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SURFACE MODIFICATION OF BLOOD CONTACTING BIOMATERIALS

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Abstract

Surface modification, ie. improving or changing surface characteristics of biomaterials in a controlled way, has been attracting attention in biomaterials research because of the low cost and the versatility. Some applications of surface modifications, such as immobilization of albumin, heparin and poly(ethylene oxides) (PEO) on polymer surfaces, seeding of endothelial cells on blood vessels, forming of self-assembled monolayer model surfaces, binding of phospholipid polar group on dialysis membrane, etc., are discussed in the present paper. Some surface modification techniques and principles are also introduced. Investigations and synthesis of ceramic films, such as TiN, TaN, DLC, C-N, Ta doped TiO_2, and TiO_{2-x} films. are presented.

Keywords: Surface modification, Biomaterials, Blood compatibility, Biomoleculer binding, Chemical modification, Energy carrier media, ceramic film

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Introduction

When a artificial component is implanted into an acceptant's body and contact with blood environment, if there is a strong interaction between the implanted material and blood, blood coagulation may form, or complement system may be activated, which may lead the implant fail. All these reactions, obviously, happen on the material surface. The surface characteristics of the material, therefore, play an important roll in the interaction between the material and blood.

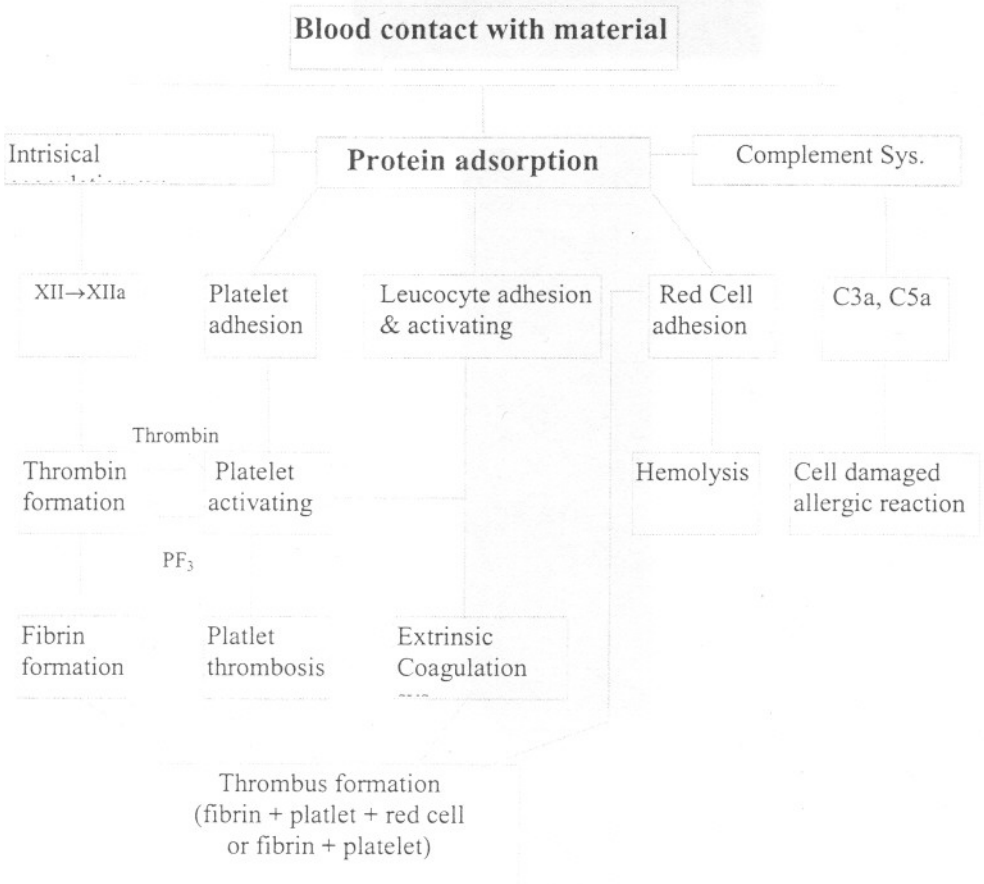

Fig. 1 Material induced blood reaction

