Physical Properties of Antithrombogenic Materials – An Electronic Model of Contact Activation

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Summary

The conversion of the protein fibrinogen to fibrin is a major irreversible process in the interaction of biomaterials with blood. For the transformation to fibrin, the fibrinogen molecule must first be activated. This activation can occur when fibrinogen comes into contact with the surface of an artificial implant. To elucidate the origin of the contact process, electrochemical studies with SnO_2 as a model surface and fibrinogen containing electrolytes were performed. Using high-performance liquid chromatography, the exchange current from the fibrinogen molecules to the SnO_2 electrodes observed and the detection of specific peptides in the electrolyte released during the conversion to fibrin strongly support the notion that the first step in the transformation from fibrinogen to fibrin is an electron transfer from the fibrinogen molecule to the solid surface. The electron transfer, and consequently the conversion to fibrin, thus depend on the electronic structures of the fibrinogen macromolecule and the implant surface. Local tunneling spectroscopy on fibrinogen molecules shows an electronic structure similar to amorphous intrinsic semiconductors with an energy gap of 1.8 eV. Based on these findings, the requirements for an antithrombogenic material are defined. It is shown that amorphous hydrogen-rich phosphorous-doped silicon carbide (a-SiC:H) fulfils all those requirements. In vitro, in vivo and clinical results of a-SiC:H-coated coronary stents, like the Tensum® and Tenax® (BIOTRONIK, Germany), show superior antithrombogenicity and hemocompatibility, confirming the developed electronic model of contact activation.

Keywords

Thrombogenicity, biocompatibility, contact activation, fibrinogen, fibrin, electron transfer

Introduction

The biocompatibility of a material is mainly determined by its surface properties. For intravascular stents, the interaction with blood and with the adjacent vessel wall determine the risks of complications such as thrombosis or restenosis. The interactions of proteins, or living cells, with an implant surface at the phase boundary are the origin of irreversible processes such as thrombosis, leukocyte activation, cell proliferation and complement activation. The activation, cleavage or deformation of biomolecules triggers further biochemical reactions that often result in a loss of the implant functionality or are even life-threatening. The development of biomaterials is thus oriented toward those physical properties that distinguish 'non-activating' from 'activating' materials.

In the present work, the guidelines for the development of intravascular stents have been defined by an analysis of the physical processes of interaction between fibrinogen and a solid surface. A model has been developed for the primary electron transfer; and the physical properties that hinder or favor this process have been derived. Based on this knowledge, amorphous hydrogen-rich phosphorous-doped silicon carbide (a-SiC:H) has been selected and optimized as an effective antithrombogenic coating for intravascular stents.

The conversion of fibrinogen into fibrin

One of the key processes of the blood-biomaterial interaction is the activation of the coagulation cascade at the phase boundary formed by the implant and

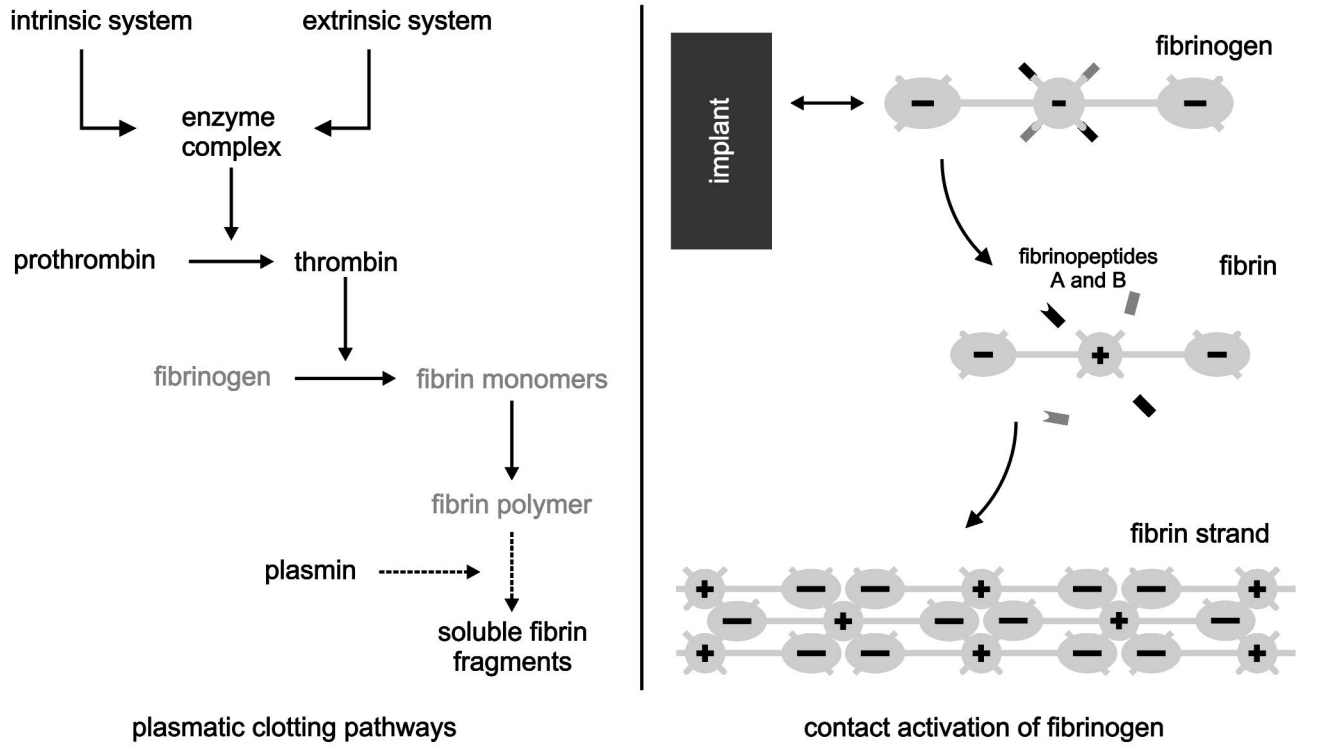

Figure 1. Schematic diagrams of the plasmatic coagulation cascade and the process of contact activation at artificial surfaces.

blood. The plasmatic coagulation cascade is a complicated and interrelated series of biochemical processes (Figure 1). Numerous enzymes catalyze various steps in the cascade, which results in the conversion of the plasma protein fibrinogen into fibrin monomers triggered by thrombin. The fibrin monomers polymerize into fibrin strands that form and stabilize the thrombus. Parallel to the process of clotting, the thrombus is disintegrated in the process of fibrinolysis by the action of the enzyme plasmin.

