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REVIEW PAPER

Plasma Surface Modification of Biomedical Polymers: Influence on Cell-Material Interaction

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Abstract Polymers are commonly used in industry because of their excellent bulk properties, such as strength and good resistance to chemicals. Their surface properties are for most application inadequate due to their low surface energy. A surface modification is often needed, and plasma surface modification is used with success the past decades. In the past few years, also plasma surface modification for biomedical polymers has been investigated. For biomedical polymers, the surface properties need to be altered to promote a good cell adhesion, growth and proliferation and to make them suitable for implants and tissue engineering scaffolds. This review gives an overview of the use of plasma surface modification of biomedical polymers and the influence on cell-material interactions. First, an introduction on cell-material interaction and on antibacterial and antifouling surfaces will be given. Also, different plasma modifying techniques used for polymer surface modification will be discussed. Then, an overview of literature on plasma surface modification of biopolymers and the resulting influence on cell-material interaction will be given. After an overview of plasma treatment for improved cell-material interaction, plasma polymerization and plasma grafting techniques will be discussed. Some more specialized applications will be also presented: the treatment of 3D scaffolds for tissue engineering and the spatial control of cell adhesion. Antibacterial and antifouling properties, obtained by plasma techniques, will be discussed. An overview of research dealing with antibacterial surfaces created by plasma techniques will be given, antifouling surfaces will be discussed, and how blood compatibility can be improved by preventing protein adhesion.

Keywords Plasma · Biomedical polymer · Surface modification · Cell-material interaction

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Introduction

In the past decades, modern medicine has been challenged with complex problems, which have led to technological advancements in the area of healthcare. However, in the domain of tissue engineering, many complex problems still remain. It is a multidisciplinary field combining principles of biology, medicine and engineering, that aims at replacing damaged, injured or missing organs and tissue with a functional artificial substitute [1, 2]. This substitute can be a combination of both a scaffold and cells, an acellular scaffold or cells only [3]. The complexity of the problems arising when replacing tissue, set very high and diverse demands on the used materials. Biocompatibility, biodegradability, providing strength and structure if needed, enabling cell attachment, proliferation and sometimes even differentiation are just some of the possible necessities. In some other cases including, catheters and stents, prevention of cell attachment and adsorption of proteins is required. Moreover, no inflammatory responses, formation of unusual tissues or other deleterious reactions should occur. Most of the demands and problems involve the reaction to and interaction with the surrounding tissue of the implanted material once it is implanted in the body. In this respect, the surface of the material plays a key role [4]. The final purpose of the implant determines the required properties and thus also the optimal surface characteristics (composition and topography).

It is very difficult to find a material that meets all the requirements. One strategy is to use composite materials that combine the properties of its components. Another way is to use a material that has the required bulk properties (biodegradability, strength, …) and to perform a surface treatment to modify the surface characteristics. Biomedical polymers (see Fig. 1), such as polylactic acid (PLA), poly-ε-caprolactone (PCL), poly(lactic acid-co-glycolic acid) (PLGA) and poly(hydroxybutyrate), are materials with good bulk properties for biomedical applications [5]. They are biocompatible, in some cases also biodegradable, and have good mechanical and structural properties. However, their surface properties are unsuitable to attract cells and a surface treatment is often required. In the past decades, surface treatment of polymers with non-thermal plasmas has been extensively studied [6], and it has become evident that also for biomedical polymers this is a promising approach [7, 8]. Plasma modification of biomedical polymers gives the opportunity to change the surface characteristics of polymeric implants to achieve a better biocompatibility without altering the bulk properties. Due to the versatility of the technology, it can be useful in many different applications [9].

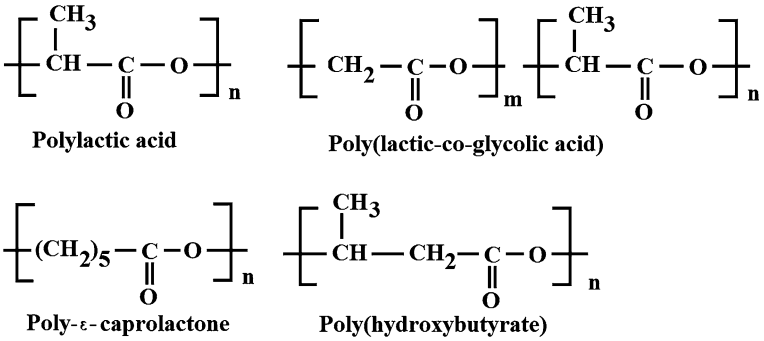

Fig. 1 Chemical structures of common biomedical polymers

In the next paragraph, the interactions between a material (implant) and cells (surrounding tissues) will be described. After that, the importance of antibacterial and antifouling properties of a surface in specific applications will be explained. Then, different plasma modifying techniques that can be used to enhance biocompatibility of biomedical polymers will be discussed. In the second section, an overview of literature on plasma surface modification of biomedical polymers and the resulting influence on cell-material interaction will be given. After an overview of plasma treatment for improved cell-material interaction, plasma polymerization and plasma grafting techniques will be discussed. Finally, some more specialized applications will be presented: the treatment of 3D scaffolds for tissue engineering and the spatial control of cell adhesion. In the third section, antibacterial and antifouling properties, obtained by plasma techniques, will be discussed. First, an overview of research dealing with antibacterial surfaces created by plasma techniques will be given. Afterwards, antifouling surfaces will be discussed, and how blood compatibility can be improved by preventing protein adhesion. At last, general conclusions and an outlook will be given.

Cell-Material Interactions

As mentioned above, the interaction of the biomedical material with the surrounding tissue is a key factor in the final success of the implant. The response of a cell in contact with the surface and the adhesion of cells to the material play an important role in the biocompatibility of the implant. It is thus important to understand how cells interact with their environment.

Cells sense their surroundings through so-called protrusions. These are micrometer sized sheet-like structures composed of an actin filament mesh. At the extremes, smaller hair-like protrusions, called 'filopodia', composed of long, thin actin filament bundles, 'sense' the extracellular matrix (ECM), and the materials surface [10]. For example, when the filopodia find a suitable binding site for adherence, a feedback signal within the cell allows for so-called integrin receptors to bind to that specific binding site.

Receptors are located on the outer wall of the cells and are responsible for the intracellular interaction and communication. When these receptors bind specifically with a ligand, a receptor response occurs, starting a cascade of events within the cell, leading to an appropriate trigger response.

One very important class of cell receptors called 'integrins' bind selectively to binding sites such as arginine-glycine-aspartic acid (RGD) tripeptide found in cell adhesive proteins such as laminin, fibronictin and vitronectin [11, 12]. When the filopodia find such a binding site, a feedback signal allows for the intergrin receptor to bind to that site and allows more integrin receptors to be localized in that region of the cell. This leads to the adhesion of the cell to that region.

Integrins also function as signal transducers, activating various intracellular signaling pathways when activated upon ECM binding. The signals the cell receives through the integrin can be related to cell growth, proliferation (division) and differentiation.

When a material is placed inside a biological environment, a water shell is created around the material within nanoseconds. In the next seconds to hours, the surface becomes covered with a layer of adsorbed proteins, such as fibronectin and vitronectin, initially present in the ECM. In the third stage, the cells of the surrounding tissue reach the material, interacting through the adsorbed protein covering. This stage occurs from as fast as minutes to days after the implantation, and adhesion, migration and differentiation of cells takes place. It is influenced by biological molecules, the biophysical environment and

surface properties. The fourth stage, the useful life of the implant, is the continuing development of the early implant stages [3, 10]. The duration of this stage can vary from days to several decades.

Antibacterial and Antifouling Properties

Besides the cell-material interaction, also the antibacterial properties play an important role in medical implants. When an acellular scaffold is implanted, both cells and bacteria compete to adhere and grow onto the surface. When the situation is in favor of the bacteria, the attached and growing bacterial colonies soon produce an extracellular polysaccharide matrix [13]. This protects the bacteria against antibiotics and the body's defense system and allows the bacteria to form a biofilm. Studies of biofilms have shown differentiated and structured groups of cells with community properties [14]. Antibiotics are thus much less efficient in destroying the bacterial biofilms than circulating bacteria. This biofilm leads in most cases to further infections and inflammations, which can result in the (partial) removal of the infected implant.

For the correct functioning of an implant, it is thus critical that the attachment of bacteria is prevented. This can be achieved by making the surface of the implant antibacterial. One way is to deposit a coating on the implant surface that offers resistance to bacterial colonization. There exist some antibacterial polymers, that kill bacteria or prevent them from attaching, which can be used for such a coating [15]. Antibacterial properties can also be achieved by the release of low molecular weight antibiotics from the biomedical device, by loading these antibiotics into polymers or polymer composite films [16]. Another possible approach is grafting a layer of antibiotic molecules that prohibits the adhesion of bacteria to the surface. However, it should be kept in mind that the antibacterial properties of the surface should not compromise the attachment of cells of the surrounding tissue.

Besides antibacterial properties, sometimes antifouling properties are needed, where the adhesion of certain cells, proteins, platelets, or any other biological entities are prevented. For example for blood contacting materials, the prevention of thromboembolism formation is a key requirement. For contact lenses, wound healing materials, catheters and biosensors, it is important to avoid unspecific protein adsorption. Moreover, the formation of an adsorbed protein layer can provide a conditioning layer for microbial colonization and biofilm formation [17]. Further application can be found in marine equipments, like ship hulls, were antifouling surfaces can be used to prevent biofouling by sea microorganisms, diatoms and algae [18]. Antifouling surfaces can be obtained by coating the surface with heparin, which is often used for blood contacting materials to prevent the adhesion of blood proteins [19]. The grafting of polyethylene glycol (PEG) or polyethylene oxide (PEO) (possessing the same chemical structure but only differing in molecular weight) onto surfaces has shown to have excellent protein resistance properties. Coatings containing polysaccharides, fluorinated coatings, polydimethyl-siloxane (PDMS) elastomers, zwitterionic polymers, are some of the other possibilities [20].

