TISSUE COMPATIBILITY OF BIOMATERIALS: BENEFITS AND PROBLEMS OF SKIN BIOINTEGRATION

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The integration of biomaterials with skin is necessary to enable infection-free access to vasculature and body cavities. Also, integrating plastics and metals with skin increases options for the reconstruction of surgical and traumatic defects and enables the permanent implantation of robotic and electronic devices. Until now, attempts to integrate biomaterials with skin permanently have failed because of epidermal marsupialization and infection. This article reviews the general properties required of biomaterials to optimize integration with body tissues, the modifications that increase biocompatibility, focusing particularly on surface functionalization and the specific requirements for biomaterial integration into skin. Critical pathophysiological processes relating to biocompatibility are discussed with particular emphasis on the skin–biomaterial interface. Future directions are speculated on, in particular, the specific utility of subatmospheric pressure dressings in facilitating tissue integration into biomaterials.

Key words: biocompatible materials, prostheses and implants, reconstructive surgical procedure, tantalum, titanium.

Abbreviation: PMMA, polymethyl methacrylate.

INTRODUCTION

In 2007, The Economist opined that humanity is on the verge of biology’s ‘Big Bang’. Many of the important problems facing our society and their solutions are biological. Global warming, infection pandemics and the ageing population are biological problems.1

Harnessing the explosion in biological knowledge will see a world reshaped by robotics,2 nanotechnology,3,4 genetic engineering,5 stem cell research6,7 and tissue engineering.8 The line separating humans from machines will blur and integrating artificial materials with tissues will become commonplace.

Cinematic images of artificial materials fused with skin are commonplace, Luke Skywalker’s robotic hand, the Bionic Woman and Asimov’s androids, to name a few. Until now, the concept of externally integrating plastic or metal with humans has been the stuff of science fiction. Recent advances in cell biology, metallurgy, dental implant technology, chemistry and surgery have brought it into the realm of possibility.

A key step necessary for interfacing humans with machines is the integration of artificial materials with skin. Successfully integrating metal and plastic with skin also expands options for the reconstruction of surgical defects and permits infection-free access to vasculature and body cavities. Potential applications are limited only by imagination; after all, only skin separates us from computers, phones, watches, iPods (Apple Inc., Cupertino, CA, USA) hearing aids and spectacles.

This article reviews the terminology and basic concepts of biocompatibility along with the factors promoting the integration of artificial materials with human tissues and the barriers to be overcome in creating an interface with skin. In addition, the specific utility of integrating plastic and metal with skin will be highlighted and the highly biocompatible nature of titanium and tantalum will be reviewed.

BIOMATERIALS

Biocompatible materials, also known as ‘biomaterials’, are designed to function in contact with living tissue. For a material to be biocompatible, it needs to be non-inflammatory, immunologically inert and non-carcinogenic. It should be able to withstand physical stresses (e.g. bending, compression, abrasion and tension) and needs to be adaptable, affordable and easy to sterilize and manufacture.9,10

There are a large number of materials already in use or under development that meet these criteria including biodegradable and non-biodegradable polymers, ceramics, silicone and metals. The choice of material depends on the anticipated use. Metal biomaterials consisting of iron, cobalt, tantalum and titanium are used extensively as surgical implant devices. Titanium and tantalum, have excellent mechanical properties and consequently are commonly chosen for implantation where structural strength is required (e.g. joint replacements).11,12 Favourable mechanical and surface chemistry properties make these metals ideal choices for skin implantation.
CRITICAL PATHOPHYSIOLOGICAL PROCESSES AFFECTING SKIN IMPLANTS

Inflammation
Following prolonged implantation, cells surrounding many biomaterials (e.g. artificial joints) develop an inflammatory response to the materials, contributing to implantation failure. Chronic inflammation and tissue overgrowth cause problems with intravascular biomaterials. The inflammatory response to foreign bodies involves leucocyte migration into tissues. Macrophages are involved in maintaining chronic inflammatory responses. Pro-inflammatory cytokines are released mediating this process.