There are two general approaches to develop biomaterials: to synthesize bulk materials which have good biofunctions as well as biocompatibilities, or, to modify the surface of certain materials so that surfaces of the materials have good biofunctions and biocompatibilities. Since it is only surface that contacts with the environment and on surface all reactions happen, the biocompatibility of the material are actually controlled by the surface characteristics. The importance of surface on biocompatibility of the materials has been proved by many investigations. In recently years, surface modification has been one of the focuses of the

biomaterial research. In the meantime, surface modification techniques have also been developed.

Fig.1 is a schematic diagram showing a material induced blood reaction process. At beginning of the interaction, the blood-material interaction is protein adsorption and denaturation . If the surface of the material absorbs very few proteins, especially fribrinogen and globulin, or if the absorbed proteins on the material surface do not change conformation, the further activating to platelets and coagulation factors will be limited, and thrombus formation will not happen. Therefore, considering its importance, the current researchs on surface modification of blood contacting biomaterials are mainly focused on the first step of the blood -material interaction. In the present paper, techniques of surface modification and examples of applications with blood contacting biomaterials are discussed according to categorization of the modifying processes.

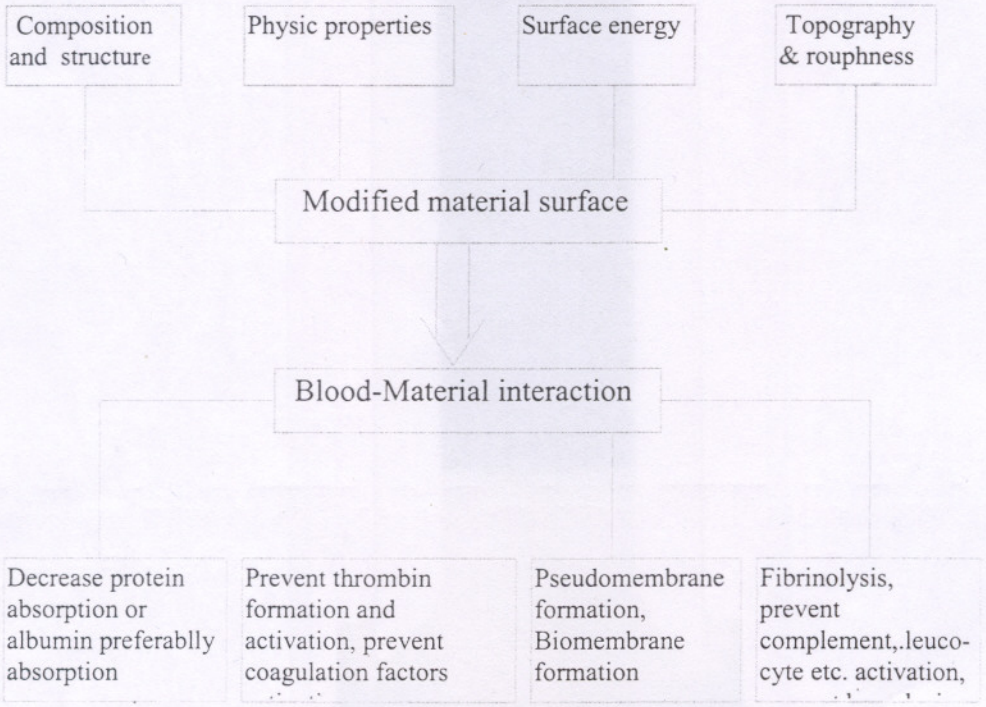

Fig. 2 Interaction of blood with modified material surface

Surface modification of blood contacting biomaterials

Fig. 2 shows the interaction between a modified material - blood system. The most important controlling factor of the material on the interaction is the surface structure and composition. However, other surface characteristics, such as surface energy, surface physical state, roughness, etc. could all affect the interaction process.