Different Plasma Modifying Strategies

Given the many different biomedical devices and implants, as well as the different cells, tissues, bacteria, and proteins that are involved, there is no universal solution to all problems, and the cell adhesion, antibacterial and antifouling properties have to be tailored to each specific need. As stated above, a common strategy is to use a material with the

suitable bulk characteristics and to modify the surface properties to meet the requirements. Biomedical polymers are excellent candidates for such an approach [5]. This has lead to a variety of polymer surface modification strategies, of which plasma surface modification will be the focus of this review paper. Plasma surface modification is a very suitable and versatile technique that does not change the bulk properties, it can be used to uniformly treat complex shaped surfaces and it is a solvent-free technology [8, 21, 22].

Plasma is often referred to as the fourth state of matter. It is a mixture of charged and neutral particles, such as atoms, molecules, ions, electrons, radicals, photons, etc. There are two main categories, thermal and non-thermal plasmas [23]. Thermal plasmas cannot be used for the surface treatment of polymers because of their high gas temperature. Non-thermal plasmas however, have a much lower gas temperature but relatively high electron temperature. They do not cause any thermal damage to the surface of heat sensitive materials, although the reactive species in a non-thermal plasma can cause chemical and physical modifications to the surface [24].

Since a plasma contains diverse active species, different interactions of the plasma with the surface can occur. As a result, different plasma modifying techniques can be distinguished, which will be discussed below. In Fig. 2, an schematic representation is shown of

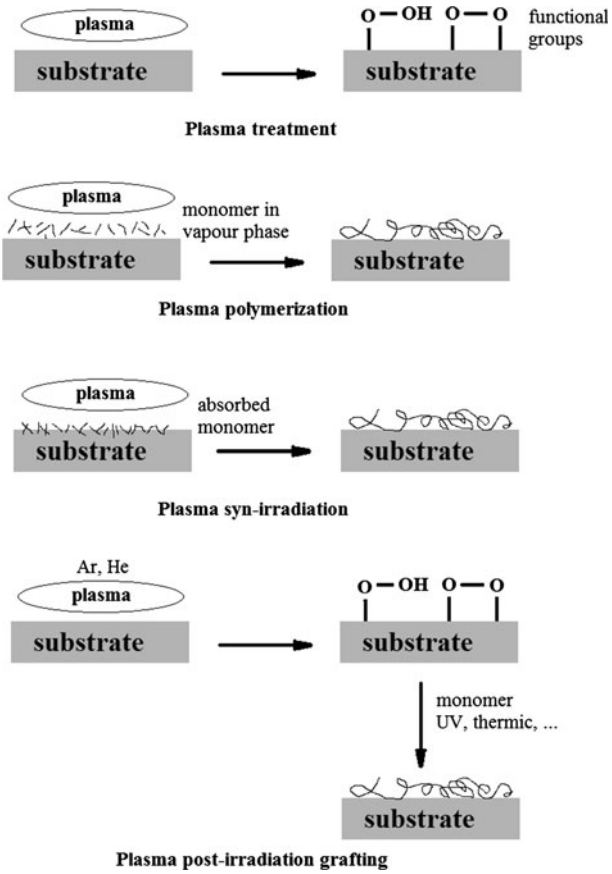

Fig. 2 Schematic representation of the different plasma modifying strategies

the different technologies. In the next section, it will be shown how each of these techniques can be used to influence the cell-material interaction.

During exposure, different chemical functional groups can be implanted at the surface [25]. This is often referred to as plasma treatment. In this case, the plasma is generated in oxygen or nitrogen containing gases or inert gases. The incorporated groups change the surface properties, mainly the surface wettability and thus the surface energy, but also the surface roughness [26]. The plasma-treated surfaces can be used to immobilize biologically active ligands. One major and important drawback of plasma treatment is the durability of the treatment effect. The surface undergoes a hydrophobic recovery after treatment and part of the generated effect is lost [27, 28].

Plasma polymerization is a deposition technique where a gaseous or liquid monomer is introduced in the plasma discharge and converted into reactive fragments [29–32]. These can react with the surface to form a so-called plasma polymer coating, that has unique physical and chemical properties. These coatings are pinhole-free, highly cross-linked and are therefore insoluble, thermally stable, chemically inert and mechanically though. Often these films are highly coherent and adherent to a variety of substrates including conventional polymer, glass and metal surfaces [33].

Rather than introducing a monomer in the plasma itself, the monomer can also be first adsorbed to the substrate, which is then subjected to a plasma. The plasma will create surface radicals in the monomer layer and the substrate surface, resulting in a cross-linked polymer top-layer. This process is called plasma syn-irradiation [8].

When depositing a plasma polymer in a plasma polymerization or plasma syn-irratiation process, the monomer is directly exposed to the plasma. However, it is also possible to firstly activate and functionalize the surface with a plasma treatment. The induced functionalities can subsequently be employed for the initiation of a polymerization reaction, by bringing the surface in contact with monomers in the gas or liquid phase [34]. Since the monomer is not subjected to the plasma, the grafted polymer will have the same composition as polymers obtained by conventional polymerization processes. This two step technique is called plasma post-irradiation grafting.

For the different plasma surface modification techniques discussed above, a wide variety of plasma sources is available. Radio frequency (RF) discharges, glow discharge plasmas, dielectric barrier discharges (DBDs), microwave plasmas, etc. are some of the possibilities. Reviews on these different discharges are available elsewhere [35, 36] and will therefore not be discussed here.

Besides the various plasma modifying strategies, also non-plasma based approaches are available to introduce chemical functional groups or to immobilize proteins and other bioactive molecules at a biomaterial's surface. Several of these strategies will be briefly discussed here, with special attention to the advantages and disadvantages compared to plasma modification. Wet-chemical methods, such as aminolysis and hydrolysis, involves the reaction between a surface and a chemical compound in a solution [37, 38]. In this way, hydroxyl, carboxyl an amino groups are created at the surface. These methods have shown to increase hydrophilicity and improve cell attachment [39, 40]. However, they are non-specific and not reproducible, cause degradation and irregular etching and produce chemical waste.

Ozone treatment, in combination with UV irradiation, UV treatment, photografting and gamma radiation are also used to introduce chemical groups [41–48]. These have all been used for the grafting of monomers and graft polymerization [49–52]. Also ozone treatment, UV-treatment and gamma radiation are techniques that cause degradation and are often non permanent and nonspecific.

Although the aforementioned techniques have proven to be valuable, plasma surface modification has several advantages that make this technology an excellent candidate for polymeric materials treatment. Firstly, it does not require hazardous solvents. It does not affect bulk properties or cause degradation. Moreover, it can be utilized to uniformly treat complex shaped structures. The deposition of coatings and the immobilization of bioactive molecules is also possible with plasma based techniques. It is thus clear that plasma modification of biomedical polymers has great potential, and will therefore be the focus of this review paper.

Improved Cell Adhesion and Proliferation by Plasma Surface Modification

In this section, an overview of literature on plasma surface modification of biomedical polymers and the resulting influence on cell-material interactions will be given. It is important to note that although cell attachment in many cases is a advantage and even a requirement, many applications require prevention of adhesion of any kind. These anti-bacterial and anti-fouling surfaces will be discussed in section "Antibacterial and Anti-fouling Surfaces by Plasma Surface Treatment".

First, an overview of literature on plasma treatment of biomedical polymers for improved cell-material interaction will be given. Subsequently, plasma polymerization and plasma grafting techniques will be discussed. Finally, some more specialized applications will be presented including the treatment of 3D scaffolds for tissue engineering and the spatial control of cell adhesion. In Tables 1, 2 and 3 a schematic overview of the various cited works can be found.

Plasma Surface Treatment

As already mentioned, plasma treatment of a polymer surface results in the introduction of different chemical groups onto the surface [53–55], thereby changing the surface properties. In this part, the focus will be on how these functional groups are able to change and improve the cell-material interactions. There is a lot of literature available on plasma surface treatment of a wide variety of biomedical polymers. However only studies which deal with cell-surface interaction will be discussed here.