Investigations into cell signalling indicate that the nature of the biomaterial determines the extent of the inflammatory response. Apart from their excellent mechanical properties, the popularity of titanium and tantalum relates to the anti-inflammatory properties of surface oxides. For example, titanium dioxide inactivates reactive oxygen species that are integral to initiating and maintaining the inflammatory response.

Immunoreactivity
Immune reactions require uptake of material by antigen-presenting cells for processing and presentation to T-helper cells. By-products resulting from wear, oxidation or dissolution are presented in this way. Hypersensitivity reaction types 1–3 have not been observed with biomaterials, but type 4 (cell-mediated) delayed hypersensitivity reactions have been documented. Type 4 hypersensitivity reactions have been described for nickel, cobalt, chromium and stainless steel. Allergic reactions to nickel-containing jewellery are well documented and are a dermatological manifestation of type 4 hypersensitivity.

Tantalum and titanium are well tolerated by most patients, even those with sensitivity to other metals, and allergic reactions are extremely rare. It is uncertain if true allergies exist because only a handful of cases have been reported. Skin contact sensitivity from titanium is rare, but has been described for pacemaker-dependent patients. Despite the rare reports of adverse reactions to tantalum and titanium, the exceptional mechanical and non-inflammatory properties of these metals make them appropriate choices for skin implantation.

Infection
Surgically implanted materials are prone to infection. Local tissue defences are compromised by tissue trauma and disrupted perfusion. These factors combined with colonization of implant surfaces at the time of implantation can lead to overt infection. Biofilms are bacterial colonies embedded in a polysaccharide matrix. This matrix protects the bacteria against hostile environmental factors. Endogenous microflora in humans occurs as a biofilm. When body surfaces with microflora (e.g. the skin, gut, nasopharynx and genito-urinary tract) are exposed to tissue without microflora (e.g. central nervous system and blood vessels), then infection may occur. Similarly, biomaterials can become colonized with biofilm after contact with microflora-contaminated body surfaces. Bacteria in biofilms cannot be eradicated by antibiotics and are resistant to normal immunological defence mechanisms. In addition, compounding the problem of biofilm, the inherent pathogenicity of endogenous bacteria, such as Staphylococcus epidermidis, is increased by the very presence of foreign bodies.

Toxicity
Toxicity refers to detrimental cell changes or interference with biochemical processing caused by chemical or physical agents. Most biomaterials in use today have negligible toxicity when intact, but recent studies suggest that many materials, such as particles of titanium, silicate and polymethyl methacrylate (PMMA), once thought to be non-toxic do, in fact, have some degree of toxicity.

It may be the case that very small particles of any artificial material possess some degree of toxicity. Despite this, the long history of negligible toxicity in the clinical setting of materials such as tantalum, titanium and PMMA will see them used well into the future.

Carcinogenesis
Tumours, especially sarcomas, have been induced in mice and rats by many biomaterials. This effect is known as ‘solid-state carcinogenesis’. Suggested mechanisms include potentiation by leaching chemicals, degradation products, physical contact with surrounding tissues and maturation of preneoplastic cells.

Despite a causal relation suggested in mice and rats, there is no evidence for a relation between foreign bodies and cancers in humans. Various biomaterials have been used for more than 30 years in humans. The very low number of cancers recorded suggests that the incidence of cancers at implantation sites will remain low. This has been supported by microscopic assessment of human foreign body granulomas. Precancerous cells have not been detected, in contrast to foreign body granulomas in mice, in which the incidence of foreign body tumours has been shown to be high. Other research has shown no evidence of solid-state carcinogenesis in humans. The reasons for this difference between humans and rodents are unknown.

Normal cellular attachment
Cell adhesion is of fundamental importance in tissue growth, repair, organogenesis, embryogenesis and the response of tissues to implanted biomaterials. Adhesion of cells to biomaterials occurs by interaction with substratum-adsorbed serum proteins, specific cell surface and extracellular matrix proteins and transmembrane proteins. Important proteins involved with cell adhesion include fibronectin, laminin and collagen. It has been shown that cells attach to substrate surfaces by plasma membrane specializations. In fibroblast cultures, three types of cell-substratum contacts have been described. (They are extracellular matrix contacts, close contacts and focal adhesions.) In epithelial cells, an additional structure called the ‘hemidesmome’ mediates cell attachment.

