, fibrous encapsulation, and membrane biofouling.
Engineering Tissue Response to Implants

- Different approaches and techniques are required to control different effects
- Protein biofouling is the first adverse effect on an implanted sensor device
- Proteins adsorb more onto hydrophobic surfaces so use hydrophilic materials?
- Poly(ethylene) glycol (PEG) is a possibility
Surface Modifications

- Hydrogels are polymer networks that are highly absorbent to water
- Typically they do not affect diffusion of analytes to a sensor membrane
- They can be modified with ligands to promote certain cells to adhere
- Growth factors to control angiogenesis and fibrosis could also be incorporated
Drug Delivery

- Controlled release of growth factors or other drugs from implant surfaces
- Biodegradable microspheres are one possible delivery method
- VEGF - Vascular Endothelial Growth Factor
- Dexamethasone - anti-inflammatory and anti-fibrotic drug
Nitric Oxide Release

• Nitric oxide (NO) is a naturally occurring compound that causes vasodilation

• It is also involved in the inflammatory process and wound healing

• It has been shown to promote angiogenesis and reduce fibrous capsule formation

• Possible interference with chemical sensors
Physical Modification

• The micro and nano-scale topography of materials influences the tissue response
• Porous surfaces can encourage tissue ingrowth but pore size is very important
• Small pores increase fibrous encapsulation
• Large pores encourage inflammatory cells
• Ideally the pores should encourage capillary development around the sensor
Sensor Adaptions

Fig. 2

Schematic illustration of potential options for modifications of an implantable biosensor to improve its biocompatibility. Development of new materials, coatings and surface texturing may enhance the sensor's function and lifetime. For example, incorporation of hydrogels or polyethylene oxide (PEO) and tissue response modifiers (TRM) may reduce protein adsorption and biofouling.

- **Biosensor**
  - Sensing layer
  - Textured surface for tissue in-growth
- **Interphase**
  - Microparticles
- **Tissue**
  - Red blood cell
  - Capillary
  - Soluble Proteins
  - Fibrin
  - Collagen
  - Angiogenic factor or other Tissue Response Modifiers
  - Cell adhesion molecules

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Regulating Implant Biocompatibility

• Medical devices are heavily regulated by
  ‣ Food and Drug Agency (FDA - US)
  ‣ European Medicines Agency (EMA - EU)
  ‣ Medicines and Health Regulatory Agency (MHRA - UK)

• Standards are set by the International Standardisation Organisation (ISO)
Active Implantable Medical Devices

- European commission directive 90/385/EEC
- Revised in 2007 with directive 2007/47/EC
- Covers the placing on the market and putting into service of active implantable medical devices (AIMDs)
- Active means they use electrical energy or some other power source to operate
AIMD Directive

• Sets out which standards the active implants must follow
• This includes things like sterilisation, labelling and other supplied information
• The bulk of the standards applied concern evaluation and testing of implants
• These are set out in ISO 10993
Standard ISO 10993

- There are 18 parts to ISO 10993
- The most important for implants are:
  1. Evaluation and testing within a risk management process
  4. Selection of tests for interactions with blood
  5. Tests for in vitro cytotoxicity
  6. Tests for local effects after implantation
• Continued:

9. Framework for identification and quantification of potential degradation products
10. Tests for irritation and delayed-type hypersensitivity
11. Tests for systemic toxicity
12. Sample preparation and reference materials
13. Identification and quantification of degradation products from polymeric medical devices
Standard ISO 10993

• Continued:
  16. Toxicokinetic study design for degradation products and leachables
  17. Establishment of allowable limits for leachable substances
  18. Chemical characterization of materials
Medical Device Categorisation

- ISO 10993-1:2009 categorises devices by level of tissue contact and contact duration
  - Surface devices - Skin, mucosal membranes or breached/compromised surfaces
  - External communicating devices - Blood path (indirect), tissue/bone/dentin or circulating blood
  - Implant devices - Tissue/Bone or blood

- Limited (<24 hours), Prolonged (1-30 days), Permanent contact (>30 days)
In-Vitro Testing

- Cells are cultured directly on samples of implant material
- Lysing of cells, cell rounding and/or growth inhibition indicates cytotoxicity
- Cell lines used are defined in the standard
Cage Method for In-Vivo Testing

- Material to be tested is implanted within a stainless steel wire mesh cage (rat)
- Exudate is collected from the cage and analysed for inflammatory cells
- This data is compared with empty controls or controls with “safe” materials
Post-Explantation Testing

• Implanted sensors used in in-vivo testing should be recovered

• The function of the device after explantation needs to be confirmed

• Thickness of the fibrous capsule and other histopathological testing is required
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