Cell adhesion on plasma-treated PLA surfaces has been widely investigated [56–63]. Different plasma gases have been used, and different cells have been cultivated on the modified surfaces, mostly with satisfying results. Khorasani et al. [56] modified PLLA films with an RF plasma in oxygen at low pressure. After plasma treatment, the hydrophilicity was greatly increased. The contact angle dropped from about 85° for untreated PLLA films, to approximately 10° after oxygen plasma treatment. Attenuated total reflectance Fourier transform infrared spectroscopy (ATR-FTIR) studies confirmed the presence of oxygen containing functional groups (acidic, carboxylic, hydroxyl and carbonyl groups) at the surface of the treated films. Cell culture tests using nerve tissue B65 cells revealed a better cell attachment and growth on the treated PLLA samples. The cells were observed to be in a webbing and flattening state (active adhesion or activation state). The authors attributed this behavior to a combined effect of the surface chemistry and—wettability. In another study [57], researchers used a CO_2 plasma to modify PLA samples. The contact angle was decreased to 45°, and more oxygen containing functional groups were found on the surface of treated samples. Using atomic force microscopy (AFM), it was shown that after treatment, the surface is rougher and micro-spherulites appear. For

Table 1 Representative overview of plasma treatment of polymers and influence on cell-material interactions

Substrate	Plasma	Cell type	Observations	References
PLA	O_2	Nerve tissue B65	Flattened cells	[40]
PLA	CO_2	Glial B65	Flattened cells	[41]
PLA	CO_2	L929 fibroblasts	No difference	[41]
PLA	Air	Osteoblast MC3T3-E1	Improved proliferation and adhesion	[42, 43]
PLA	Ammonia	HUVEC	Increased cell density	[44]
PLA	Ammonia	3T3 fibroblasts	Spindle shaped cells	[45]
PLA	Ammonia	3T3 fibroblasts	Better adhesion under sheer stress	[47]
PLA	Sulphur dioxide	Rat osteoblasts	Decreased cell adhesion	[46]
PCL	O_2	7F2 osteoblasts	Increased proliferation, confluent cell layer	[48]
PCL	Air	HPEC	Improved proliferation and adhesion	[49]
PCL	Ar and mixtures	HPEC	Increased cell attachment	[50]
PLGA	O_2	Nerve tissue B65	Flattened cells	[40]
PLGA	O_2	3T3 fibroblasts	Improved attachment	[51]
PLGA	O_2	3T3 fibroblasts	Improved adhesion under sheer stress	[52]
PLGA	Air	Hepatoma HEP G2, osteoblast MG 63, CPAE, 3T3 fibroblasts	Spreaded and flattened cells	[53]
PLGA	Ammonia	3T3 fibroblasts	Improved attachment and more spreading of cells	[54]
PHBV	O_2	Dog bone marrow stromal cells	Improved attachment and proliferation	[55]
PHBV	O_2	Human retinal pigment epithelium	Improved attachment and proliferation	[56]
PHBV	O_2, Ar, N_2	HaCaT	Better attachment, flattened cells	[57]
PHB	Ammonia/ water vapour	HUVEC	Flat confluent monolayer/formation of capillary-like networks	[58]
PHBHHx	Ammonia	HUVEC, SMC	Evenly distributed and spread (HUVEC), no difference (SMC)	[59]
PEGT/ PBT	Ar	Chondrocytes	Increased cell number and pseudopodia formation, reduced re-differentiation capacity	[60]

The table presents a comprehensive overview of the substrates, the plasma type, cell type, results on modified cell-material interactions

cell culture tests, two cell types were used: glial B65 cells and L929 fibroblasts. The results for the B65 cells were comparable to the study of Khorasani et al. [56]. For the L929 cells however, no significant difference in cell adhesion and growth was observed. The authors reaffirmed conclusions by other groups in the field using other materials that cell-polymer interactions depend on both surface wettability, and—morphology.

Table 2 Representative overview of plasma polymerization and grafting of polymers and influence on cell-material interactions

Substrate	Grafted monomer/ molecule	Cell type	Observations	References
PCL	Collagen	SMC	Increased cell number, spindle-like morphology	[61]
PCL	Collagen	HDF, human myoblasts	Flattened cells with spindle morphology	[62]
PCL	Collagen	HUVEC	Higher proliferation rate, elongated and flattened cells	[63]
PHB/PHV	Insulin	Fibroblast	Improved proliferation, fully spread cells	[64]
PTFE	RGDC peptide	HUVEC	Improved attachment level	[65]
Acrylic acid thin film on Ti surface	RGD peptide	MC3T3-E1	Improved differentiation	[66]
PLLA	Gelatin	HUVEC	Enhanced cell adhesion, spreading and proliferation	[67]
PCL fibres	Collagen	HDF	Confluent layer of long spindle chaped cells, protrusions between cell and collagen-coated fibres	[68]
PLGA	Collagen	3T3 fibroblasts	Improved attachment, spreading and viability	[69]
PLA	Collagen	3T3 fibroblasts	Increased cell number and improved attachment	[70]
PLA-co-PCL fibres	Collagen	Endothelial cells	Improved attachment, spreading and viability	[71]
PLA	Chitosan	L929 fibroblast and L02 hepotocyte	Poor adhesion and spreading, proliferation rate comparable to cells cultured on glass plate	[73]

Substrate	Polymerized monomer	Cell type	Observations	Reference
PLA	Allylamine	Euglypha, vorticella	Dence adhered biofilm	[74]
PLLA, PCL	Allylamine with PEG	Hepatocyte	Improved attachment	[75]
Silicone	Allylamine	Fibroblasts	Improved adhesion and proliferation, elongated triangular cell morphology	[76]
PGA, PLA, PLGA	Acrylic acid	Fibroblasts	Improved adhesion and spreading, increased cell number	[77]
PS	Isopropyl alcohol	Fibroblasts	Improved adherance, flatter cell morphology and increased cell density	[78]

The table present a comprehensive overview of the substrates, the modification type, results on modified cell-material interactions

Table 3 Representative overview of plasma modification of 3D scaffolds and spatial control of cell attachment, together with the influence on cell-material interactions

Scaffold	Modification	Cell type	Observations	References
3D scaffolds				
PLA	Ammonia plasma	3T3 fibroblasts	Improved cell attachment	[81]
PLA	Deposition of allylamine	3T3 fibroblasts	Cell grow and attach inside the scaffold	[82]
PLA	Polymerized aclylic acid	Chondrocytes	Improved attachment and proliferation	[83]
PLA	O_2 plasma	Embryonic palatal mesenchyme	Better adherance, spindle-shaped cells with filopodia, cells inside the scaffold	[84]
PLA	O_2 plasma	CHO	Increased attachment, no improved proliferation	[85]
PLA	RGDS immobilization	Osteoblast-like cells	Higher cell censities, bone-like tissues	[86]
PLLA	Gelatin anchoring	Chondrocytes	Better proliferation and ECM production, tissue-like cell contstructs	[87]
PCL	Air plasma	Schwann cells	Improved proliferation	[88]
PCL	O_2 plasma + fibronectin adsorption	7F2 osteoblasts	Increased attachment and proliferation	[89]
PHBV	O_2 plasma	Osteoblast	Adhesion and spreading inside scaffold	[90, 91]

Substrate	Modification	Cell type	Observations	References
Spatial control				
PE	Air plasma	Pheochromocytoma PC-12	Maximum adhesion at WCA 55°, typical neuronal morphology	[95]
PE	Air plasma	3T3 fibroblasts	Maximum adhesion at WCA 55°, protruding fillopodia, flattened morphology	[96]
PE	Air plasma	CHO, endothelial cells	Maximum adhesion at WCA 55°, protruding fillopodia, flattened morphology	[97]
Glass	Polymerized hexane and allylamine	3T3 fibroblasts	High cell density on allylamine side, low density on hexane side	[98]
Glass	Polymerized oxcadiene and acrylic acid	Mouse embryonic stem cells	Cells attached better to hydrophilic region, improved differentiation, flat mololayered colonies	[99]
PS	Polymerzied isopropyl alcohol	Fibroblasts	Cells attached preferentially to treated zones	[100]

Table 3 continued

Substrate	Modification	Cell type	Observations	References
PS	Polymerized aceton	Fibroblasts	Cells attached preferentially to treated zones	[101]
PS	Polymerized n-hexane	CHO	Cells grow preferentially to untreated zones, aligned and elongated cells	[102]
PS	Deposition of PEO	Fibroblast	Alignment of cells along predefined directions	[103]
FEP	Polymerized acetaldehyde and deposition of PEO	Epithelial cells	Inhibition of cell grow on PEO coated regions, enhanced cell grow on acetaldehyde coated regions	[104]
Petri dish	Ar and acetylene plasma	Mammalian cervical caner cells	Increased cell density, elongated cells	[105]

The table present a comprehensive overview of the substrates, the modification type, results on modified cell-material interactions

Nakagawa et al. [58] and Teraoka et al. [59] modified PLA surfaces with an atmospheric air plasma jet. After plasma treatment, the contact angle decreased from 80° to approximately 40°. X-ray photoelectron spectroscopy (XPS) indicated that oxygen-containing groups such as C–O, C=O and O–C=O were incorporated. Cell culture tests with mouse osteoblast-like MC3T3-E1 cells showed that both cell adhesion as well as cell proliferation could be improved with a plasma treatment.

Some authors have used ammonia plasma to modify PLA [60–63]. In an study by Chu et al. [60], the surface of PLA displayed a better proliferation of human umbilical vein endothelial cells (HUVEC) and rabbit microvascular endothelial cell (RbMVEC cells) after ammonia plasma treatment. After 7 days, an increased surface coverage by both animal and human cells was observed (see Fig. 3). The cell density increased from 4.8×10^2 HUVEC/cm^2 for untreated PLA to 8.11×10^4 HUVEC/cm^2 for plasma modified PLA; similar results hold for the RbMVEC. The authors state that ammonia plasma treatment leads to the incorporation of amine and amide groups on the substrate materials, of which the amines specifically interact with the cells through ionic bonding with acidic groups of N-acetylneuraminic acid on the surface of the cell membrane. According to the authors, also a more hydrophilic surface can contribute to a better attachment of cell binding proteins. In the study of Chu et al., no results are available on the type and amount of incorporated groups nor on the change in wettability of the samples after plasma treatment. Jian Yang et al. [61], Gugala et al. [62] and Wan et al. [63] also used ammonia plasmas to modify the surface of PLA, and observed an improved cell attachment of mouse 3T3 fibroblasts and rat osteoblasts. The fibroblasts appeared spindle shape, were evenly distributed and very well stretched [61]. From chemical analyses performed, it was found that both nitrogen and oxygen containing functionalities were incorporated, leading to an increased wettability, and thus a better cell attachment [61]. Wan et al. [63] clearly showed that the attachment of cells was better on treated samples, by placing the samples under shear stress conditions: on treated samples, more cells stayed attached.