By surface modification treatment, the characteristics of the materials will be changed, the material - blood interaction will, of course, be affected or changed. According to the modification mediums, the surface modification techniques can be classified as shown in fig. 3. These techniques are discussed in the following section.

Surface modification process

Biological molecular binding and coating

Endothelial cell (EC) seeding

ECs naturally exist on the inner surface of blood contented organ of a living body. ECs have several functions: adjusting blood coagulation, anticoagulation, immunity, endocrine, transferring energy and substance, etc.[1] Since 1970's, immobilization of EC on the wall of artificial blood vessel of small diameters has been studied. In the early studies [2], vascular tubes were pre-coated with blood containing added endothelial cells. EC coated tube surface shows an excellent anticoagulation behaviour[3]. But the seeded EC can be washed away upon restoration of blood flow through the graft [4].It is found that pre-coating some kinds of proteins, such as fibronectin, collagen, vitronectin, extracelluar matrix etc. could improve theadhesion behaviour of EC. Recent study shows that with cell-adhesive oligopeptide(REDV, etc)[5,6] immobilization by covalent combination on material surface could adhere EC preferably. These cell seeding methods show some promising results of obtaining a single, all covered strong bound EC layer on the wall of polymer blood vessel. But it is still a problem for this EC layer to maintain the specific biofunction in a long term[7].

Heparinization

Heparin is a natural sulfated glycosaminoglycan consisting largely of alternating O-and N-acid (D-glucuronic o L-iduronic) and D-glycocyamine residues. Heparin takes effect in anticoagulation in several aspects. During the coagulation cascade reaction, heparin combines with antithrombin III to prohibit activation of thrombin and the decomposition of fibrinogen, and it also prevents the activating of coagulation factors XII, XI, IX, X, VIII, V etc.. The most simple method of heparinization is mixing heparin into the polymer material, such as epoxy resin, during fabricating. The disadvantage of this method is that only limited number of heparin can be used with the materials contacting blood. More attention has been paid on immobilization of heparin on materials surface by covalent bound[8]. It is a problem to maintain the activity of heparin and the integrity of substrate surface. Recent researches particularly regard the role of space type and length, such as immobilization of heparing on PEO chains shown a significantly increase the activity of heparin[9].

Phospholipid polar group

In about the beginning of 1990's, a method of making blood-compatible polymer materials utilizing natural phospholipid molecules in plasma was proposed. It was considered that if a polymer surface possesses phospholipid polar groups, the phospholipid molecules in blood could be adsorbed onto the material surface, and play a role for anticoagulation[10]. 2-methacryloyloxyethyl phosphoylcholine (MPC) is a typical material for this method. It is proved that when the MPC on the surface of compolymer MPC and BMA (n-butyl methacrylate) is over 30 mol.%, platelet adhesion and activation can be significantly suppressed. Excellent nonthrombogenic properties of MPC coated cellulose dialysis membrane, glucose sensor and on segmented polyurethane surface are reported [12,13]. The liposomal structure was observed on the coated surface after it contacted plasma[14].

