BIOMATERIAL SURFACES: MODIFIED TITANIUM SURFACES AND MICROFABRICATED MATERIALS

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Introduction

Most "biomaterials" in use today were originally developed for other applications than biological. The tissue responses they give rise to are often far from optimal. One major bottle-neck for developing new and better (functional) biomaterials is the lack of understanding of how different material properties influence the biological response and vice versa.

The material-specific biological response to an implanted material is mainly determined by the chemical and structural properties of the biomaterial surface [1]. Research on properties and processes at interfaces between biomaterial surfaces and biological systems is therefore a key issue in the biomaterials area. A systematic research approach should include *surface modification* by different preparative techniques combined with careful *surface characterization* using modern analytical tools, to produce well-defined model surfaces which can be used in biological evaluation studies in vitro and in vivo (Fig. 1). Biological evaluation can be done at different levels of complexity, including simple model experiments of water, ion and biomolecule adsorption, cell cultures, and tissue response in vivo. Such an interdisciplinary research program opens up a way to systematically search for correlations between different surface properties and biological response. Two models systems based on these ideas are briefly described, with emphasis on the surface preparation and analysis aspects.

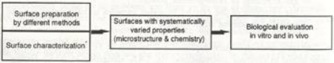

Fig. 1 - Research approach where surface preparation and analysis are combined to prepare model surfaces that are used in biological evaluation studies aiming at finding correlations between surface properties and biological response.

SYSTEMATIC MODIFICATION OF SURFACE PROPERTIES FOR STUDYING BIOLOGICAL RESPONSE

Modified Titanium Surfaces

Titanium is a suitable material for studying material-tissue interaction for two major reasons: (i) It is widely and successfully used in several clinical applications (dental implants, orthopedic implants, heart valves, ...), and is considered to have a good compatibility with bone and soft tissues. (ii) It is a relatively simple material and its surface properties can be modified over a wide range. Despite its wide use in clinical applications the factors and mechanisms that underlie the tissue response to titanium implants are poorly understood. It is, however, likely that the surface oxide which almost always covers the metal plays an important role. The question is then: How do different oxide properties (e.g. thickness, microstructure, crystallinity, chemical composition, impurities, ...) influence the biological response to titanium? The obvious approach to investigate this is to vary the surface (oxide) properties and test for the response in different biological experiments (protein adsorption, cell cultures, and animal experiments).

We have carried out a broad characterization, using surface spectroscopies (AES, XPS/ESCA, SIMS), electron microscopies (SEM, TEM) and scanning nanoprobes (STM, AFM), of Ti surfaces prepared by different methods (machining, thermal oxidation, electrochemical methods, and glow-discharge plasma methods) [2-8]. This work has resulted in a good understanding of how different preparative procedures influence the physical and chemical properties of Ti surfaces. Selected results from such studies are briefly summarized in Table 1. The table also demonstrates that the properties of Ti surfaces can be modified over a wide range. Different modified Ti surfaces are presently being used in protein adsorption studies [9] and evaluation of bone response in vivo [4]. The former do not show any marked differences between different Ti surfaces, while the in vivo results indicate that the rate of bone formation around Ti implants is influenced by surface morphology (roughness) and oxide thickness [4].

Microfabricated Model Materials

Surfaces are expected to influence the biological response either by structural properties (topography, microstructure, crystallinity, ...) or chemical properties (composition, stability, adsorption properties, ...). Synergistic effects between different properties are very likely. It is therefore desirable to be able to investigate these properties independently, and preferably on well defined scales of dimension. Chemical variations and or structural features on size scales ranging from atomic dimensions (0.1 nm) up to several microns are expected to play different roles, since they will match different biological components at the interface [1, 10]. So, for example, it may be expected that nm-size features will

	Parameters	Thickness	Composition	Structure	Impurities	Dopants
"Clinical" oxides	Machining, cleaning, sterilization, handling,...	2-6 nm	TiO_2 + sub-oxides (Ti_2O_3, TiO) + small amounts of TiN_x	Quasi-amorphous, dense	C, Ca, P, Si, Cl, S, Na,... at %-levels	-
Thermal oxides	Temperature, pressure, time, oxidizing gas (O_2, O_3, H_2O)	10 - 40 nm	TiO_2 + sub-oxides (+ OH in humid atmospheres)	Quasi-amorphous to crystalline (anatase or rutile)	Depends on gas composition	-
Anodic oxides	Anode voltage, electrolyte, temperature,...	Up to several microns (µm)	TiO_2	Quasi-amorphous to crystalline, heterogeneous, dense to porous	Anions from electrolytes, (SO_4^{2-}, PO_4^{3-})	Anions (~1 %)
Plasma oxides	Plasma gas composition and pressure, sample voltage, temperature, time,...	Up to several 100 nm	TiO_2, variable	Quasi-amorphous to crystalline, dense	None (but care in handling is important)	Almost any
Electro-polished Ti	Electrolyte, temperature, time.	3-5 nm	TiO_2	Quasi-amorphous	Cl	-
Alloyed Ti, Ti6Al4V...	Bulk metal composition, and as above	As for pure Ti	TiO_2 + % levels of AlO_x and VO_x	As for pure Ti	Al, V, and as above	As for pure Ti

Table 1

influence the interaction with biomolecules, while structures and/or chemical variations on the 1-10 µm scale will influence cellular behavior at surfaces.

In our group we have adapted the methods that are used in fabrication of microelectronic devices — microfabrication and nanofabrication based on lithography, etching and thin film deposition — for preparing model surfaces for biological evaluation that have variations in chemical composition and/or microstructure on well-defined size scales (Fig. 2). This type of surfaces offer unique possibilities to study how biological response at different levels are influenced by surface structure and chemical composition.

Microfabricated model surfaces have been used, for example, for studying the influence of chemical composition on the adhesion and colonization of *Staph. Epidermidis* bacteria in the Ti-Al-V metal system [11]. The choice of the Ti-Al-V metal system was in this case motivated by the wide-spread use of the Ti6A14V alloy in orthopaedic implants. This alloy, which is a two-phase material form surface oxides that have a relatively heterogeneous morphology in which the alloy elements are enriched and laterally non-homogeneously distributed [2, 3]. It was therefore interesting to investigate whether there existed any preference in bacterial adhesion to the different elements present at the surface. Using substrata with different combinations of either Ti, Al, or V (10 x 10 µm squares at 10 µm separation) it could be shown that the bacteria adhered to the

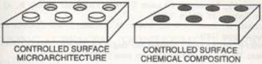

Fig. 2 - Schematic illustration of microfabricated model surfaces for studying biological responses to variations in surface structure and/or chemical composition. Feature sizes may be varied in the range from a few 10 nm up to hundreds of microns.

surfaces with a preference following the order V > Ti > Al [11]. Microfabricated model surfaces with well-defined surface structures on the 10 μm level are also presently used in studying macrophage responses in vitro.

Concluding Remarks

Biomaterials is an extremely complex field and its advancements requires interdisciplinary approaches. The area offers many challenges and opportunities for materials scientists. Modern preparative and analytical methods from surface science are particularly useful, since they open up a way to systematically investigate relationships between material surface properties and biological response.

Most biomaterials in use today give rise to non-optimal tissue responses which are difficult to predict and control. The current trend in biomaterials research is to attempt to develop more active biomaterial surfaces which have specific surface properties designed to give a desired tissue response. Such future biomaterials will most likely be sophisticated materials, produced by a combination of high-tech materials preparation techniques and methods from molecular biology.

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