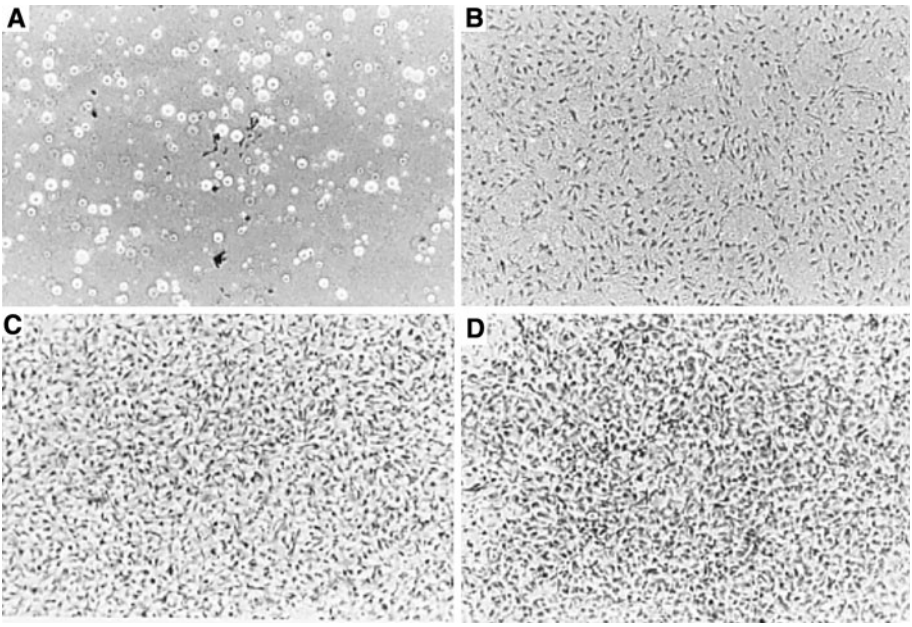

Fig. 3 Photomicrographs of HUVEC grown on various PLLA substrates. HUVEc were plated on various PLLA substrates at a density of 2.5×10^4 cells/cm^2. After 7 days, samples were fixed with 4 % glutaraldehyde and stained with 0.1 % toluidine blue. **a** Control PLLA; **b** Fn-coated control PLLA; **c** modified PLLA; **d** Fn-coated modified PLLA (×100) [167]

Besides ammonia plasma treatment, also sulfur dioxide plasma treatment of PLA has been investigated in [62]. The authors found that cell attachment was decreased and conclude that this is due to the—SH groups present at the surface which make it resistant to nonspecific adsorption of proteins. This, in turn, diminishes the attachment and proliferation of cells. These results indicate that the plasma gas can have a great influence on the cell attachment.

Besides PLA, also PCL and PLGA are commonly studied with respect to plasma treatment to improve cell-material interactions. By using an atmospheric pressure DBD oxygen plasma, Yildirim et al. [64] were able to decrease the water contact angle of PCL samples from about 80° to about 35° and to increase the surface roughness. The cell proliferation rate of mouse 7F2 osteoblasts on plasma-treated samples increased 90 % in comparison with untreated samples. A confluent cell layer was observed on plasma-treated samples, in contrast to untreated surfaces where cells were hardly spread out.

Lee et al. also used an atmospheric pressure DBD operating in air to modify PCL films [65]. Similarly, they found an increased surface wettability and an increased surface roughness. By FT-IR spectroscopy and XPS, a higher amount of oxygen containing hydrophilic groups (C–O, COOH, C=O and OH) could be detected on the plasma-treated films. The cell attachment and proliferation of human prostate epithelial cells (HPECs) was found to be ten times better on plasma-treated PCL films compared to untreated film. The authors suggest that the proteins of the cell membrane, which contain hydrophilic amino acids, posses a better affinity towards the hydrophilic surface of the plasma-treated films.

In another study [66], the same authors used different gas mixtures for plasma treatment and determined the effect on surface wettability, - morphology, - chemistry and cell

attachment. When Ar + H_2 was used as a discharge gas, the contact angle was found to increase after treatment, while the surface became smoother. Opposite results were found for Ar + N_2, Ar and Ar + O_2. For the Ar + H_2 treated samples, more CH_2 and CH_3 functional groups and less oxygen containing groups were detected at the surface compared to the untreated samples whereas for the Ar + N_2, Ar and Ar + O_2 treated samples, more C=O, COO and NH- groups were detected. To determine the influence of each gas plasma treatment on cell material interactions, the authors studied the cell attachment and proliferation of HPECs on the various samples. After 12 h of culture, cell attachment increased from 32 % on the pristine films to 76 % for the Ar + O_2 plasma-treated film. Also for Ar and Ar + N_2, the cell attachment increased, however for Ar + H_2, cell attachment decreased to less than 20 %. Moreover, the number of cells after 7 days of culture decreased for Ar + H_2 treated samples to 1×10^5 cells/ml compared to 2.75×10^5 cells/ml for untreated samples. For Ar + O_2 treated samples, this number was increased to 1.82×10^6 cells/ml. This clearly indicates the better cell proliferation on Ar + O_2 plasma-treated films. The authors concluded that the incorporated hydrophilic groups play an important role in enhancing the cell-material adhesion strength. The main reason is that the protein of the cell membrane, hydrophilic amino acids, is present in the outer region of the membrane. The increased affinity between the protein and the PCL surface, caused by the hydrophilic properties of the Ar + N_2, Ar and Ar + O_2 plasma-treated surface, improves the extent of cell attachment.

In [56], Khorasani et al. plasma-treated besides PLA also poly(lactic-co-glycolic acid) (PLGA) with an RF plasma in oxygen at low pressure. The cell adhesion improved, however to a lower extent than for the PLA films. Similar to Khorasani et al. [56], Hasirci et al. used an RF oxygen plasma to modify the surface of PLGA films [67]. In addition, Wan et al. have used an oxygen plasma to treat PLGA films [68]. Both research groups found an increased concentration of oxygen containing groups (C–O, COOH, C=O, C–O–C=O), leading to an improved hydrophilicity, and an increased surface roughness. It was also observed that 3T3 mouse fibroblasts could attach better to plasma-treated PLGA [67]. On the untreated films, the cells were observed as aggregates most probably due to a weak spreading of the initially added drop of cell suspension on the hydrophobic surface. In contrast on the treated films, the borders of the attaching cells could be easily seen. Wan et al. studied the cell detachment of mouse 3T3 fibroblasts from the samples under shear stress. For untreated samples, cell detachment rates were higher than for the plasma-treated samples. After 60 min of applied shear stress, 90 % of the cells were still attached to the surface of the plasma treated samples. For untreated samples however, the cells detached completely within 10 min, clearly indicating the improved cell adhesion after plasma treatment.

In another study, PLGA films were subjected to different physicochemical modification techniques, including air plasma and corona discharge treatment, before different cell types (hepatoma (Hep G2), osteoblast (MG 63), bovine aortic endothelial cells (CPAE), fibroblast (NIH/3T3)) were cultured on the surfaces obtained [69]. After plasma treatment, the water contact angle decreased from 73° to 52°, and the O1 s/C1 s ratio increased from 0.46 to 0.65. The cells adhered better on the surface-modified PLGA samples regardless of the cell type. Moreover, the cell morphology was different on the treated PLGA than on the pristine PLGA: the cells had protruded fillopodia and lamelliopodia that spread out and flattened more (see Fig. 4). After 2 days of culturing, the cells were almost flattened on the plasma-treated samples, whereas the untreated samples still showed round cell morphology, indicating poor cell attachment.

Besides air and oxygen, also the effect of ammonia plasma treatment on PLGA has been investigated [70]. Electrospun PLGA nanofiber matrices were treated with an ammonia glow discharge plasma. The contact angle of untreated nanofibers was approximately 140°,

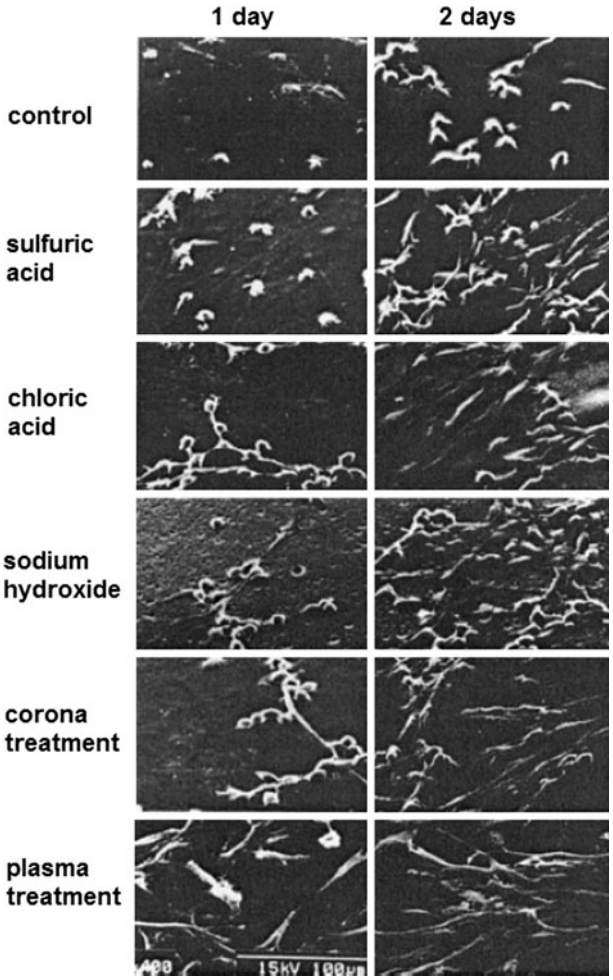

Fig. 4 SEM microphotographs of fibroblast cells attached to physicochemically treated PLGA surfaces after 1 and 2 days of culturing (original magnification: ×400) [69]

while after plasma treatment of 30 s, 60 s and 180 s, the contact angle decreased to 53°, 51° and 47°, respectively. However, only a small nitrogen content of 1, 2 and 3 % was detected after plasma treatment of 30, 60 and 180 s, respectively. Mouse 3T3 fibroblasts, seeded on the plasma-treated PLGA samples, could adhere better and spread out more thus occupying a larger surface area than cells on non-treated matrices. However, for matrices treated longer than 60 s, the cell attachment and viability decreased. This finding indicated that an optimum concentration of N-containing functional groups such as amines might be essential for cellular adhesion and spreading, as hydrophilicity of plasma-treated nanofiber matrices used in this study was almost constant.