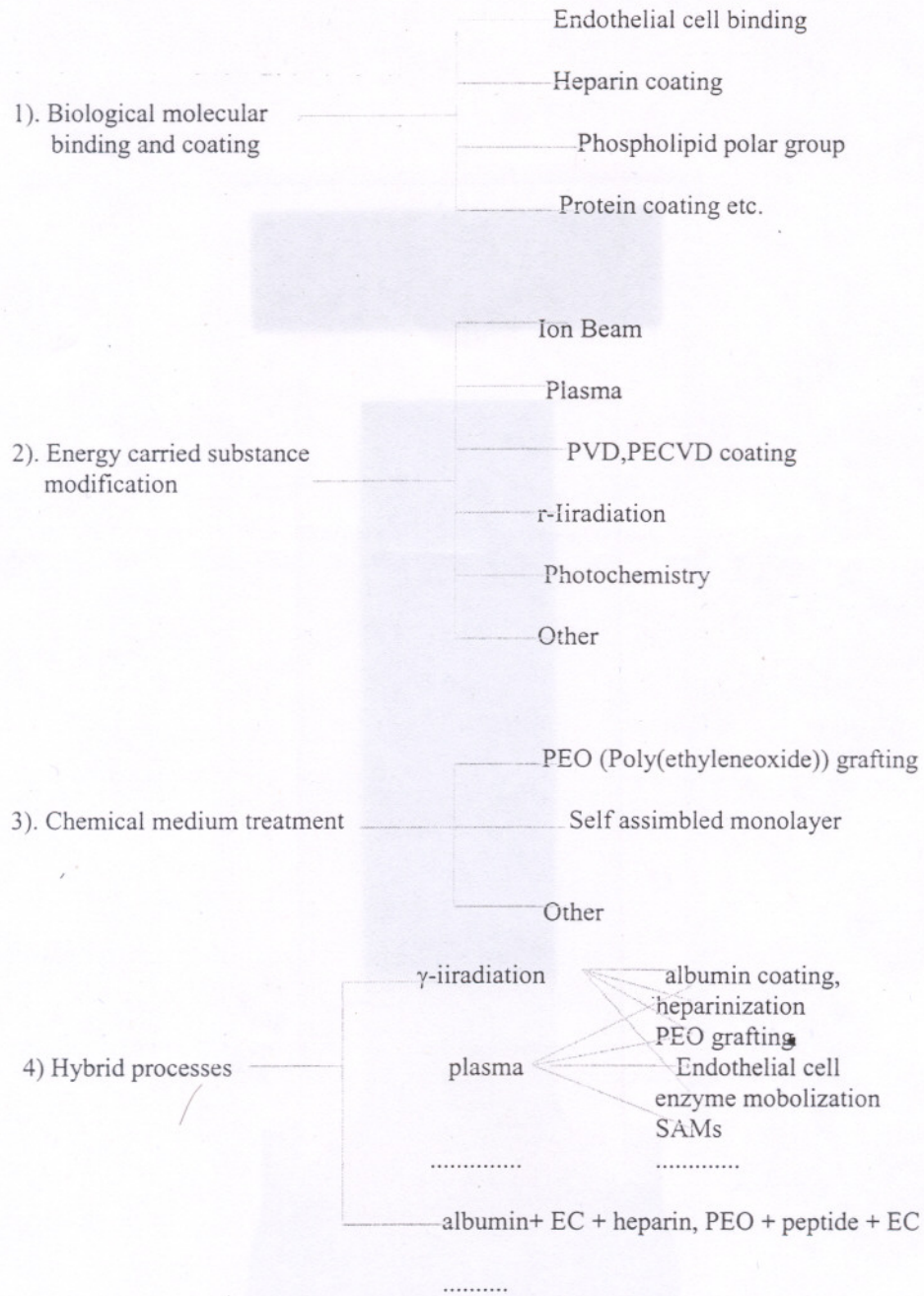

Fig.3 The Category of surface modification

Albumin grafting

Pre-absorption of albumin on material surface can effectively improve thromboresistance[15,16]. For a hydrophobic polymer surface, physically adsorption of albumin can be realized relatively easily. But the albumin layer is not stable and may be displaced by other thrombogenic proteins which then leads to platelet adhesion. Covalent attachment of albumin to surface can considerable improve the adhesion of albumin protein layer on the material surface. To produce the covalent grafting of albumin on chemically inert polymers, processes such as γ-irradiation, photo grafting, plasma treating, etc., are needed to prepare an active surface.

A recent study[17] about immobilizing albumin on polypropylene hollow fiber by functionalization of albumin by means of reaction with glycidyl acrylate and then grafted on fiber and further treated by γ-irradiation, the fibers showed high adhesion of albumin bound on material surface even after exposure to blood for prolonged time periods and a significant decrease of platelet adhesion.

