Design of Blood Compatible Titanium Oxide Film for Surface Modification of Blood Contacting Biomaterials

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1. Introduction

Blood compatibility of a blood contacting biomaterial is a critical property for its applications. Coagulation of blood on material surface due to unexpected interaction of blood with the material surface frequently cause failure of artificial device and bring patients in danger. It is commonly agreed that the surface characteristics of a materials play an important role in the interaction between the material and blood. And surface modification has been considered as important means to improve anticoagulation properties of the material. However, few work has been done deal with the theoretical consideration of design of surface modification.

This paper reported the author’s consideration of an expression of the interaction of blood protein with materials in the viewpoint of charge transfer from protein to material. And analyzed the affects of material characteristics such as energy band structure, the defects state and the interface energy state to the charge transformation behavior. According to this consideration, the paper described the blood compatibility development of titanium oxide films in vitro and in vivo.

2. Theory consideration of the design of surface modification

When the blood comes in contact with an artificial surface, the first major event to occur is protein adsorption on the material. If the native configuration of the proteins is altered, it lead coagulation factors or platelet activating etc. and further cause a series of cascade reaction of blood coagulation. Finally, the thrombosis is formed.

It is commonly considered that prevent the first step of blood — material interaction, protein adsorption and denaturation is effectively to prevent blood coagulation. Some works have been done attempting to find the relations of material surface characteristics and the behavior of blood-material interaction. A regarding correlation between surface charge or its binding properties and thrombogenesity proved not to be effectively [1]. Based on thermodynamic point of view, free energy and surface energy parameters play a role for protein adsorption. And very hydrophlic or hydrophobic surface lead to adsorb less protein[2]. But it has been realized that such concepts alone is not to be enough to explain the complex processes of interaction of protein with materials, especially for inorganic surface coatings.

A promising approach to an understanding of surface-induced blood clotting is considering the charge transfer process between protein and material described by Gutmann. Bolz etc [3,4]. When fibrinogen adsorbed on material surface and transfer its electrons into material, fibrinogen will decomposed as fibrin monomer and fibrinpeptides, and fibrin monomer will be combined each other as intermediate product to further activate the clotting process. Fibrinogen has an electronic structure similar to that of a
semiconductor because of its period. The valence band and conduct band is 0.9 eV below and above the Fermi level. Transfer process is through the occupied valence band of fibrinogen into the free states of the material surface. From this viewpoint, considering to design a suitable electronic structural state of the artificial surface could be possible to prevent the charge transfer process. Fig.1 is the interaction model of fibrinogen with materials of different kinds of energy band characteristics. Is the case of metal to the energy band is overlapped, it is not possible to prevent electrons transfer from adsorbed fibrinogen to material, as shown in Fig. 1a. In the case of insulator shows as in Fig. 1b, the band gap is very wider, and no electrons exist in the conduct band. Some local state and surface state will be existed and can not be compensated, which could still serve as charge acceptor to obtain electrons from fibrinogen. Therefore it cannot effectively prevent fibrinogen from decomposition. Fig.1c shows an interaction of fibrinogen with n-type semiconductor. Electron density in conduct band is higher, which could play a role to compensate the local state and surface state of the semiconductor. As the energy level of the valence band for fibrinogen is located in the band gap of semiconductor, it is difficult for charge transfer from valence band of fibrinogen to material. On the other hand, the n-type semiconductor with a higher Fermi level can decrease the work function of the material, which make electron move out from the material easily. As a result it is possible to prohibit charge transfer from fibrinogen to material and maintain the native configuration of fibrinogen.

\[
\begin{align*}
E_{\text{vac}} & & E_{\text{vac}} \\
E_{\text{cav}} & & 1.8 \text{eV} \\
E_{\text{cav}} & & E_{\text{vac}}
\end{align*}
\]

According to semiconductor electrochemistry, the charge transfer process of fibrinogen to material could be expressed as following (5):

\[
\begin{equation}
\begin{aligned}
j_{\text{f-m}} &= \int_{E_{\text{cav}}}^{E_{\text{cav}}} AD_m(E)D_f^{-}(E) dE \\
\end{aligned}
\end{equation}
\]

where 
\(AD_m(E)\) is the current of charge transfer from fibrinogen into material 
\(D_m(E)\) is the density of charge acceptor in material 
\(D_f^{-}(E)\) is the density of electron of fibrinogen 
\(A\) is a coefficient related with possibility of electron transfer from fibrinogen into material in matter of channel effect. 
\(E\) is energy. 
\(E_{\text{cav}}\) is top energy level of valence band of fibrinogen.
Above formula provided the approaches to decrease the interaction current of electrons from fibrinogen to material:

Firstly, to achieve low density of electron acceptor $D_a(E)$, a material with a suitable band gap (such as the band gap wider than the band gap of fibrinogen) is necessary so that the energy level of valence band of fibrinogen is located in the band gap of the material. Secondly, the defect density of the material such as point defect, cavity, grain boundary should be decreased as low as possible so that less possibility could be realized for the material to accept electron. In the case of n-type semiconductor, electron acceptor in the valence band, band gap and surface state can be decreased effectively because of the compensation of electron from conduction band.