Some studies reported on the cell attachment after plasma treatment of the a 3-hydroxybutyrate-3-hydroxyvalerate (PHBV) copolymer [71–73]. PHBV surfaces were treated with an RF plasma operating in oxygen [71, 72]. Both studies showed an increased

hydrophilicity caused by a higher oxygen content at the surface after treatment. Both dog bone marrow stromal cells [71] and human retinal pigment epithelium D407 cells [72] could attach and proliferate better on treated surfaces. More recently, RF plasma treatment of PHBV in oxygen, nitrogen and argon was studied by Garrido et al. [73]. After plasma treatment, the surface became more hydrophilic, indicated by the lower water contact angle. The water contact angle decreased from 73° for untreated samples, to approximately 55° after 20 s of treatment, independent of the discharge gas. Only for oxygen plasma treatment, a longer treatment time led to an even lower contact angle value of about 49°. It was also observed that the chemical composition of the surface after treatment depended on the applied gas: oxygen plasma led to the incorporation of C–O, nitrogen led to the incorporation of C=N and C≡O groups. For argon plasma, more C=C bonds were detected. Non-transformed, immortal human keratinocytes (HaCaT) were seeded on the surface of PHBV films. The results showed that cells attached better to oxygen and argon treated samples than to nitrogen treated samples, which still showed better results than the untreated film. The attached cells had a flattened appearance. Surprisingly, the best cell adhesion was found on samples treated for 10 s, while samples treated for 90 s showed a much lower cell adhesion. The authors suggest that after the initial decrease of hydrophobicity, the chemical functionality of the surface plays an important role, more specifically the presence of unsaturated bonds after treatment.

Pompe et al. used an ammonia and a water vapour plasma to modify the surface of poly(hydroxybutyrate) (PHB) films to influence cell adhesion [74]. XPS analysis showed that oxygen was built in for water vapour plasma treatment and nitrogen for ammonia plasma treatment. The cell culture tests with HUVECs showed that on NH_3 plasma-treated films, the cells exhibited a flat monolayer morphology, while on H_2O plasma-treated surfaces the formation of capillary–like networks was observed with an elongated and branched pattern of the cells assemblies (see Fig. 5).

Qu et at. treated copolymers of 3-hydroxybutyrate and 3-hydroxyhexanoate (PHBHHx) with an ammonia plasma [75]. The contact angle decreased from 82° to 68°, and oxygen (C–O, C=O) and nitrogen (C–N) groups were incorporated on the surface. Both HUVECs and rabbit aorta smooth muscle cells (SMCs) were used for cell culture tests. The HUVECs grew well on the plasma treated PHBHHx film, however, there was no significant difference in cell proliferation between treated and untreated films when SMCs were seeded on the films. The HUVECs were evenly distributed and spread on treated films in contrast to the untreated films. The SMCs, on the other hand, were flat and well spread on both untreated as well as treated samples. This might indicate that the effects of surface properties on SMCs are not as pronounced as on HUVECs.

The polymer blend poly(ethylene glycol)-terephthalate-poly(butylene therephthalate) (PEGT/PBT) has also been treated with an RF plasma operating in argon [76]. Expanded human nasal chondrocytes were seeded on untreated and plasma treated PEGT/PBT films. The plasma treatment lead to an increased cell number. Also, the cells exhibited a spread morphology and pseudopodia formation. However, the re-differentiation capacity of chondrocytes was markedly reduced. The authors therefore concluded that for clinical cartilage tissue engineering strategies relying on post-expansion re-differentiation of expanded human chondrocytes, gas plasma treatment may not be a suitable surface modification technique.

From this overview, it is clear that the plasma surface modification of biomedical polymers can have a significant influence on the cell-material interaction. However, the basic understanding of the mechanisms of cell adhesion are still not well understood. To be able to explain and comprehend how cells interact with the (modified) material is crucial to

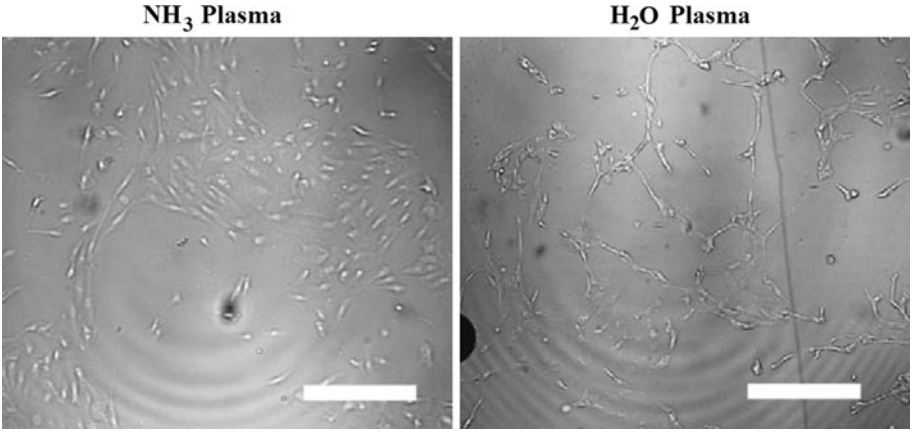

Fig. 5 Endothelial cell morphology after 5 days of cell culture on P(3HB) samples visualised by differential interface contrast demonstrating a dense packing and flat morphology on NH_3 plasma-treated samples (and on untreated samples, not shown) and frequent occurrence of capillary-like network formation on H_2O plasma-treated samples (*scale bar*: 250 μm) [168]

adapt the modification process to the best possible standards. Some studies, like [60] from Chu et al. and [65, 66] from Lee et al., discuss some cell-material interaction mechanisms, but further research on this matter is required. In [70, 73], the role of the implanted chemical groups on the cell attachment is discussed. Some authors also discuss the influence of plasma surface treatment on surface roughness and consequences for cell adhesion [64, 65, 67, 68]. In [77], it is proven that the surface roughness has a considerable influence on cell attachent. However, as Yildirim points out in [64], a detailed understanding of the interrelationship between particular surface properties, such as chemical composition or roughness, and cell attachment needs further research.

Most studies focus on cell numbers, shape and morphology, since they are rather easy to evaluate. They are important parameters to consider, but also cell re-differentiation, see for example the paper of Woodfield et al. [67], is for some applications also important. The intended application will not only determine which of these factors are important to take into consideration, but will also impose the needed surface properties. Most of these applications are very specific, so that probably tailor-made solutions will be necessary.

Plasma Polymerization and Grafting

Plasmas can not only be used for the introduction of chemical groups, it is also suitable for the covalent immobilization or grafting of bioactive molecules and for polymerization of different monomers. When cells reach the modified surface, they sense the grafted molecules and will interact with them rather than with the underlying surface. The main advantage of this approach is that the applied surface modification strategies are less or not affected by ageing.

The covalent immobilization of collagen on PCL surfaces by a post-irradiation technique and the influence on cell adhesion and proliferation has been widely investigated [78–81]. A schematic representation of this process is given in Fig. 6. A plasma treatment is used as a pre-treatment step, before acrylic acid is grafted onto the surface by UV-induced grafting. The carboxylic acids groups introduced were activated by exposure to a

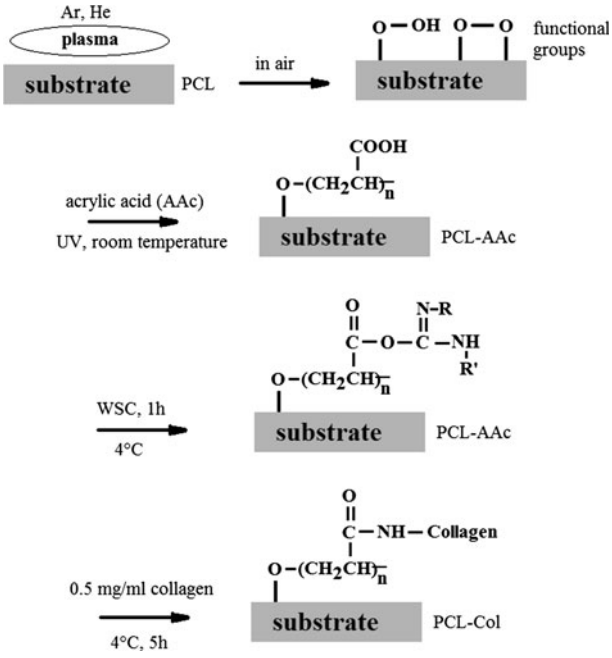

Fig. 6 Schematic representation of the immobilization of collagen on PCL films

water-soluble carbodiimide followed by collagen enabling the biopolymer immobilization onto the surfaces.