BIOMATERIAL INTEGRATION INTO SKIN

Failure at the skin–biomaterial interface
Binding at the biomaterial–skin interface has been shown to fail because of epidermal cell migration causing marsupialization and infection. In addition, mechanical forces cause avulsion at the interface.

In speculating on a solution to biomaterial integration with skin, von Recum theorized that the major requirement is a material that allows tissue into its pores, forming a dynamic interface.
In addition to tissue growth into the pores of the material, the prevention of epidermal migration is critical. In theory, if epidermal cell attachment to the implant can be enhanced, marsupialization can be prevented (Fig. 1).

Functionalizing surfaces

Cell binding to biomaterials is most effectively achieved by attaching proteins to the biomaterial. Proteins do not bind to inert surfaces; optimal binding requires surfaces replete with ‘functional groups’. ‘Functional groups’ are the groups of atoms within molecules that are responsible for the characteristic chemical reactions of these molecules. Examples include hydroxyl, carboxyl, amine, phosphate and methyl. Functional groups are critical in biological reactions and their creation on inert surfaces is one of the important goals of biomaterials research.

In general, surface functionalization of biomaterials can be achieved by chemical methods or by the use of plasma.

Methods of plasma functionalization are being investigated at several Australian universities. Plasma is considered to be the ‘fourth state of matter’ because, while it is neither liquid nor gas, it has properties similar to both. It generally takes the form of gas-like clouds or charged ion beams. Plasma is created by complex processes involving excitation and dissociation of electrons from atoms. The effects of plasma are witnessed daily in televisions, fluorescent lights, lightning, the polar aurorae and the Sun and other stars.

Energetic species in plasma include electrons, ions, radicals and ultraviolet photons. Energy is transferred from the plasma to the biomaterial from these species by mechanisms, termed ‘polymerization’, ‘treatment’ and ‘etching’. A detailed explanation of these terms is beyond the scope of this article, but in brief, ‘polymerization’ involves depositing organic monomers onto a substrate; ‘etching’ involves bombarding substrate with ions and ‘treatment’ uses gases, such as argon, nitrogen and oxygen, to create or insert functional groups onto a substrate.45

Chemical methods of surface functionalization include

(1) Self-assembled monolayers: Single layers of phosphate groups can be bound covalently to metal oxide surfaces, such as titanium dioxide (TiO$_2$), tantalum oxide (Ta$_2$O$_5$) and niobium oxide (Nb$_2$O$_5$).46–49 Functional groups attached to the phosphate group allow tailoring of surface properties.

(2) Polymer adlayers: Polymers can be bonded to substrates through their vinyl ether side functional groups. The bound polymers can then be functionalized in additional steps.

(3) Chemical vapour deposition: Surfaces are exposed to volatile precursors that react on the substrate. Deposited materials can include tungsten, silicon, carbon and titanium nitride. This process is used to create artificial diamonds.

(4) Nanotechnology: Nanotechnology involves the creation and use of materials 100 nm or smaller. In functionalising biomaterials, this technology is still in its infancy but holds great promise. Modern synthetic chemistry permits the creation of a vast array of small molecules and enables the production of a wide variety of pharmaceuticals and commercial polymers. The ability to create larger molecules, “supramolecular assemblies”, is close. In the future it may be possible to create patterns or scaffolds on biomaterials reproducing the molecular structure of proteins.

(5) Silanization: Many of the techniques to functionalize surfaces for protein binding use chemicals known as ‘silanes’.50–54 Silanes are silicon analogues of alkanes. The simplest silane is SiH$_4$, the silicon analogue of methane (CH$_4$). Silanes can be chemically bifunctional; that is, they can have dual reactivity.

\[ \text{R} \quad \text{O} \quad \text{Si} \quad \text{X} \quad \text{O} \quad \text{R} \]

For example X (above) is a functional group that reacts with organic materials. RO is a functional group that reacts with inorganic materials, such as glass and metals. Silanization has many advantages over other methods of surface functionalization. It has proven efficacy for more than 30 years for example, in restoration dentistry, is relatively cheap, and does not require specialized equipment.