Hybrid utilization of biomoleculer and modification methods are studied in the current research of biomoleculer binding, such as EC-heparin-albumin binding[18], EC-peptide-PEO grafting[19], utilization of ion beam, plasma, irradiation etc. process to enhance the adhesion of the binding are frequently adopted.

Chemical medium proces

There are many chemical methods for biomaterial surface modification. Chemical methods are to introduce new molecules onto the material surface by coupling or grafting. Two processes, polyethyleneoxide (PEO) binding and self assembled monolayer, are discussed below.

Polyethyleneoxide (PEO) chain binding

Polyetheleneoxide has a high molecular weight with a macromolecular chain structure (the repeating unit (-CH_2CH_2O-)n). The unique properties of polyetheleneoxide are that it has a very low interfacial energy against water and it is water soluble. Another feature of polyetheleneoxide is that one end of its structural chain is anchored to the substrate and the another end is flexible. It is showed by experiments that the anticoagulation properties of the PEO is related with the length the chain structure. It is found that when the repeating unit of the chain is over 100, the material has an excellent blood compatibility [20]. One of mean hypothsis of blood compatibility of PEO chain is focued on ist flexibility of the hydrated chain, regard the rapid movent of long PEO chain influence the micro-hemodynamics at blood material interface more effectively than do the short PEO chains[20,21]. Several techniques have been developed to produce PEO-coverd polymer surfaces, such as coating, blending, grafting and coupling. Recently, grafting of PEO on inorganic material surfaces, such as glass and carbon, by coated with a primer layer of trichlorovinysilane (TCVS) and γ-irradiation grafting after PEO was adsorbed on TCVS surface. Blood compatibility experiments show that fibrinogen adsorption and platelet adhesion can be significantly depressed[22].

Self-assembled monolayer (SAMs)

To understand the interaction of blood with surface characteristics of a material is the fundament for developing blood contacting materials. However, the surface structure of many commercial biomaterials is rather complicated, and may contain different kinds of function group, process aids, multiphase etc. Recently, a novel approach - self assembled monolayers

(SAMs) has been developed. This method can produce highly ordered precisely controlled surfaces in molecular level. It is based on absorption of terminally functionalized long chain alkanethiols $HS(CH_2)_nX$, trichloroalkylsilanes $SiCl_3(CH_2)_{17}X$, etc. on gold, silicon, silicone, glass metal oxide etc. matrixes. X is CH_3, CF_3, CO_2CH_3, COOH, , $(CH_2CH_2O)_3COCH_3$, $(OCH_2CH_2)_3OH$, etc. functional group at the top of SAMs. Using SAMs it is possible to investigate blood -functional group interaction, such as protein adsorption, peptide adsorption, cell attachment, platelet adhesion and aggregation, etc, separately and distinguish the specific functions of the groups[23-26]. Therefore, SAMs is also called model surface. This method is important for developing the next generation of biomaterials.

Surface modification by energy carrier substance

Different types of energy carrier modification methods have been used with biomaterials. These methods treat materials using different high energy media. During the process, the structure of surface can be changed, coatings with new composition and structure on the surface can also be synthesized.

Plasma processes

Plasma processes include three methods: plasma polymerization, plasma treating and plasma grafting. During the process of plasma polymerization, organic monomor vapor is introduced into a reactor. RF or microwave energy source is applied to produce glow discharge to form plasma. The monomer is decomposed as active energy carrying groups, and collided together or onto material surface to form a highly cross-linked thin polymer film. This method can be used on different material matrixes, including polymers, metals, ceramics and glass. Component of complicated shapes and small sizes, such as small vessel tubes, can be modified using this method. The cost of plasma processing is relatively low.

Plasma modification have been widely used to synthesize blood compatible film, directly improve blood compatibility of a material by modifing the surface structure or preparing an active surface for heparinization, PEO, Albumin, EC etc. binding[27-30].