Chong et al. seeded the collagen-modified PCL films with human coronary artery smooth muscle cells and found an increased cell number on the modified films and observed that the cells spread out more to adopt spindle-like morphologies compared to the untreated films [78]. They found no degradation in mechanical properties due to the surface modification. Human dermal fibroblasts (HDFs) and human myoblasts also elongated and flattened to a spindle morphology, indicating an improved attachment to the surface, and proliferated better covering the entire surface of PCL collagen immobilized films after 8 days of incubation [79]. Similar results were found by Foo et al. for HUVECs [80].

Besides the covalent immobilization of collagen, the immobilization or grafting of other biomolecules like insulin, chitosan, gelatin, Arg-Gly-Asp (RGD) or Arg-Gly-Asp-Cys (RGDC) has been pursued leading to a better cell-material interaction [81–84]. Insulin functionalization of PHBV lead to an increased cell proliferation of human fibroblast cells and full cell spreading on the surface [81]. By using a spacer arm bNH_2PEG (O,O'-bis-(2-aminopropyl)-polyethylene glycol 500), the RGDC peptide could be immobilized on the surface of acrylic acid grafted poly(tetrafluoroethylene) (PTFE) [82]. The attachment level of HUVECs was observed to be four times higher for the modified polymer than for the non-modified one. However, the authors could not confirm whether this trend was related to a specific cellular recognition mechanism or to the increase of wettability of the modified sample. The RGD peptide immobilization on an acrylic acid (AA) thin film layer on Ti surfaces has an effect on osteoblastic differentiation of MC3T3-E1 cells and has a potential use in osteo-conductive bone implants [83]. Gelatin immobilization was found to enhance cell adhesion, spreading and focal adhesion formation and proliferation of HUVECs on PLLA surfaces, as shown in Fig. 7 [84].

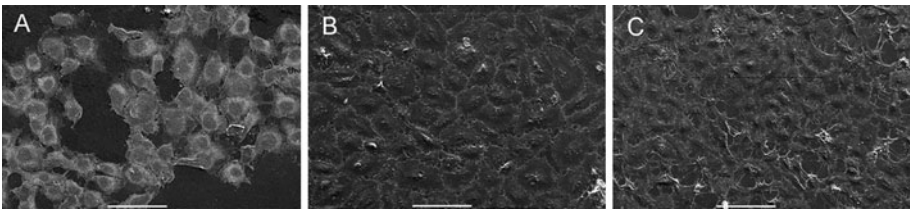

Fig. 7 Cell morphology observed on **a** PLLA, **b** PLLA-gAA-gelatin, and **c** PLLA-gAA-chitosan by SEM at day 7. Complete endothelialisation was observed on both modified PLLA substrates, but not on PLLA substrate. Scale = 100 μm [169]

Duan et al. used a post-irradiation technique for collagen immobilization on PCL nanofibrous mats [85]. The pristine PCL nanofibers were smooth and beadless, while the surface of collagen-coated fibers became rough and thick due to the coating layer and possessed an increased wettability. The proliferation of primary HDFs was increased and a confluent layer of long, bipolar, spindle-shaped layer was formed. Also, a number of discrete filopodia-like protrusions between the cells and collagen-coated fibers were observed, indicating good interaction between the cells and the scaffold. The cells were found to migrate through the pores of nanofibers, which was not observed for the pristine fibers.

Besides the covalent immobilization, some authors have been immersing plasma pretreated biomedical polymers into protein containing solutions leading to non-covalent linking of proteins to the surface. Although these proteins can be easily removed, they also lead to a better cell attachment and proliferation onto the modified surface [86–89]. The anchorage of collagen on PLGA leads to a better cell attachment, spreading and viability of mouse NIH 3T3 fibroblasts [86]. On PLA, the anchorage of collagen could lead to an increased cell number and a better attachment of 3T3 fibroblasts [87]. He et al. used a nanofiber mesh out of the co-polymer poly(L-lactide acid)-co-poly(ε-caprolactone). Upon collagen coating, the cell spreading, viability and attachment of human coronary artery endothelial cells onto the mesh was enhanced [88].

In a study by Ding et al., the plasma syn-irradiation technique was used to immobilize chitosan onto PLA films [90]. The two cell types they used for cell culture tests (L929 mouse fibroblasts and L02 human hepatocytes) showed a poor cell adhesion and hardly spread, but they proliferated at the same speed as cells cultured on glass.

The plasma polymerization technique has also been investigated by many authors [91–95]. It can be used to coat the substrate rather than covalently bind species. Guerrouani et al. plasma polymerized allylamine onto PLA surfaces [91]. Microorganisms such as euglypha and vorticella formed a dense biofilm. Carlisle et al. used PLLA and PCL plasma polymerized with allylamine to link cell adhesion peptides polyethylene glycol (PEG) to the polyester surface [92]. These surfaces were found to significantly increase hepatocyte cell adhesion from 31 to 53 % on PCL surfaces and from 42 to 76 % on PLLA. Allylamine can also be plasma polymerized on a silicone elastomer to improve the biocompatibility [93]. Cell culture tests with human skin fibroblasts showed that the cells attached and proliferate better onto the modified elastomer. The cell shape changed from round shape to an elongated triangular morphology.

Besides allylamine, acrylic acid can also be plasma polymerized on biocompatible polymers to improve cell material interaction. When acrylic acid is deposited onto polyglycolic acid (PGA), PLA or PLGA, the adhesion and spreading of fibroblasts was enhanced [94]. Also the total cell number increased. Mitchell et al. used an isopropyl

alcohol (IPA) plasma to modify polystyrene surfaces [95]. Fibroblasts adhered and proliferated to a higher extend on the modified samples. The cells showed a flatter morphology and cell densities increased tenfold upon incubation for 72 h.

For plasma grafting and plasma polymerization, the same conclusions about the importance of knowledge of cell-material interaction can be made than for the previous chapter about plasma treatment. The main difference with plasma grafting or plasma polymerization is that the cell-material interaction can be mimicked to comply with the normal in vivo cellular recognition mechanisms. By grafting the appropriate bioactive molecules, the cells will 'sense' these molecules as a biological environment and not the foreign surface. As a result, the normal cell responses for adhesion can be triggered. An important factor is the graft density, which also depends on the size of the biologically active molecules which are immobilized [96, 97]. Often, achieving a higher graft density is not always necessary or even beneficial to achieve a better cell-material interaction [98]. This indicates that the graft density should be carefully monitored and optimized.

Use of Plasma Modification Techniques for Specialized Purposes

3D Scaffolds for Tissue Engineering

The development of 3D porous scaffolds is crucial for the final success of tissue engineering approaches. Since cells without their native ECM do not enable three dimensional tissue growth, administering cells alone is not adequate in large size defects [2]. The design of an artificial ECM to induce tissue regeneration by allowing cells to adhere and proliferate is thus essential [99]. Cells seeded on the scaffolds and from the native surrounding penetrate the porous scaffold, adhere and start to proliferate. During these processes, natural ECM is being synthesized. It is desirable to have scaffolds that produce a minimal immunogenic reaction, since this leads to failure of the implant. Hence, adhesion of cells on the scaffolds and the overall biocompatibility of the implant are key issues [100]. Moreover, in some cases the ingrowth of blood vessels should also be promoted, as cells need sufficient nutrients to grow and proliferate and the possibility to drain waste products [100]. The modification of 3D scaffolds is more complicated than for 2D surfaces, such as films. For a proper functioning of the implant, a homogeneous scaffold modification is essential since cells need to adhere and proliferate at all scaffold parts. Similar to the treatment of 2D surfaces, many authors have studied the plasma modification of 3D structures and their influence on cell adhesion.

In this respect, PLA has been widely studied [101–106]. Fibroblasts were grown on PLA scaffolds modified by ammonia plasma [101] and by allylamine grafting [102]. In both studies, an improved cell attachment was observed. By the depositing allylamine onto the porous PLA scaffold, cells homogeneously populated the scaffolds after only 24 h of cell culture [102] (see Fig. 8). This was not observed after the grafting procedure. According to the authors, this was due to the lower nitrogen content on the surface. Also the graft polymerization of acrylic acid lead to a better chondrocyte adhesion and proliferation on 3D PLA scaffolds [103]. Chim et al. used a pure oxygen glow plasma treatment, and found that human embryonic palatal mesenchyme cells adhered better to treated scaffolds: the cells adopted a spindle-shape morphology with filopodia aiding attachment [104]. Confocal laser micrographs revealed an increased cell density throughout the scaffold. Cell aggregates were observed, with confluent cell sheets by day 10. Oxygen plasma treatment also had a positive effect on the cell attachment of Chinese hamster ovary (CHO) cells on PLA membranes [105]. Not only was the percentage of adherent cells