The structure of the fibrinogen molecule is essential to the mechanisms resulting in the conversion into fibrin. Fibrinogen consists of approximately 3000 amino acids that are arranged in two sets of three nonidentical peptide chains (α, β, γ) interconnected by disulfide bonds [1]. The hydrated molecule has a cylindrical trinodular structure of 55 nm in length. The diameter of the nodes is about 18 nm [2]. The transformation of fibrinogen into fibrin is characterized by the removal of two pairs of small polar peptides, the fibrinopeptides A and B, which are localized in the central node at the end of the α- and β-chain. Both fibrinopeptides carry negative charge resulting in a great difference in the charge distributions of fibrin and fibrinogen [1]. While fibrinogen carries negative charge on all three nodes, leading to repulsion between fibrinogen molecules, the middle node of fibrin is positively charged, resulting in the formation of strands due to electrostatic attraction (Figure 1).

The observation that the same end product — fibrin strands — are also formed during contact activation of blood at artificial materials [3] allows the processes involved in the thrombogenicity of materials to be identified: i) the conversion of fibrinogen into fibrin is the major irreversible step in the coagulation cascade; ii) the interaction between the fibrinogen molecule and the implant surface results in the release of fibrinopeptides or other small peptides, leading to a change of the charge distribution in the macromolecule; iii) the natural fibrinolysis reduces the requirement of a complete inhibition of the coagulation process at an antithrombogenic surface to the preservation of a balance between coagulation and fibrinolysis.

Taking these facts for granted, the physical processes underlying thrombogenicity can be defined. To identify the physical parameters of these processes, four

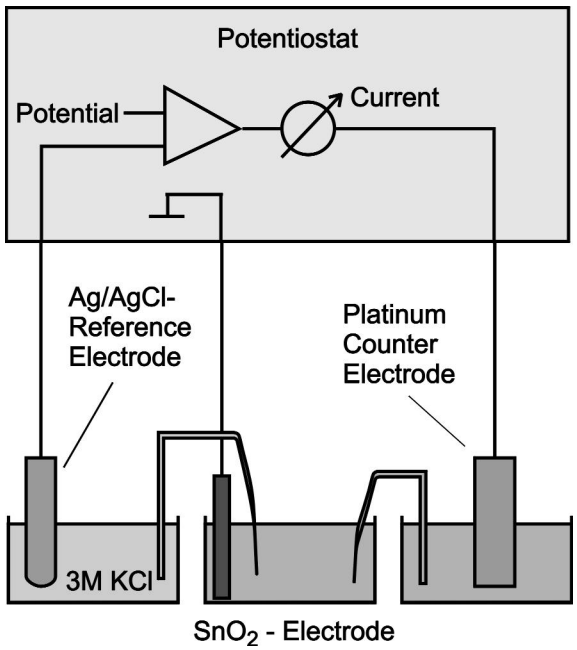

Figure 2. Electrochemical setup used for the measurement of the exchange current between the fibrinogen molecule and the electrode.

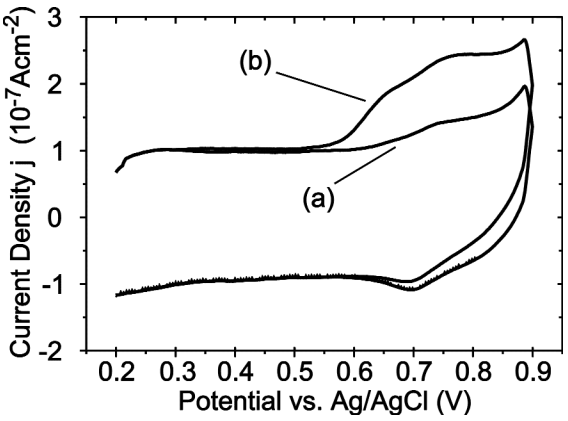

Figure 3. Cyclic voltammograms obtained before and after addition of fibrinogen to the electrolyte; potential rise 10 mV/s, TRIS-HCl-electrolyte (pH 7.4), 5 mg/ml human fibrinogen.

important hypotheses will be discussed:

a) the contact activation of fibrinogen is accomplished by an electron transfer;
b) proteins like fibrinogen have an electronic structure similar to that of amorphous semiconductors;
c) the contact activation of fibrinogen is determined by both the electronic properties of the macromolecule and the material;
d) the electron transfer entails the release of peptides from the fibrinogen molecule.

Contact activation of fibrinogen — An electron transfer

The physical nature of contact activation of blood was first studied by Sawyer, Brattain and Boddy in a classical electrochemical setup using platinum electrodes [4,5]. By electrolysis of blood, they showed that clotting only takes place at the anode, an indication for the participation of electrons at the interaction between blood and the metal electrodes. In experiments with germanium electrodes, Baurschmidt subsequently proved that an electron transfer from the fibrinogen molecule to the germanium electrode causes the irreversible formation of a fibrin layer at the electrode surface [6].

To measure and quantify this exchange current directly, thereby confirming the preceding qualitative observations, cyclic voltammetry was performed using a classical electrochemical three-electrode configuration (Figure 2). A triangular-shaped potential with a gradient of 10 mV/s was applied, and the cell current was measured with a potentiostat Model 263A (EG&G Princeton Applied Research). To exclude disturbing interactions, the electrodes were located in separate cell compartments connected by Luggin-capillaries. All potentials were measured versus an Ag/AgCl reference in contact with the main cell via a salt bridge filled with 3M KCl. As a counter electrode, a platinum wire was used. Human fibrinogen (Sigma, type IV from human plasma, 60% protein, 95% clottable) dissolved at a concentration of 5 mg/ml in TRIS-HCl-buffered saline solution (pH 7.4, 50 mM $CaCl_2$) at 37 °C was used as electrolyte. To identify the exchange current caused by the conversion of fibrinogen into fibrin, the contributions of capacitive currents to the cell current and other electrochemical processes to the cell current had to be suppressed. Therefore, the experiments were performed with semiconducting n-doped SnO_2 electrodes, showing a band gap of 3.8 eV and a conductivity of 10^4 Scm^{-1}. The electrodes were prepared by deposition of amorphous, fluorine n-doped SnO_2 on glass substrates by means of chemical vapor deposition (CVD).

