Hemocompatibility of biomedical polymeric materials

Design of anticoagulant materials

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Abstract

BACKGROUND: Polymeric materials implanted into organism *in vivo* should have two basic performances: medical function and biocompatibility.

OBJECTIVE: To review design of anticoagulant materials and clotting mechanism of hemocompatible polymeric materials.

METHODS: A computer-based online search of PubMed database and Wanfang database was performed for articles published from 1953 to 2011 with English key words “biocompatibility, blood compatibility, bio-inert surface, bio-active surface” and Chinese key words “biocompatibility, anticoagulant materials, biomedical materials, medical polymeric materials”.

RESULTS AND CONCLUSION: the material surface is designed to improve surface hydrophilicity and hydrophobicity and to enhance hemocompatibility by reducing thrombosis through introduction of charged groups and bioactive substance. However, effects of surface modification to improve hemocompatibility are limited. Tissue engineering technique enables in situ culture of human endothelial cells on material surface to endothelialize the materials and improve hemocompatibility.

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INTRODUCTION

Biomaterials are used to substitute and repair natural or artificial materials of living tissues. They are products of developing multiple subjects, such as life science, material science, medicine and engineering[1]. Narrow sense biomaterials represent biomedical materials. According to properties, biomedical materials can be classified into natural biomaterials, metal materials, inorganic non-metal materials, polymeric materials and hybridized biomedical materials.

Polymeric materials that are implanted into organism *in vivo* should have two basic performances: medical function and biocompatibility. This includes requirements of physical and mechanical function, chemical stability, toxicity, and processing. Medical function represents diagnostic or treatment effects of materials binding with biological systems. Biocompatibility is degree of compatibility between materials and living organisms[2], including hemocompatibility and histocompatibility. Biocompatibility is the most important character of biomedical materials different from other materials and regarded as the basic evidence for the evaluation of biomedical application. Therefore, biocompatibility is a focus in studies of biomedical materials.

DATA AND METHODS

Data source

A computer-based online search of PubMed database and Wanfang database was performed for articles published from 1953 to 2011 with key words “biocompatibility, blood compatibility, bio-inert surface, bio-active surface”.

Inclusion and exclusion criteria

Inclusion criteria

Articles related to hemocompatibility of polymeric materials and design of anticoagulant materials and published recently or in authoritative journals were selected.

Exclusion criteria

Repetitive studies were excluded.

Data extraction

A total of 91 articles were collected, including 21 Chinese and 70 English articles. Studies not closely correlated with the inclusion criteria, or outdated and repetitive articles were excluded. Therefore, 33 articles were included.

Quality evaluation

The 33 articles were further analyzed. Articles [1-3] discussed clotting mechanism of biocompatible materials; articles [4-31] discussed design of anticoagulant materials; articles [32-33]

discussed material surface endothelialization.

RESULTS

Hemocompatibility means that materials contact with blood do not result in plasma protein degeneration or blood coagulation or thrombosis, or damage blood effective components.

Clotting mechanism of material surface

When blood flows in blood vessels with endothelial cells as inner wall, blood coagulation does not occur. After polymeric materials enter organism and contacts with blood, blood flow and blood vessel wall are changed, and the materials are recognized as foreign body by the organism, resulting in coagulation following a serial complicated interaction between them. This process can be described by Figure 1[3].