Epidermal attachment

To integrate biomaterials with skin, epidermal attachment is critical to prevent marsupialization. Adhesion of epidermal cells has been shown to be optimized by the use of basement membrane proteins, such as collagen type 4 and laminin type 5.55–58 In theory, if basement membrane proteins can be attached permanently to biomaterials, preferably by covalent bonding, it should be possible to achieve reliable attachment of epidermal cells. As previously described, optimal attachment of proteins requires surface functionalization.

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Dermal integration

To minimize avulsion and shear forces on overlying epidermis, it is necessary to anchor dermis to the biomaterial over a relatively large area. To date, the ability to integrate dermis with biomaterials has eluded researchers. Von Recum theorized that the major requirement for skin biointegration is a material that allows tissue to grow into its pores. This supposition has been supported by several studies. Sclafani et al. assessed the clinical and histological behaviour of exposed porous high-density polyethylene implants. It was found that porous high-density polyethylene tolerates exposure well once host fibrovascular tissue has invaded the implant pores.

Promising results have been published recently regarding skin integration into porous skin-penetrating prostheses. Pendegrass et al. studied the morphology of deer antlers to develop a porous flange, which mimics the interface between deer antler and skin, creating a tight seal between the implant and the host tissues. The Flange was attached to a titanium pylon inserted into the tibia of goats. Pitkin et al. found porosity in titanium-facilitated integration with surrounding skin after implantation into rat femurs.

Despite these promising early findings, a reliable and lasting method for integrating dermis (or other tissues) into porous structures is lacking. Biomaterials research worldwide is assessing various methods for integrating tissues into porous structures. Some of the methods under investigation involve functionalizing the pores and preseeding with cells, such as fibroblasts.

THE FUTURE

Various methods for optimizing cell attachment to biomaterials are being investigated worldwide. The most effective methods involve some form of chemical or plasma surface functionalization to enhance protein binding. It is probable that future biomaterials will be functionalized, regardless of intended location. This includes bone implants, joint replacements, breast implants, hernia mesh, artificial organs and skin implants.

A variety of different polymers and metals are being assessed for suitability as biomaterials. It is likely that tantalum, titanium and their alloys will be used well into the future. The non-inflammatory, inert, non-carcinogenic, adaptable and physically robust properties of these metals make them an ideal choice.

The problem of reliably integrating tissues with porous biomaterials has yet to be solved. It may be the case that subatmospheric pressure (vacuum) is the key. Subatmospheric pressure dressings have been shown to improve wound healing and vascularization (Argenta, Morykwas et al. 2006), (Chen, Li et al. 2005), (Morykwas, Simpson et al. 2006), (Wackenfors, Sjögren et al. 2004), (Jeschke, Rose et al. 2004) and the clinical utility of these dressings has evident in surgical practice for more than 7 years. The rapid rate of granulation tissue formation under vacuum has led to its use to increase tissue growth into synthetic collagen matrices (Integra, Plainsboro, NJ, USA). In theory, similar tissue in growth should be achievable with porous metal or polymer matrices.

SUMMARY

Huge advances in the biological sciences are predicted for this century. Enormous change is predicted in the fields of cell biology, stem cell research, tissue engineering and robotics. The use of biomaterials is set to expand and a permanent, functional interface with skin is within reach. If skin biointegration can be achieved, there are significant potential benefits. Theoretical benefits include infection-free access to vasculature and body cavities, the reconstruction of surgical and traumatic defects, robotics and human–machine interfaces. Various chemical and plasma-based methods of biomaterial surface functionalization are being investigated in order to optimize protein and cell binding. Despite recent progress with tissue growth into porous biomaterials, a reliable and lasting method of ensuring tissue growth into pores has not been discovered. Research is continuing apace in solving this problem and it may be case that the answer can be found in the surgical practice of using sub-atmospheric pressure dressings.

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