In the cyclic voltammograms depicted in Figure 3, the

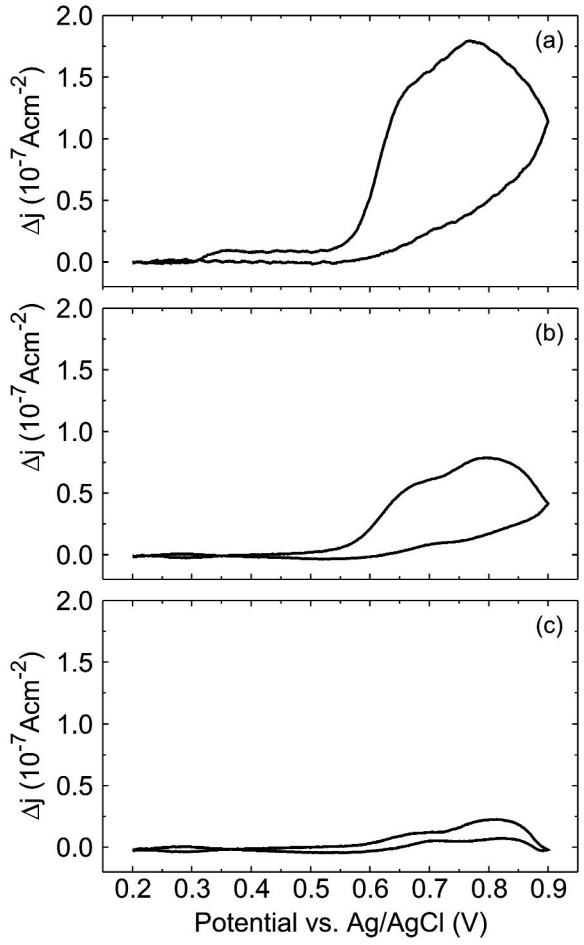

Figure 4. Time development of the current due to the presence of fibrinogen in three succeeding cycles of the potential; scan speed 10 mV/s, TRIS-HCl-electrolyte (pH 7.4), 5 mg/ml human fibrinogen.

additional exchange current caused by the presence of fibrinogen in the electrolyte is clearly recognizable. The electrochemical processes ensuing (because the SnO_2 electrode is in contact with the fibrinogen-free electrolyte) do not disturb the current due to the presence of fibrinogen. The hysteresis caused by capacitive currents that charge the phase boundary and the current above 0.8 V due to development of oxygen both show smaller currents in the potential range of interest. The increase of the current-potential curve at a potential of about 0.6 V vs. Ag/AgCl reference is significant in comparison with the fibrinogen-free electrolyte. The positive sign of this current shows that electrons are transferred from the fibrinogen to the electrode. Thus, the fibrinogen molecule is oxidized at the positively polarized SnO_2 electrode. Furthermore, the asymmetrical shape of the voltammogram is a clear indication for the correlation of the observed electronic current with an irreversible electrochemical process.

The irreversibility of the processes setting in at 0.6 V is responsible for the vanishing of the exchange current in the course of a few cycles of the potential sweep (Figure 4). Immediately after the addition of fibrinogen, the exchange current density

$$\Delta j = j_{fibrinogen} - j_{electrolyte}$$

reaches a maximum of about 1.7 10^{-7} Acm^{-2} due to the presence of fibrinogen (Figure 4a). In the following cycles, the current decreases significantly and converges to the current measured before addition of fibrinogen (Figure 4 b-c). Thus, the products formed at the electrode obstruct the electron transfer processes in following cycles. This observation is an indication for the formation of fibrin, which covers the electrode and hampers further electrochemical reactions of fibrinogen at the electrochemically controlled SnO_2 electrode. Based on these experimental results, the conclusion can be drawn that an electron transfer from the fibrinogen macromolecule to the electrode causes the contact activation of fibrinogen.

Similarities — Electronic structures of fibrinogen and amorphous semiconductors

Because an electron transfer causes the contact activation of fibrinogen at solid surfaces, the electronic structures of proteins, such as fibrinogen, are an important parameter in defining the physical properties of antithrombogenic materials. The first considerations regarding the electronic structure of proteins date back to Szent-Györgyi [7]. He formulated, for the first time, the hypothesis that under certain conditions proteins have semiconducting properties. This triggered a series of theoretical [8] and experimental studies [9,10] which showed that proteins have the electronic structure of a semiconductor. That is to say: an intermediate concentration of free charge carriers resulting in a conductivity between metals and isolators, as well as an energy interval (energy gap) where no conduction is possible. Bauerschmidt showed the size of this energy gap to be 1.8 eV for the hydrated fibrinogen molecule in solution [6].