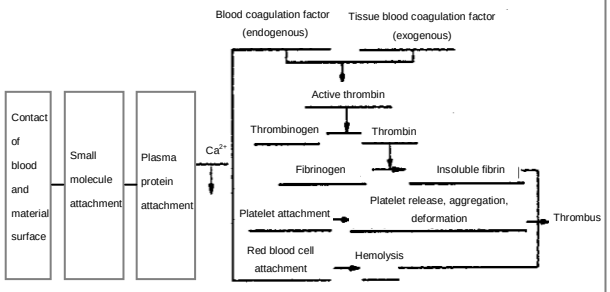

Figure 1 Clotting mechanism of material surface

First, micromolecules and plasma proteinadhere to the surface of materials, forming an adsorption layer of protein. This is a rapid process within several seconds. The surface properties of materials greatly influence amount, composition, and structure of protein adsorption layer, which is important for thrombosis. Subsequently, proteins adhered at the surface of materials degenerate and activate, and induce thrombosis by activating blood coagulation factors, platelet adherence and red blood cell adherence in the presence of Ca^{2+}. Activation of blood coagulation factors and platelet adherence play a major role in this process, and they interact with each other. In addition, biological system has anticoagulant system negative feedback, which is also influenced by surface properties of materials, and synergize with coagulation system to determine speed and degree of coagulation reaction of material surface.

Design of anticoagulant materials

Materials that do not induce irreversible thrombosis after contacting blood are regarded as anticoagulant property. According to clotting mechanism of material surface, inhibition or blocking any step of thrombosis can result in good anticoagulant effects. Currently, design of anticoagulant polymeric biomaterials includes several aspects[4-12].

Surface graft modification of materials: the surface graft modification is to reduce interaction of material and blood components, inhibit plasma protein adherence, and improve hemocompatibility by grafting hydrophilic or hydrophobic groups. Materials with high hydrophilicity exhibit excellent anticoagulation because interface free energy is significantly reduced, decreasing interaction of material surface and various components in blood. Materials with high hydrophobicity also exhibit excellent anticoagulation because the surface energy is low, resulting in minimal interaction with blood components. Therefore, surface grafting to change hydrophilicity and hydrophobicity of materials is an important approach to improve anticoagulant property of polymeric materials.

Various surface grafting methods have been used. For example, acrylamide, methacrylamide and other hydrophilic monomers have been grafted to polyurethane[13-16], polypropylene[17], polytetrafluoroethylene[17], and silicon rubber[14]. Hemocompatibility evaluation showed that the modified surface has good anticoagulant property. Interestingly, SPU grafted with perfluoroalkyl, extremely hydrophilic polyurethane, exhibited relative anticoagulant property[18].

In a serial of studies of hydrophilic surface, anticoagulant materials with long PEO grafting chain surface have aroused increasing attention. According to the hypothesis proposed by Nagaoka *et al* [19], PEO is a kind of molecule chain with high hydrophilicity and flexibility, so it can bind water to form hydrated PEO chain, which suppresses blood components adherence through steric hindrance rejection effect. In addition, rapid movement of hydrated PEO influences fluid mechanics of blood-material region and blocks protein adherence and degeneration on material surface. Further studies indicate that anticoagulant property of materials is not simply depending on hydrophilicity or hydrophobicity, but influenced by their balance[20]. This may be because materials with balanced hydrophilicity and hydrophobicity are similar to natural hydrogel in human tissue[21].

Material surface loading electric charge: many blood components, such as hemoglobin, platelet, some plasma protein, are electronegativity in blood and vessel inner wall[21-23]. Therefore, electrostatic repulsion may inhibit plasma protein and platelet adherence to benefit anticoagulation. Anion modified surface has been extensively studied to improve anticoagulant property of materials. However, in fact, due to cation in adhesion protein layer on material surface and blood[24], it has many limitations to design anticoagulant materials based on material-blood electrostatic interaction.

Biolization of material surface: coagulation and anti-coagulation in organism is a dynamic balance system. A variety of bioactive substances have high

anticoagulant activity. Therefore, loading those bioactive substances on material surface through covalent bonding, ionic bonding, crosslinking and adherence has become an effective method for improving hemocompatibility of materials. According to anticoagulant mechanism of surface loading bioactive substances, the materials can be classified into two types: one type of anticoagulant materials surface load heparin, prostaglandin, albumin and other active substances to inhibit activation of various thrombinogens and block platelet adherence. In particular, a large number of studies focus on heparinized polymeric materials. The other type of anticoagulant material is fibrinolytic material[25-27], whose surface loads urokinase, fibrinolysin, and streptokinase to dissolve thrombus on material surface. Studies regarding this type of materials are few, but they have aroused more and more attention. Anticoagulationand fibrinolysis are two important characters of materials with hemocompatibility, so recent studies have attempted to design a novel hemocompatible polymeric materials using substances with the two activities[28-29].