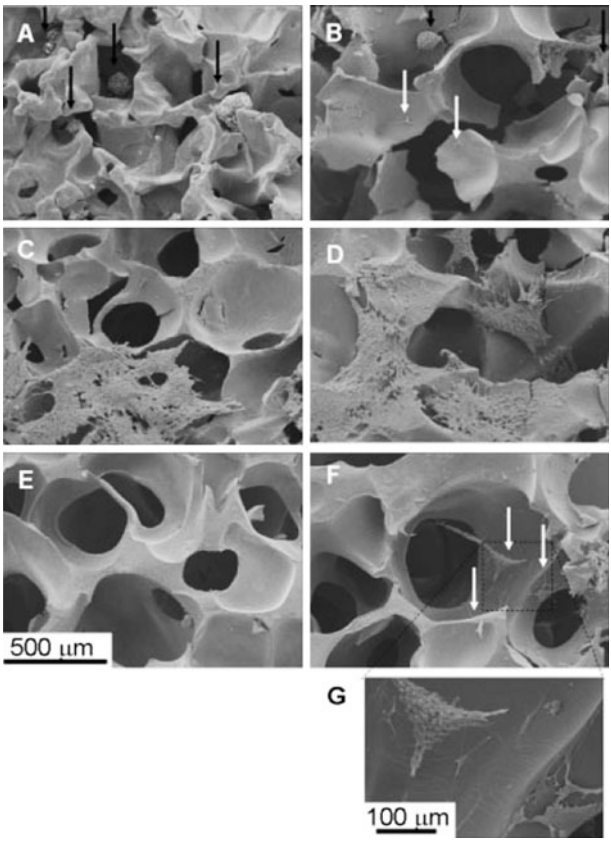

Fig. 8 SEM images of murine 3T3 fibroblasts cultured for 24 h on **a** unmodified $P_{DL}LA$; **b** allylamine-grafted $P_{DL}A$, and **c** 3 W and **d** 20 W plasma-polymerized allylamine-deposited surfaces. Images **a–d** are from the outer surfaces of the scaffold, while **e**, **f** are representative of the unmodified/grafted (**e**) and plasma-polymerized 3W(F) inner surfaces. All images are the same magnification. Images (**e**, **f**) were taken from approximately the middle of the diameter of the sample. In all images, the *white arrows* denote cells that have assumed characteristic fibroblast morphology, while the *black arrows* denote cells that have not. **g** Higher-magnification image of **f** showing cells adhering to the modified $P_{DL}LA$ surface [102]

greatly increased by plasma treatment, also the cells spread out resulting in sheet like formation. However, cell proliferation was not improved by plasma treatment. Ho et al. used the immobilization of RGDS (Arg-Gly-Asp-Ser) peptides to promote the cell growth of rat osteosacroma osteoblast-like cells on porous PLA scaffolds [106]. Cell attachment was promoted, resulting in higher cell densities while the cells were found to form bone-like tissues, indicated by the deposition of calcium salts. The authors were able to uniformly immobilize the RGDS inside the scaffold, however they did not investigate whether cells were able to attach and grow inside the scaffold. The anchoring of gelatine by oxygen plasma pretreatment on PLLA nanofibers led to a better cell proliferation of chondroyctes and ECM production [106]. Moreover, the seeded cells grew into tissue-like contructs.

Some authors reported on plasma modification of PCL and PHBV scaffolds. Air plasma treatment of porous nanofibrous PCL scaffolds led to a better cell proliferation [108], and a combined oxygen plasma modification followed by fibronectin adsorption has shown to increase cell attachment and proliferation of 7F2 mouse osteoblasts [109]. The influence of

oxygen plasma treatment on PHBV foams was studied by Köse et al. [110, 111]. They showed that adhesion and spreading of osteoblasts inside the foams structure could be improved, and interconnections between cells were observed indicating that PHBV matrices could have a potential in bone tissue engineering.

Spatial Control of Cell Adhesion

Instead of a uniform surface modification, several authors investigate the creation of so called gradient or patterned surfaces on biodegradable polyesters by plasma modification techniques. On a gradient surface, the chemical composition (or another surface characteristic such as roughness, wettability, etc.) gradually varies along one dimension. Such a surface is of great interest for studies on the interactions between biological species and surfaces, as the dependence of the surface property on this interaction can be examined in a single experiment on one surface [112]. It is a simple and fast method for investigating optimal surface conditions for cellular responses such as attachment and growth. In this subsection, we will focus on the interaction of cells with these gradient surfaces, information on preparation of such surfaces can be found in other excellent reviews in the field [112, 113].

On a patterned surface, the chemical composition is different from one region of the surface to another, thus creating a pattern. Depending on the chemical composition, the cell adhesion will be either promoted or reduced. In this way, the cells are 'guided' to grow in a specific pattern on the surface. One can correctly align and position cells by providing the proper (chemical) cues, which offers numerous possibilities for tissue engineering [114].

Lee et al. [115], Choee et al. [116] and Lee et al. [117] used an air corona discharge treatment from a knife-type electrode whose power gradually increases along the sample length to create a wettability gradient on polyethylene (PE). The water contact angle of the PE surface was shown to gradually decrease along the sample length from 93° to 43°. When 3T3 fibroblasts were seeded on the surface of such samples (see Fig. 9) they found that the cells grew significantly more on the positions with moderate hydrophilicity (i.e. water contact angle about 55°). In addition, on this position more cells with protruding fillodopia and lamelliopodia and with flattened morphology were observed [116]. Also CHO cells and bovine pulmonary artery endothelial cells were found to adhere better to regions of moderate hydrophilicity and similar observations regarding cell shape were found [117]. Rat pheochromocytoma PC-12 cells appeared to have maximum adhesion to the gradient surface where the water contact angle was about 55° [115]. As the surface wettability increased along the sample length, the adhered cells were induced to differentiate into cells with typical neuronal morphology. The maximum number of neurites of the PC-12 cells on the PE surfaces appeared at the position with a contact angle of 55°. Higher hydrophilic position showed no further increase of neurites.

Zelzer et al. [118] and Wells et al. [119] used a plasma polymerization technique of hexane combined with allylamine and octadiene with acrylic acid respectively to produce gradient surfaces. On the hexane (hydrophobic) side of the sample, 3T3 fibroblast were hardly adhering, while on the allylamine (hydrophilic) side, the cell density was high [118]. Also, a gradually varying cell density was observed along the gradient surface from one side to the other. Also plasma polymerization of octadiene combined with acrylic acid lead to a wettability gradient caused by a gradient in acid (COOH) functionalities [119]. Mouse embryonic stem cells were found to adhere better on the hydrophilic side of the gradient. On these regions, the cells appear to form flat monolayered colonies where many cells are differentiated.

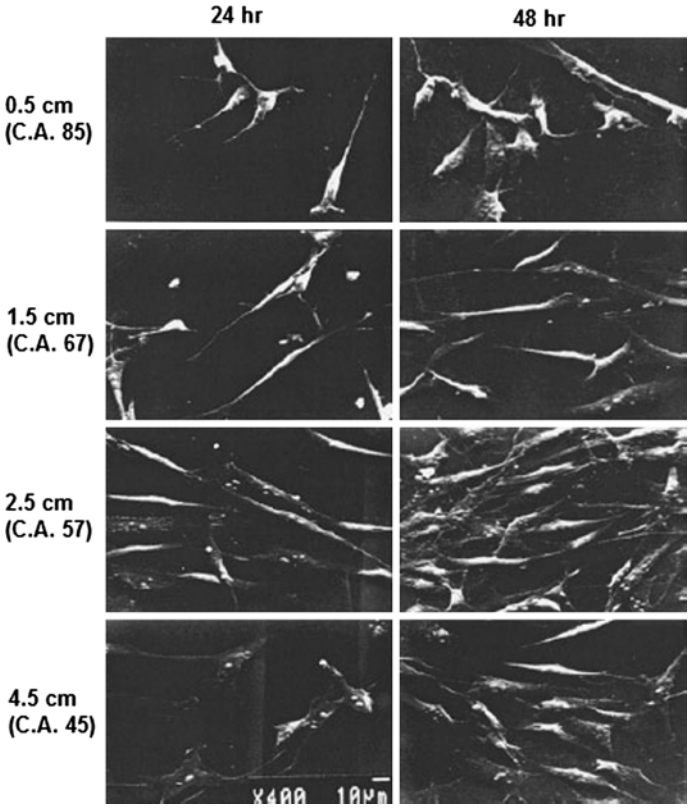

Fig. 9 SEM pictures of the fibroblast cells adhered on wettability gradient PE surfaces after 24 and 48 h of culture (original magnification: ×400). CA: water contact angle (degrees) [116]

Several authors also studied the creation of patterned surfaces on polystyrene (PS) by combining plasma polymerization with a simple masking technique [120–123]. By placing a transmission electron microscope (TEM) grid on the surface during plasma exposure, a patterned surface could be created. Human fibroblast cells grown on such a patterned surface created with isopropyl alcohol plasma [120] or acetone plasma [121] preferentially attach to the unmasked, hydrophilic, treated zones. After longer incubation times, when the treated areas have become nearly confluent, cells also begin to spread onto the untreated areas. HCO cells were found to preferentially grow on the untreated areas of a patterned surface created with n-hexane plasma polymerization [122]. The cells were also found to spread preferentially in the direction of the untreated surface, resulting in aligned and elongated cells. Sardella et al. deposited patterned PEO-like coatings, and found that fibroblast cells would not adhere to PEO regions deposited at low power, and they could thus create a cell pattern onto the PS surface and induce the alignment of cells along predefined directions [123].

Thissen et al. used a similar technique to deposit a patterned surface of acetaldehyde plasma polymer adhesive regions and PEO non-adhesive regions onto perfluorinated poly(ethylene-co-propylene) (FEP) to precisely control the outgrowth of bovine corneal epithelial tissue on the surface [124].

By using an atmospheric pressure plasma jet operating in argon and acetylene, a patterned polymer film could be deposited onto a petri dish surface [125]. After 4 h of inoculation, mammalian cervical cancer cells showed cell alignment on the edge of the organic film, and these cells were more elongated. On the plasma polymer film, the cell density increased twofold over the next 48 h.