The physical origins of the semiconductivity of pro-

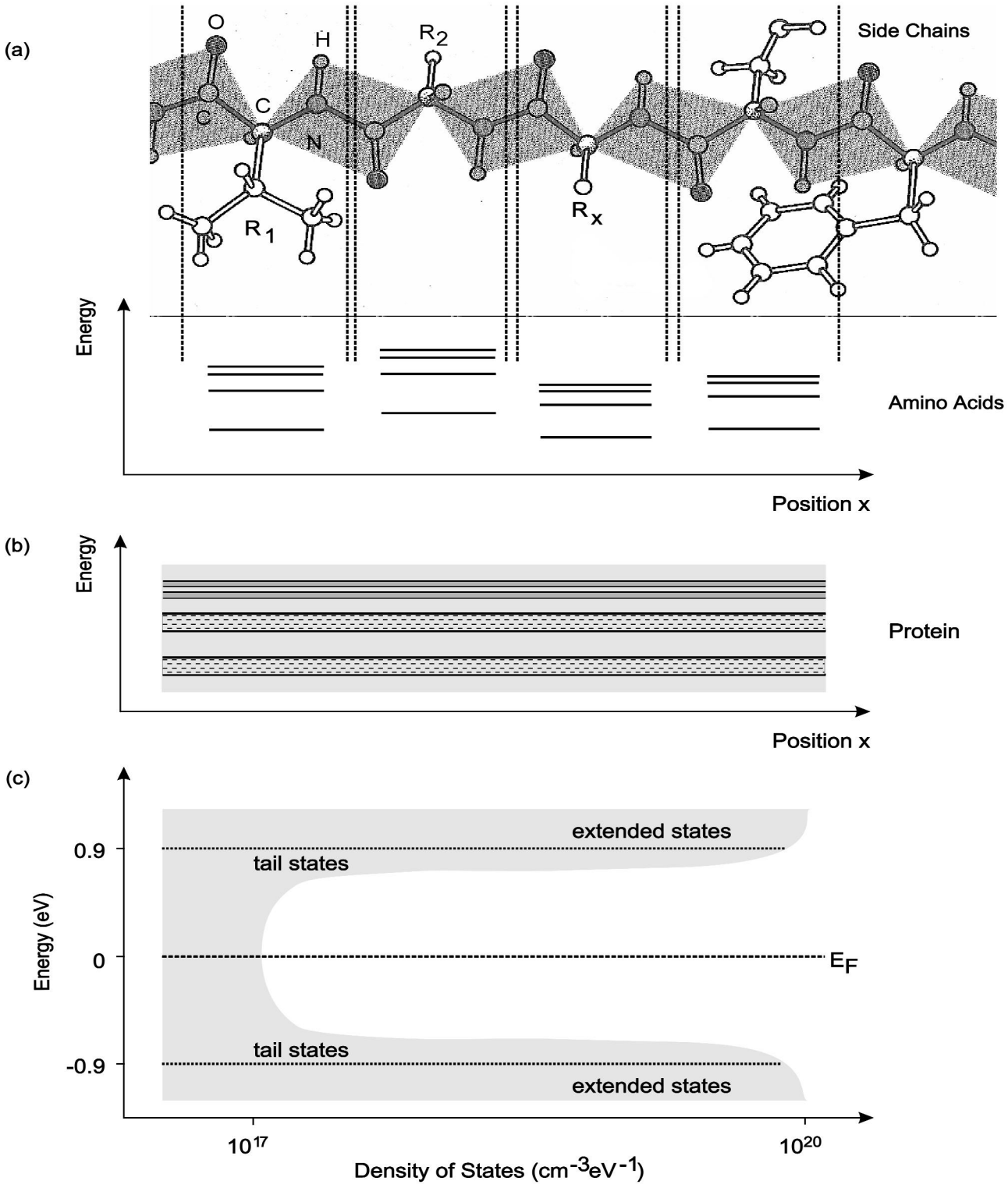

Figure 5. The physical origins of the electronic structure of proteins: (a) the amino acids in the peptide chain have an electronic structure similar to atoms; (b) the interaction between neighboring amino acids results in an electronic structure of an amorphous solid; (c) the density of electronic states is characterized by regions of high and low density / electronic states are occupied up to the Fermi level E_F / the energy gap between occupied and unoccupied states is 1.8 eV for fibrinogen.

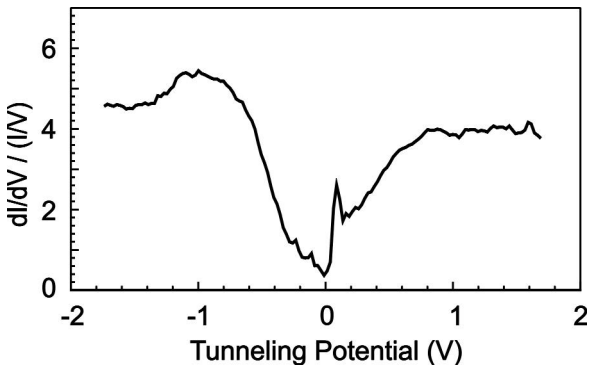

Figure 6. Density of electronic states of the fibrinogen molecule measured by local tunneling spectroscopy [13]. As in an amorphous semiconductor, the regions of high and low density are separated by an energy gap (about 1.8 eV).

teins are basically the same as those of amorphous silicon or germanium. Due to the large number of structural units in the macromolecule, the amino acids linked by peptide bonds, it is justified to apply concepts for the description of the electronic structure of proteins similar to those commonly used for solids. The fibrinogen molecule, for example, contains about 3000 amino acids. Each amino acid shows an electronic structure similar to an atom: electrons may occupy a set of electronic states — a ground state, an excited state or a continuum of free electrons [11]. The energy level of the states is determined by the type of the specific side chain of the amino acid and the ionic environment (Figure 5a). The complicated arrangement of these structural units in peptide chains and the folding of these chains in three dimensions lead to a situation that is analogous to an amorphous solid where the structural units are not molecules but atoms. Due to electronic interactions between the single amino acids, the energy levels shift and split. This results in an electronic structure of the whole macromolecule that is characterized by energy intervals with higher (10^{20} $cm^{-3}eV^{-1}$) and lower (10^{17} $cm^{-3}eV^{-1}$) densities of electronic states (Figure 5b). The electronic states are occupied up to the Fermi level E_F (electrochemical potential), which is located in a region of low density (Figure 5c). The energy gap between occupied states, the valence band of the protein, and unoccupied states, the conduction band of the protein, is about 2 eV in theoretical calculations [12] and thereby in accordance with the experimentally observed values (see above).