In addition, based on active functional groups and active fragments of natural anticoagulant and fibrinolytic substances, modifying surface of materials using sulfonic group, sulfanilamide, carboxylic acid and phospholipid polar group is also an effective method to obtain hemocompatibility.

Microphase separation of material surface: tunica intima contacting blood is composed of epithelial cells. Cell membrane is the core part of cell surface structure. According to biomembrane fluid mosaic model, the biomembrane skeleton is lipid bilayer, with protein mosaicism. The nonpolar groups of lipid bilayer are opposite and polar groups are outward, forming hydrophilic region. The hydrophilic region and protein hydrophobic region construct microcosmic non-homogeneous phase structure. Therefore, microphase separation of material surface is also effective to obtain hemocompatibility.

A large number of studies on segmented polyetherurethane demonstrated that materials with microphase separation structures, especially with balanced hydrophilic and hydrophobic components, exhibit good anticoagulant property[20, 30-32]. In regarding to the anticoagulant mechanism of this type of materials, some researchers proposed “covering control hypothesis”[33]. That is, when microphase separated materials contact blood, they absorb plasma protein. Proteins with different hydrophilicity and hydrophobicity are selectively adhered to different microregions. This kind of specific protein adherence layer cannot activate glycoprotein on platelet surface, so platelet does not recognize them as foreign substance, thereby inhibiting coagulation.

Endothelialization of material surface: surface endothelialization is a novel tendency of anticoagulant studies. Endothelialized surface represents pseudo-intima surface or hybridized surface with endothelial cells and polymer[16].

Pseudo-intima surface is a red thrombus membrane forming at interface of material and blood, comprising plasma protein, platelet, fibrin, and white blood cells. Subsequently, fibroblast and endothelial cells grow on the membrane, forming an intima with similar structures as vessel wall, *i.e.* pseudo-intima. Currently, polytetrafluoroethylene artificial blood vessels with pseudo-intima surface have been clinically applied[16]. Notably, over-thick pseudo-intima of artificial blood vessels can lead to nutrition deficiency, cell necrosis and detaching, and coagulation at naked region. To solve this problem, number of studies has focus on controlling pseudo-intima thickness. Pseudo-intima formed on artificial vessels is not real tunica intima. As the forming protein layer components and thickness cannot be well controlled, some measures should be taken. However, this pseudo-intima on artificial vessel wall is not well compatible with grafting site.

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生物医用高分子材料的血液相容性研究：抗凝血材料的设计○

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文章亮点：

从材料表面的接技改性、材料表面负载电荷、材料表面生物化、材料表面微相分离、材料表面内皮化等几个方面论述了抗凝血材料的设计及血液相容性高分子材料的凝血机制。

摘要：

背景：对于植入生物活体内的高分子材料，应具有医用功能性和生物相容性。

目的：论述抗凝血材料的设计及血液相容性高分子材料的凝血机制。

方法：由第一作者检索 1953/2011 PubMed 数据库及万方数据库文献。检索词为“生物相容性材料，抗凝血材料，生物医用材料，医用高分子材料”。

结果与结论：通常对材料进行表面分子设计，改善表面的亲硫水性、引入带电基团、负载生物活性物质等，以尽量减轻血栓形成来提高材料的血液相容性。然而，表面修饰的方法对血液相容性的改善有限。因此，应用组织工程方法在材料表面原位培养人体内皮细胞使材料内皮化，成为改善血液相容性的重要途径。

关键词：血液相容性；材料表面；抗凝血材料；生物医用高分子材料；天然生物材料；抗凝血性；生物相容性；内皮细胞

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