A recently research[31] using triethylene glycol monoallyl ether as monomer for plasma polymerization, polymer films containing PEO on poly(ethylene teraphalata) (PET) were obtained under both continuous and pulsed plasma. Protein adsorption dramatically decreased to 5 present of that on the original PET surface.

During plasma treating, inorganic gas plasma is used. The ultroviolet produced by plasma and activated gas molecules interacts with the material surface, activates the surface and produces function groups such as -OH, -OOH groups. The activated surface provides a favorable condition for further grafting or biomolecular attachment.

Plasma grafting is a further treatment of the material in a liquid or gas monomer agent after plasma treating.

Segmented polyurethane (SPU) is a hopeful material as blood vessel material due to its flexibility, but it is difficult to bind endothelial cell on its surface. In a novel research [32], SPU tube of 1.5 mm diameter is treated using plasma treating using atmosphere gas. After plasma treating, EC is bound on the materials surface of both plasma treated and untreated, then using a liquid with the shearing stress of 9Pa to flow over the surface for 90 minutes. It is found then that on the plasma treated surface most of *EC* maintained tightly bound to the

matrix, while untreated SPU surface there is no EC left. It is believed the reason for this is that oxygen active groups formed during plasma treatment resulted in the strongly absorption of fibrinectin.

Because that plasma reaction is very complicated, the plasma modification process is not completely clear, and the control of the process also needs improvement. Further development of in situ gas phase and surface diagnostics as well as good knowledge of hardware and design criteria, are needed.

Vapor deposition

Vapor deposition process has been widely used in industry for about twenty years. Typical techniques are physical vapor deposition (PVD) or plasma enhanced chemical vapor deposition (PECVD), used to form hard coatings on surfaces of tools to improve their durability. In recently ten years PVD and PECVD have been used to modify blood contacting biomaterials. TiN, SiC, DLC etc.films have been considered as coating materials to modify mechanical heart valve[33-37]. Pryolytic carbon film deposited metallic heart valve scage and polymer sewing cuffs have been applied[38]. DLC has also been studied to coat left ventricular assist device[39]. To increase the adhesion between DLC film and matrix, multilayer DLC/TiC/TiN/ Ti matrix has been studied in the synthesis process[40]. The advantages of these process are that they can be used with components of complicated shapes, relatively lower cost, and higher hardness and wear resistance. So far few work on comparison of blood compatibility of PVD and PECVD synthesized films with low temperature isotropic pryolytic carbon (LTI-carbon) has been carried out. LTI-carbon material has been used as the heart valve material since the end of 1970's and is considered as the best heart valve material in blood compatibility. If synthesized films can not achieve a superior blood compatibility to that of LTI-carbon, their application to substitute LTI-carbon material would not be possible, even though the synthesized films have better durabilities.

Ion beam processes

Ion beam processes include ion implantation, ion beam assisted deposition and ion beam dynamic mixing. In these processes ions of high energy (from several tens eV to several hundred KeV) bombard and implant into the material surface (ion implantation), or combine with second source (evaporation source or sputtering source) to deposit as a film on the material surface(ion beam assisted deposition and ion beam dynamic mixing). Ion beam processes has been successful used in semiconductor industry and in new film synthesis. In the ion beam processes, the ion doses can be precisely controlled. It is possible to implant required ions with expected doses into expected position of the surface layer. The implantation and deposition processes can be performed at ambient temperature. They can be used to treat metal, ceramics and polymer materials. Therefore, more and more attentions have been paid to apply the implantation and deposition techniques to modify biomaterial surfaces. In the investigation of implantation silicone with Na^+, H^{2+}, He^+, O^+, O^{2+}, N^+, N^{2+}, Ar^+, K^+, Kr^+ and other ions, it is found that the platelet adhesion decreases significantly on the material surface implanted with O^{2+} with energy of 150KeV and dose $1 - 2 \times 10^{17}$ ions/cm^2. It is considered that the formation of >C=O groups and an amorphous carbon film on the surface is the reason of the modification [41]. Moreover, experiments show that ion implantation can effectively alter the surface polarity and wettability of polypropylene and polystyrene and improve anticoagulation and anticalcification, increase EC adhesion, etc. of the materials [42]. Ion beam techniques have also been used in endothelial cell seeding process[43]. He^+ ions of energy 150KeV and dose 1×10^{14} ions/cm^2 are implanted into collagen coated polytetrafluoroethylene (ePTFE) tubes to improve the endothelial cells binding on the surface.