To verify these physical considerations by experimental data, the electronic structure of the fibrinogen molecule was analyzed by local tunneling spectroscopy. For the investigations, a Nanoscope II (Digital Instruments) scanning tunneling microscope was used. Measurements were performed in air on substrates of amorphous silicon. The substrates were moistened with fibrinogen containing twice-distilled water. The tunneling tip was placed above the center of the macromolecule; the tunneling current was measured as a function of the applied voltage. By presenting the data as plots of (dI/dV)/(I/V) vs. V, it is possible to get a

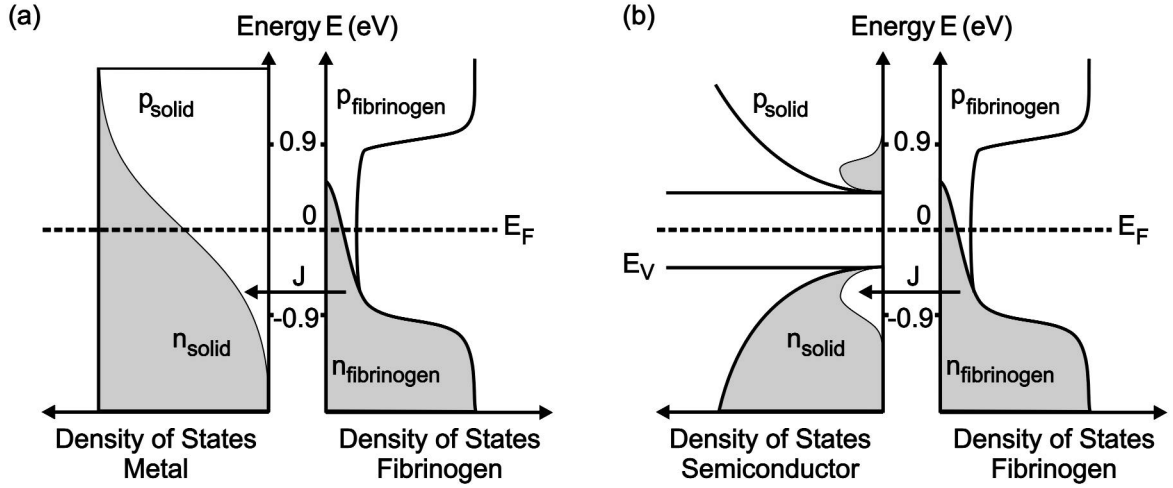

Figure 7. Density of electronic states D(E), number of occupied states n(E) and number of unoccupied states p(E) at the phase boundaries of (a) metal-fibrinogen and (b) semiconductor-fibrinogen.

qualitative image of the density of electronic states [13]. The density of electronic states of the fibrinogen macromolecule shows two regions of high density (below -0.9 V and above 0.9 V) separated by a gap of approximately 1.8 V (Figure 6). The peak in the region of low density at 0.1 V is founded in the type of the plot (division by zero) and is not an intrinsic property of fibrinogen. Thus, the density of electronic states in the fibrinogen molecule as measured by tunneling spectroscopy is similar to those of amorphous semiconductors with an energy gap of about 1.8 eV.

The electron transfer is determined by the electronic properties of macromolecule and material

Because of the electronic structure of the macromolecule and the electron transfer from fibrinogen to the solid, which provides contact activation, the irreversible oxidation process of fibrin formation can be described as an elastic electron tunneling process.

In Figure 7 two cases are depicted, the metal gold and silicon (an intrinsic semiconductor). Fibrinogen has the density of electronic states like an intrinsic amorphous semiconductor with a filled valence band, an empty conduction band, an energy gap of 1.8 eV and the Fermi level E_F in the center of the energy gap. At thermal equilibrium, the Fermi level of the solid-fibrinogen system is balanced. With the metal, the majority of electronic states is occupied up to the Fermi level. However, a certain number of electronic states $p_{solid}(E)$ is empty due to thermal excitation (Figure 7a). The same applies to the case of the semiconductor (Figure 7b) where a smaller number of electronic states is empty because of the energy gap.

An electron tunneling process from the fibrinogen molecule into the solid is only possible from occupied electronic states of the fibrinogen molecule $n_{fibrinogen}(E)$ into empty electronic states of the solid $p_{solid}(E)$ at the same energy level. The exchange current is therefore given by

$$J = C \int_{-\infty}^{-0,9eV} dE\, T(E)\, p_{solid}(E)\, n_{fibrinogen}(E)$$

where C denotes a constant factor and T(E), the tunneling factor; the Fermi level is set to 0 eV as the reference. The upper limit of the integral is fixed to -0.9 eV, because the conduction band of fibrinogen is empty.

To confirm these theoretical considerations, it is necessary to measure the exchange current J as a function of $p_{solid}(E)$. A sophisticated way to perform this measurement is to move the electronic states in the solid and fibrinogen against each other by an external potential applied to the system. The corresponding electrochemical setup was already discussed (Figure 2), and the measured exchange current is depicted in Figure 3. Obviously, the exchange current is a function of external potential and, therefore, a function of the electronic

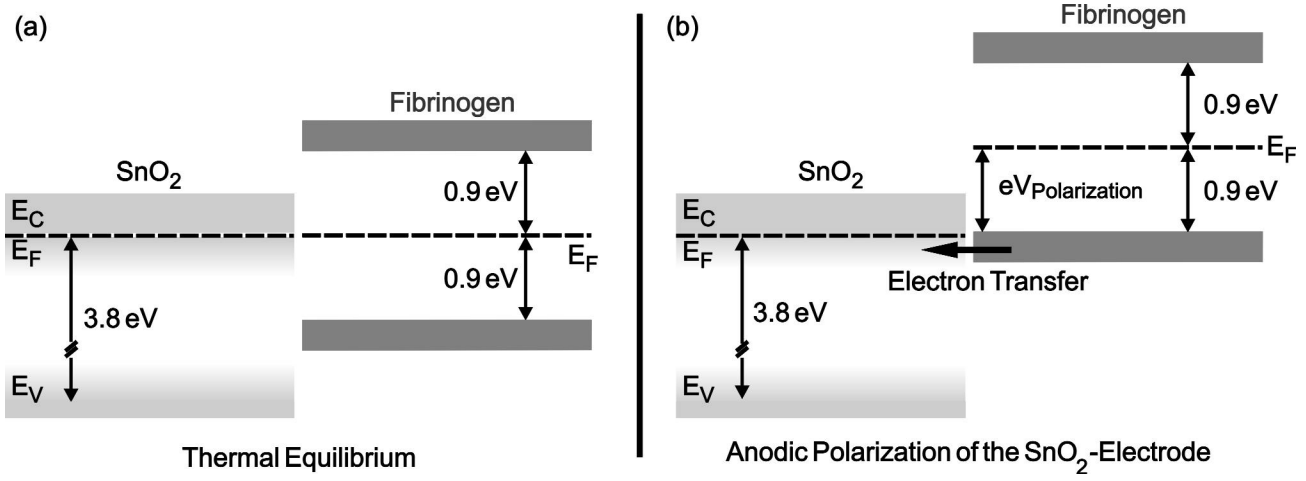

Figure 8. The distribution of the density of electronic states at the SnO_2-fibrinogen phase boundary: (a) thermal equilibrium and (b) anodic polarization of the SnO_2 electrode.

density of states $p_{solid}(E)$ of the SnO_2 electrode. The distribution of the density of electronic states at the phase boundary SnO_2-fibrinogen is depicted in Figure 8 for the cases of thermal equilibrium and anodic polarization of the SnO_2 electrode.