It is considered that the term of density of electron provided from fibrinogen $D_a(E)$ could be affected by the surface energy, interface energy characteristics, if the interface energy between protein and material surface is low, less protein will adsorbed on the material surface, and less electrons could be released to material.

3. Experimental

3.1 Non-stoichiometric Titanium oxide films

Titanium oxide films was developed as surface modification material for the reason that it possess suitable band gap and easily become n-type semiconductor, and its high level of biocompatibility is also another important reason.

Amorphous non-stoichiometric Ti-O films were synthesized by ion beam enhanced deposition. In vitro experiment of clotting time measurement, platelet adhesion, hemolysis analyses proved that the blood compatibility of the films was better than low temperature isotropic pyrolytic carbon (LTIC) which has been regarded as the best artificial heart valve material applied in clinic [6]. The amorphous Ti-O film was further heated in vacuum up to 750°C, and the structure became rutile. As shows in Fig.2, the behavior of platelet adhesion was further improved [7].

It is considered that the structure changing of the film is connected with the change of energy band structure. Hall effect measurement provided that the carrier density of crystal Ti-O film is $3 \times 10^{25}/cm^2$ while for amorphous is $7 \times 10^{25}/cm^2$. The vacuum annealed crystal Ti-O films possess relative lower local state in the bad gap comparing with the amorphous Ti-O film. This case supported that decrease the density of charge acceptor $D_a(E)$ is effectively improving blood compatibility.

3.2 Doping effect
Ta doped titanium oxide films were synthesized by argon ion sputtering Ti-Ta alloy targets which contain Ta from 1 to 6 w% to form Ti-Ta films, and then the deposited Ti-Ta film further thermal oxidized to form rutile structure Ti-O films. The band gap measured by optic spectroscopy using Tauc method was 3.2 eV. X-ray photoelectron spectroscopy detected that the valence state of Ta was Ta⁵⁺, which means the Ta was doped in TiO₂ matrix to form n-type semiconductive film. Blood compatibility evaluated by clotting time measurement, platelet adhesion, thrombin time and protein adhesion shown that the doped titanium oxide film was significantly superior to LTI carbon [8,9].

The doped titanium oxide films were also formed by ion implantation process. Fig. 4 shows the morphology of platelet adherent on LTI carbon a(1), a(2), TiO₂ film b(1), b(2), ion implanted Ti-O film c(1), c(2), and then vacuum annealed d(1), d(2).

After ion implantation, the morphology of platelet was not improved significantly comparing with un-implanted TiO₂ film. While further treating by vacuum annealing, the situation was modified dramatically. The number of adherent platelet decreased about one order, and the pseudopodium was depressed sufficiently. The phenomenal supported the formula (1). For ion implantation Ti-O film, accompany the n-type dopant was implanted into Ti-O film, structure defects due to ion implantation also increased. The density of charge acceptor D⁺(E) in the film was higher, which lead to promote electron transformation from protein into material. After annealing, structure defects caused by ion implantation was decreased to very lower level, in this case the film present semiconductor nature, the density of charge acceptor D⁺(E) was decreased into much lower level. The film possess excellent ability to prevent proteins on material surface from denaturation. Therefore which lead to further improve the behavior of platelet activation.

Investigation on the morphology of fibrinogen adsorbed on doped Ti-O film detected by atom force microscopy (AFM) shown the adsorption state of fibrinogen on the doped Ti-O film was mostly in separated state, and it could be believed that the adsorbed protein on doped Ti-O film can maintain their inactive single molecular state as in blood [10].
In vivo results of the doped Ti-O film samples implanted into dogs' ventral aorta for 17 days as shown in Fig. 4.

4. Discussion
The above in vitro and in vivo experiments proved that design of n-type semiconductive Ti-O film can effectively improve blood compatibility of a material. Some other researches on SiC, Ta doped TiO2 ceramic etc. also proved that the proper n-type semiconductor possess high level of blood compatibility [3,11]. The basic consideration of prohibiting charge transfer from protein into material surface provided a series of routines for designing of biomaterial surface: a, suitable band gap; b, relative higher Fermi level; c, very low level of local state and surface state. d, lower level of interface energy between material and protein. And last it should be biocompatible.

This consideration may not be very suitable for polymer because of the difficult of achieving considered semiconductive properties. and some effective approaches such as surface grafting of heparin, albumin, or binding of endothelium cell have been achieved for polymer. However, the design seems to be suitable for the modification of inorganic blood contacting materials because it is possible to achieve suitable semiconductive characteristics in material surface by means of film deposition or doping.

Formula (1) provided a series of factors for designing consideration of blood compatible material surface. However quantitative determination of the interaction currents $I_{e-w}$ and some terms as such as the density of electron...
released by fibrinogen D2(E) is still difficult. More precise measurement approaches are expected to achieve a deeper understanding of the interaction process between proteins and material.

5. Conclusion

The theoretical consideration of design of surface modification for blood compatible material is proposed. Titanium oxide films with n-type semiconductive characteristics were prepared according to this design. And advanced blood compatibility of the films was achieved.

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References


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