In vivo test of the EC bound tubes implanted into dog artery and vein for 120 days showed no thrombogenicity, while the untreated ePTFE tubes were occluded in 3 days after implantation. The disadvantages of ion beam processes are that the process is a line-of-sight treatment and the cost is relatively high. To overcome these disadvantages, a new technique - plasma immersion ion implantation(PIII), is developed in recently years.

Great efforts have been paid by the author of the present paper to develop titanium oxide system materials by means of ion beam processes. Titanium oxide films of TiO_{2-x} with an amorphous structure is synthesized using IBAD method. Experiments showed that better blood compatibilities than LTI-carbon could be obtained [44,45]. Further improvement can be obtained by vacuum annealing of the material and changing the amorphous surface structure to rutile crystal (Fig.4). Ta doped titanium oxide films is also synthesized by sputtering deposition. Excellent anticoagulation behaviours are observed by series investigations, including in vitro and in vivo tests[46]. It is considered that one reason of the improvement in the blood compatibility of the TiO_{2-x} with oxygen vacancies and Ta doped TiO_2 materials is that the materials have the n-type semiconductor characteristics. According to electrochemical process of the material induced thrombogenicity, the n-type semiconductor characteristics of the materials could prohibit fibrinogen in the blood from denature [47]. It is also found that protein adsorption is significantly decreased on the Ti-O films than that on LTI-carbon. This may be another reason for the blood compatibility of the materials. Blood - material interaction for several popularly interested films, including TiN, C-N, DLC, and TaN, are also investigated. TiN, C-N and DLC do not show any significant improvement in blood compatibility comparing with LTI-carbon (Fig.5, Fig.6). TaN film, however, shows a tendency of decreasing platelet adhesion and aggregation. Most recently, Ti-O films have been synthesized using plasma immersion ion implantation technique (PIII) (work by the author of the present paper). Excellent blood compatibilities of the films are obtained. The PIII method does not have the line-of-sight disadvantage, and the synthesized film has a good adhesion on matrix. It shows a large potential of application of this technique with blood contacting materials.

Conclusion

Several techniques and examples of surface modification of biomaterials are described in the paper. Surface modification is a powerful method to improve the surface characteristics of blood contacting biomaterials. The aim of the modification is to obtain a more precisely controlled surface structure, more specific function, such as rejection of proteins, preferably adsorption of albumin, preferably reception of endothelial cell and maintaining the activity of EC. Development and hybrid utilization of the surface modification to obtain better blood contacting biomaterials could be expected.