The Fermi level in the heavily n-doped SnO_2 electrode is near the conduction band edge. No band bending occurs at the surface because of the high conductivity (10^4 Scm^{-1}) of the SnO_2 electrode. Due to an energy gap of 3.8 eV, no electron transfer is possible at thermal equilibrium: no electronic states are opposite to the valence band of fibrinogen (Figure 8a). As observed in the cyclic voltammogram, an anodic polarization of the SnO_2 electrode is necessary to shift the electronic densities of states against each other and make the electron transfer possible. The exchange current sets in at a potential of 0.6 V vs. Ag/AgCl. Together with a 0.15 V equilibrium potential of the SnO_2 electrode and a position of the Fermi level 0.1 eV above the conduction band edge, there is an energy gap of 1.7 eV for the fibrinogen molecule. This value is in good agreement with the results of other studies [6] and the energy gap determined by tunneling spectroscopy. Thus, the electrochemical studies with SnO_2 show very good agreement with the theoretical considerations regarding the electronic exchange current J. Based on these results, the conclusion is drawn that the distribution of the density of electronic states of fibrinogen and the respective solid is crucial for the fibrin formation. Therefore, the contact activation of fibrinogen is determined by the electronic properties of both the fibrinogen macromolecule and the material.

Electron transfer — Release of peptides from the fibrinogen molecule

The results of the electrochemical investigations prove the electronic nature of the interaction between fibrinogen molecules and solids. In the following, experimental results of chromatographic analyses are presented that correlate the electron transfer with the release of peptides from the fibrinogen macromolecule. This release leads to a different charge distribution in the macromolecule and attractive forces between fibrin molecules that give rise to the development of fibrin strands and thus thrombus formation.

The transfer of an electron from the fibrinogen molecule to the solid is equivalent to an oxidation of one of the 3000 amino acids — the structural units. Quantitative numerical simulations performed for glycinamide show that the oxidation of the smallest amino acid results in the release of a relaxation energy of about 2 eV [14]. If one takes the relaxation of the whole macromolecule into consideration, even higher energies will be released. These energies are of the order of the splitting energy of peptide bonds [15]. These considerations show that an electron transfer can result in a cleavage of the peptide chain and in the release of peptides from the macromolecule.

To correlate the exchange current observed in the electrochemical studies with the SnO_2 electrodes with the release of peptides from fibrinogen, the electrolyte used in the electrochemical experiments was analyzed by means of reversed phase high-performance liquid chromatography (RP-HPLC). The examined electrolytes were pretreated by precipitation with perchloric acid, centrifugation and filtration in an RP18 column (to suppress high molecular components) before injection into the RP18 column of the HPLC unit. The composition of the mobile phase water is varied by linearly increasing the content of acetonitrile from 10% to 80% during a period of 50 minutes. A UV spectrometer working at a wavelength of 205 nm and a fluorescence detector (with fluorescamin as the marker) were used.

Figure 9a shows the unspecific HPLC spectrum of an electrolyte in contact with SnO_2 for 15 hours at thermal equilibrium. Apart from a broad background, no specific peaks are present showing the inert behavior of the SnO_2 electrode. The peaks at a retention time of about 42 minutes are present in all spectra and can be attributed to a pollution of the HPLC system. The linear increase of the signal with measuring time is caused by the gradient in acetonitrile content. The HPLC spectrum depicted in Figure 9b was taken for a fibrinogen electrolyte where the physiological clotting process was induced by addition of human thrombin. Two specific peaks are clearly resolved, indicating the presence of the fibrinopeptides A and B. This gives evidence that the human fibrinogen used in the studies is biochemically active in the electrolytes. Figure 9c shows the HPLC spectrum of an electrolyte having being in contact with an SnO_2 electrode that was under an external load of an anodic triangular-shaped potential alternating between 0.2 V and 0.9 V vs. Ag/AgCl reference (gradient 10 mV/s) for 15 hours. At retention times similar to that of the fibrinopeptides A and B (Figure 9b), several peaks appear in the HPLC spec-

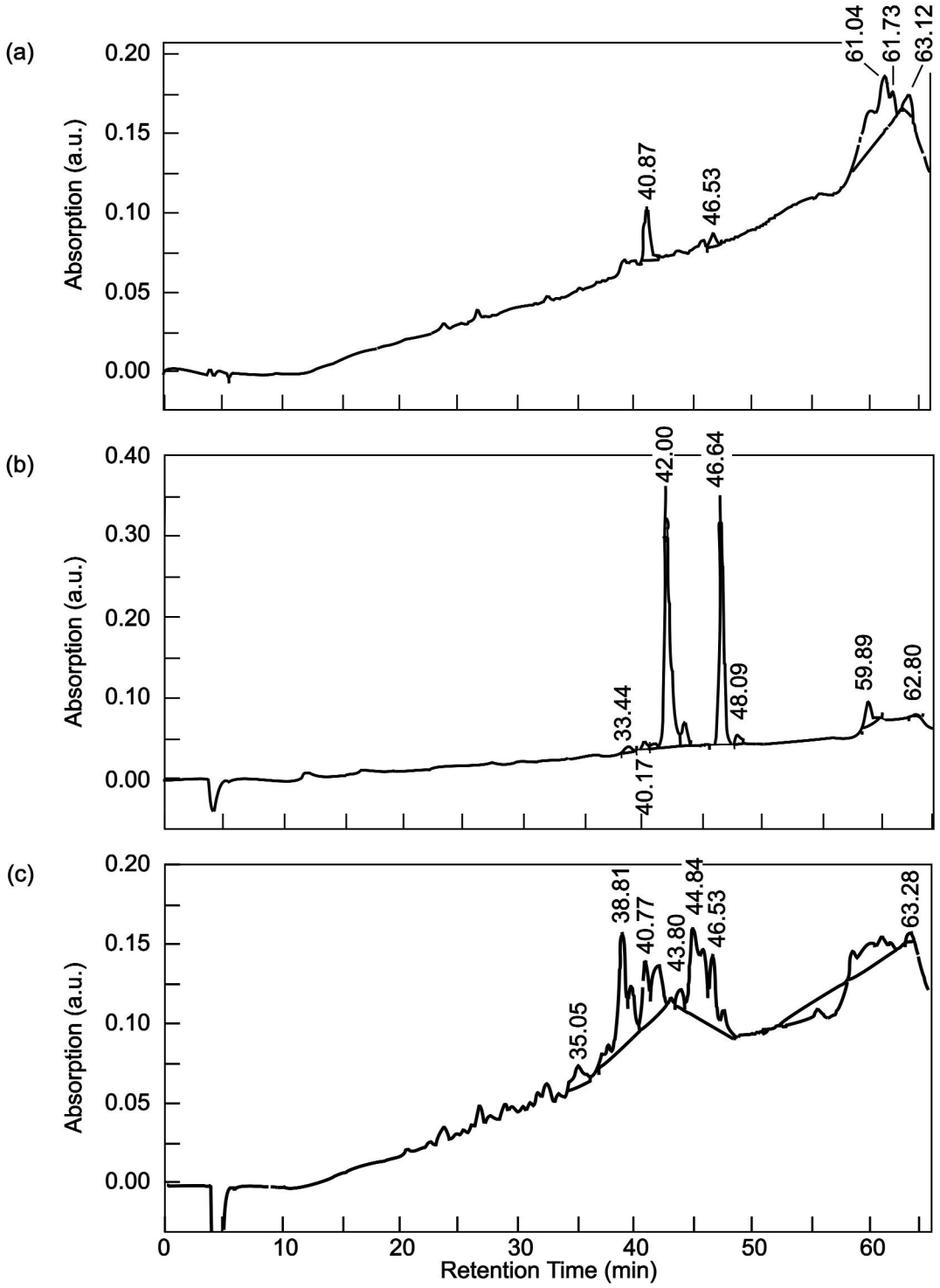

Figure 9. HPLC spectra of fibrinogen containing electrolyte (TRIS-HCl-buffer, pH 7.4, 5 mg/ml human fibrinogen): (a) SnO_2 at thermal equilibrium for 15 hours in contact with electrolyte, (b) electrolyte after addition of thrombin, (c) SnO_2 under external potential load (0.2 V - 0.9 V vs. Ag/AgCl reference, gradient 10 mV/s) for 15 hours in contact with electrolyte.