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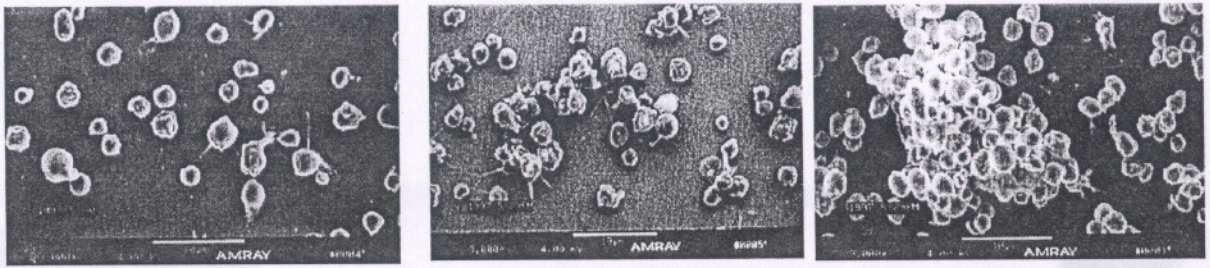
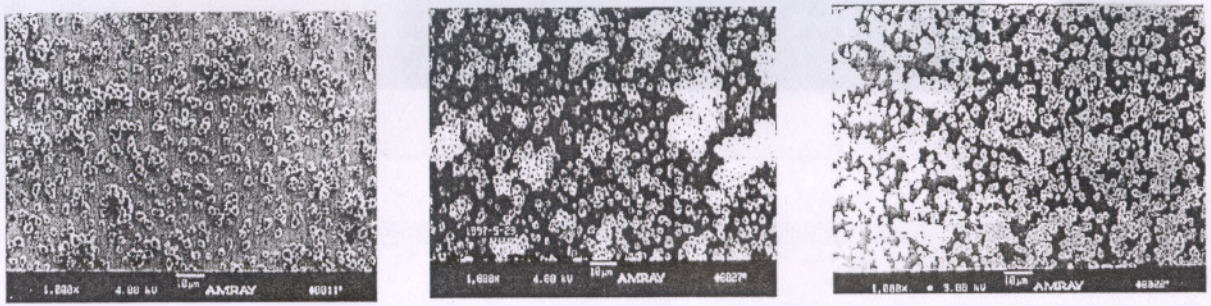


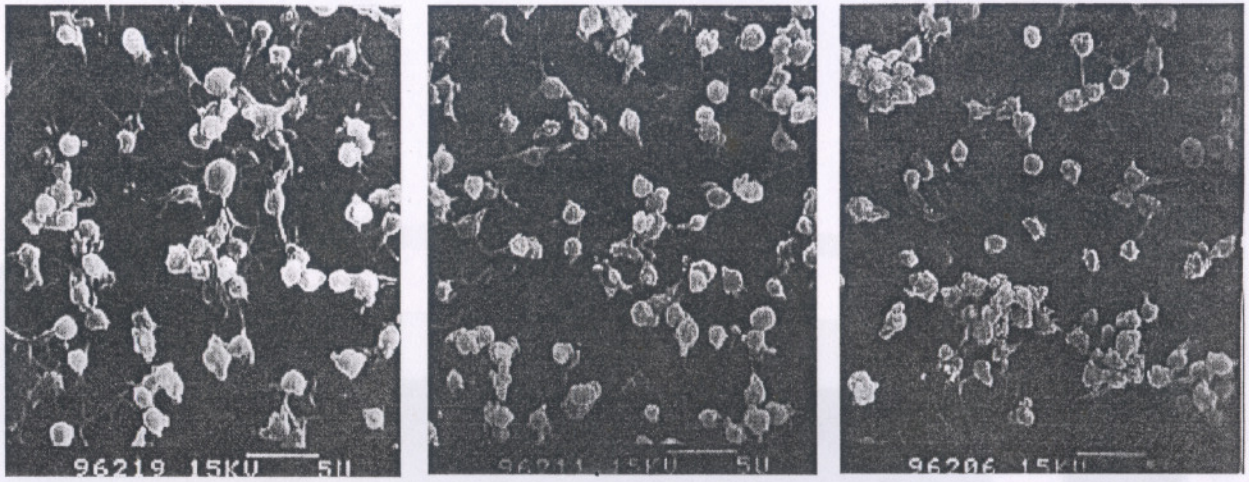
a. Rutile crystallic Ti-O film b. amorphous Ti-O film c.LTI carbon

Fig. 4 The morphology of platelet adherent on Ti-O film and on LTI carbon
Incubation in PRP plasma for 1 hour



a.TaN film b. TiN film c. LTI carbon

Fig. 5 The morphology of platelet adherent on TaN film, TiN film and on LTI carbon
Incubatuon in PRP plasma for 3 hour



a. DLC film b. C-N film c.LTI carbon

Fig. 6 The morphology of platelet adherent on DLC film, C-N film and on LTI carbon
Incubation in PRP plasma for 3 hour