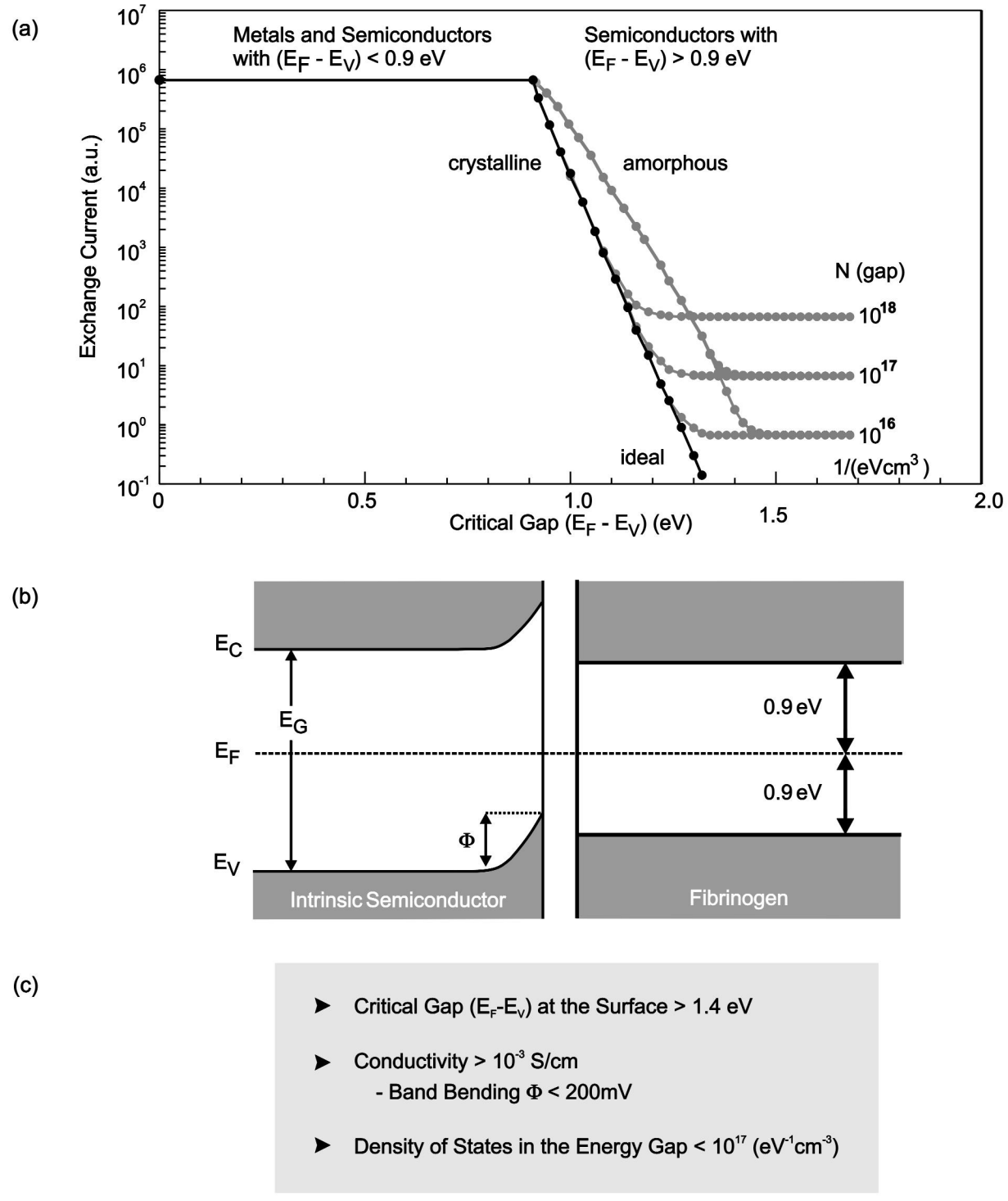

Figure 10. Physical parameters of antithrombogenic materials. (a) Theoretical exchange current between the fibrinogen molecule and solids of crystalline or amorphous structure with different critical gaps E_F-E_V. (b) Potential- and charge-distribution at the semiconductor-electrolyte phase boundary; due to a positive space charge in the surface region, the energy bands are bent upward. (c) The crucial physical parameters regarding the electronic structure of antithrombogenic materials.

trum. Thus, the electron transfer from the fibrinogen molecule to the SnO_2 electrode entails the release of peptides, i.e., the formation of fibrin. It must be noted that the separation of peptides from the fibrinogen due to electron transfer is not specific. Peptides are released at sites of the peptide chain where thrombin is not biochemically active.

The physical parameters of antithrombogenic materials

With experimental results, it has been shown that an electron transfer is the origin of contact activation of fibrinogen at solids. Because the protein fibrinogen has an electronic structure similar to amorphous intrinsic semiconductors (energy gap = 1.8 eV), the physical properties of an antithrombogenic material can be defined. The exchange current J caused by the electron tunneling processes from the fibrinogen molecule to the solid critically depends on the distribution of empty electronic states in the solid. The exchange current can only be suppressed if no empty electronic states in the solid are present at the same energy level as occupied electronic states in the valence band of fibrinogen. Thus, it has to be avoided that empty electronic states are generated by thermal excitation.

The relevant parameter for the rate of thermal excitation is the difference between the Fermi level E_F and the upper edge of the valence band E_V, designated as the critical gap in the following. For metals and semiconductors with a critical gap less than 0.9 eV, the exchange current is limited solely by the transport of fibrinogen molecules to the surface of the solid (Figure 10a) [14]. Due to the small critical gap, a large number of empty electronic states is available. For instance, a typical metal with a homogenous density of electronic states of 10^{22} $cm^{-3}eV^{-1}$ has 10^{7} $cm^{-3}eV^{-1}$ empty states at an energy 0.9 eV below the Fermi level (upper edge of the fibrinogen valence band). In semiconductors with a critical gap above 0.9 eV, the upper edge of the valence band of fibrinogen is opposite to the energy gap with no electronic states. Therefore, the number of states contributing to the exchange current is reduced, as is the exchange current. In solids with critical gaps above 1.4 eV, the exchange current (i.e., the rate of fibrin formation) becomes so small that the process of fibrinolysis is able to retain a dynamic equilibrium and avoid critical situations at the surface due to thrombosis. Thus, an antithrombogenic material must exhibit a critical gap of more than 1.4 eV.

This condition has to be fulfilled throughout the whole solid, but especially at the surface. Due to electrochemical processes at the solid-electrolyte phase boundary, the surface region of a semiconductor carries a space charge that causes a bending of the valence and conduction band. In the case of a positive charge, the bands bend upward (Figure 10b). The critical gap is reduced in the surface region of the semiconductor, resulting in an increased exchange current and thus higher thrombogenicity. To avoid this surface effect, an antithrombogenic material must have a conductivity greater than 10^{-3} Scm^{-1}, limiting the band bending to approximately 200 meV.

For an ideal crystalline solid, the theoretical exchange current decreases with an increasing critical gap, because less and less empty electronic states are available as the overlap with the valence band of fibrinogen decreases. This behavior only applies to ideal crystalline semiconductors. In real materials, defects cause a finite density of electronic states in the energy gap that depends on the number of defects (Figure 10a). Thus, the exchange current does not vanish, but it reaches a saturation value dependent of the density of states in the energy gap (N_{gap}). To keep the rate of fibrin formation sufficiently low, a density of states in the energy gap below 10^{17} $cm^{-3}eV^{-1}$ is demanded for an antithrombogenic material. The physical parameters regarding the electronic structure of antithrombogenic material are summarized in Figure 10c.

Conclusion

The conversion of fibrinogen into fibrin is the decisive and irreversible step in the coagulation cascade and the blood-biomaterial interaction. In electrochemical studies with SnO_2 electrodes and subsequent analyses of the electrolytes by HPLC, it could be shown that the contact activation of fibrinogen (i.e., the conversion into fibrin due to the release of peptides) is triggered by an electron transfer from the fibrinogen molecule to the electrode. The electron transfer (i.e., the exchange current) caused by a tunneling process from occupied states in the valence band of fibrinogen into empty states in the solid is determined by the electronic structure of the fibrinogen macromolecule. With tunneling spectroscopy, it was possible to show that the electronic structure is equivalent to that of an amorphous intrinsic semiconductor with an energy gap of 1.8 eV.

Based on these findings, the physical parameters that determine the degree of antithrombogenicity of a given material could be identified and specified (Figure 9).
A direct confirmation of the importance of these physical parameters for the antithrombogenicity of materials is the performance of coronary stents coated with amorphous hydrogen-rich phosphorous-doped silicon carbide (a-SiC:H). The a-SiC:H coating has been designed with regard to these requirements. The coating has a critical energy gap above 1.4 eV, a conductivity above 10^{-3} Scm^{-1} and a density of states in the energy gap below 10^{17} $cm^{-3}eV^{-1}$. Excellent in vitro [14], in vivo [16] and clinical [18,19] results have been shown in the Tensum® and Tenax® (BIOTRONIK, Germany) slotted tube designed coronary stents [17]. The results in this article elucidate the major aspects of the electronic processes influencing hemocompatibility in alloplastic materials with the assistance of the electronic model of contact activation.

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