By combining the spatial control of cell adhesion with 3D scaffolds, the basis of tissue engineering can be developed. In this respect, the results obtained by Chim et al. [104], Yamaguchi et al. [105], Chen et al. [107] and Wells et al. [119] concerning the observation of so-called cell sheets or cell layers and tissue like constructs is very promising. Moreover, the differentiation of cells was also detected by Wells et al. [119]. This shows that the cells exhibit abilities to form tissues on the modified biomedical polymers.

Antibacterial and Antifouling Surfaces by Plasma Surface Treatment

In this last part, antibacterial and antifouling surfaces, obtained by plasma techniques, will be discussed. Antibacterial refers to the prevention of bacterial adhesion, whereas antifouling refers more generally to the prevention of attachment large molecules, microorganisms and cells. As mentioned before, the prevention of bacterial and protein adhesion is needed in many applications, such as medical implants, intraocular lenses, catheters and blood contacting materials [8, 9]. When an implant is placed into the body, both cells of the surrounding tissue as well as bacteria present compete to attach to the surface. This process is called the 'race for the surface' [126]. If the tissue cells win the race, the surface of the implant is covered by tissue. But if the race is won by bacteria, the surface will be covered by a biofilm and an inflammatory reaction may be the consequence and removal of the implant may be necessary [127, 128]. Excellent reviews on the mechanisms of bacterial adhesion can be found in [126, 129, 130].

For blood contacting materials, like heart-valve or vascular prosthetics, the adhesion of platelets and fibrinogen should be prevented, since this can lead to the formation of a thrombus (blood clot).

First, an overview of research dealing with antibacterial surfaces created by plasma techniques will be given. Afterwards, antifouling surfaces will be discussed, and how blood compatibility can be improved by preventing protein adhesion.

Antibacterial Surfaces

Several groups have studied plasma created antibacterial surfaces of medical grade PVC to be applied as endotracheal tubes [131–136]. An oxygen glow discharge has been used to modify small coupons of PVC to prevent the adhesion of several *Pseudomonas aeruginosa* strains [131, 132]. The treatment made the surface more hydrophilic, and a 57–70 % reduction in bacterial adhesion was observed. This reduction is believed to be attributed to the incorporation of oxygenated functional groups. The authors stated however that it is unlikely that the effect will be sufficient to delay or prevent biofilm formation. Therefore, the same authors also combined the oxygen glow discharge with an $NaOH/AgNO_3$ incubation for the treatment of PVC [133]. Using this technique, they found a complete reduction in bacterial adhesion, and the biofilm formation could be reduced. According to the authors, the silver content is essential to provide anti-bacterial properties to the surfaces.

Asadinezhad et al. used plasma co-polymerization of acrylic acid followed by irgasan [134] and benzalkonium chloride, bronopol or chlorhexidine coating [135] to modify PVC surfaces (see Fig. 10). The irgasan coating was capable of inhibiting bacterial growth of *S. aureus* and *E. coli* bacteria; however, it was unable to hamper bacterial adherence and biofilm formation after 24 h culture [134]. Benzalkonium chloride and bronopol coatings were able to reduce the *E. coli* adhesion (85 % resp. 75 %), but no reduction was observed in adhesion of *S. aureus* for both coatings [135]. The chlorhexidine was found to be effective against both bacteria: a reduction of 50–60 % in the adhesion was observed [135].

Oxygen plasma pretreatment, followed by triclosan or bronopol coating and a argon plasma ion bombardment has also proven to give antibacterial properties to PVC surfaces [136]. Triclosan was able to reduce the number of active *S. aureus* and *E. coli* bacteria with 82.2 % resp. 79.5 % compared to the untreated PVC. For bronopol, the reduction was 98 % resp. 77.3 %.

The combination of a plasma treatment followed by a deposition, coating or grafting of a polymer or other molecule, is a rather common technique. The grafting of poly(ethylene glycol) (PEG) has proven to effectively reduce the adherence of *S. aureus* bacteria, as shown in Fig. 11 [137]. When this PEG layer was end group functionalized with RGD-peptide, fibroblast and osteoblast attachment was enhanced, while bacterial adhesion was still greatly reduced. The plasma pretreatment of poly(methyl methacrylate) (PMMA) followed by a TiO_2 coating gives the PMMA surface bactericidal properties caused by TiO_2 photocatalysis [138], while the grafting of N-vinyl-2-pyrrolidone onto plasma treated nonwoven polyethylene terephthalate PET restrained *S. aureus* bacteria from growing onto the nonwoven [139]. Another example of this technique is the coating of PS with polysaccharides alginic acid and hyaluronic acid, which leads to an adhesion reduction of *S. epidermidis* and *E. coli* bactiria [140].

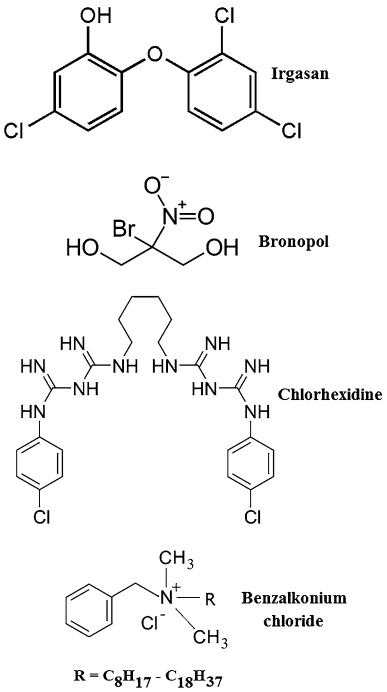

Fig. 10 Chemical structure of irgasan, bronopol, chlorhexidine and benzalkonium chloride

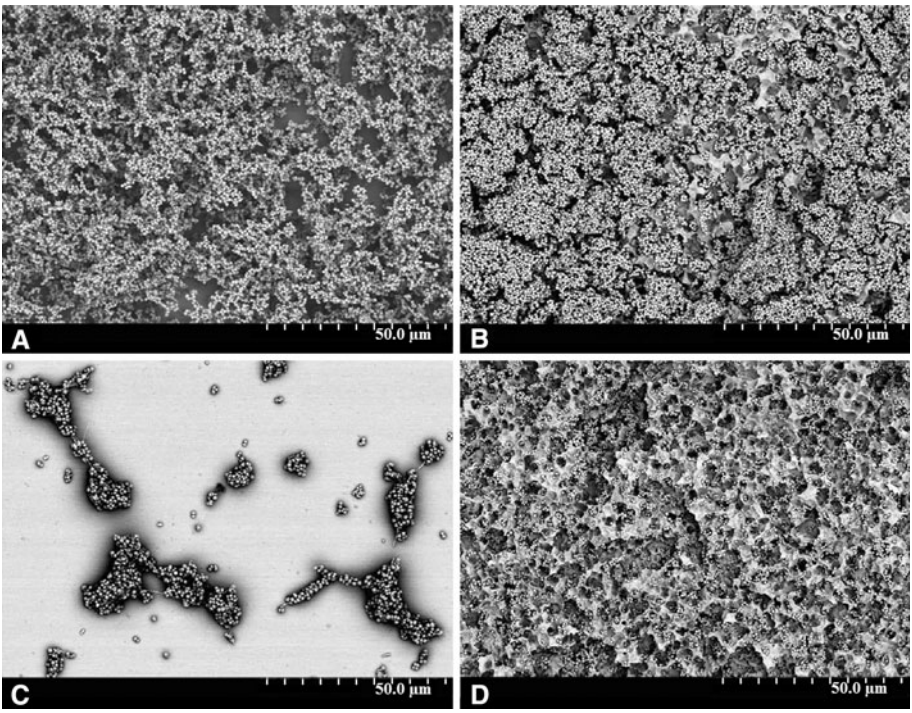

Fig. 11 BSE images of *S. aureus* cultured on the different surfaces for 4 h at 37 °C: **a** Ti (smooth), **b** Ti (rough), **c** Ti (smooth)-PEG, and **d** Ti (rough)-PEG. A confluent layer of *S. aureus* is observed on the Ti (smooth) and Ti (rough) surfaces. Less bacteria are seen on the Ti (smooth)-PEG surface, whilst bacteria are seen clumping in the acid-etched crevices of the Ti (rough)-PEG surface [170]

Some authors also used a single plasma treatment step to achieve anti-bacterial properties. Cordeiro et al. [141] used a low pressure CF_4 plasma to make the surface of PDMS coatings less prone to marine bacterial attachment while Katsikogianni et al. [142] used He and He/O_2 plasmas to treat PET films leading to a reduction in the adhesion of *S. epidermidis* compared to untreated PET, even 58 days after plasma treatment.

Antifouling Surfaces and Improving Blood Compatibility

Like antibacterial surfaces, antifouling surfaces can easily be created by plasma techniques. Both a single plasma step, as a plasma pretreatment followed by a polymerization, grafting or coating step have been used. Some authors have studied the grafting of PEG onto surfaces to generate antifouling characteristics. The grafting of PEG onto PET reduces the adhesion of macrophage-like human leukocytes [143], while polyethylene glycol acrylate grafting onto PP has shown to reduce the fibrinogen adsorption with almost 85 % [144]. The grafting of PEG onto allylamine plasma polymerized on silicon wafers prevented the adsorption of horseradish peroxidase enzyme and collagen [145], while grafted onto plasma modified poly(dimethylsiloxane) (PDMS) it can prevent the avidin protein adsorption [146].

For membranes used for separation processes, including biological, pharmaceutical and sterilization filtration, antifouling properties are most important [147]. The immobilization of PEG onto poly(vinylidene fluoride) membranes leads to a significant reduction in

γ-globulins adsorption [148]. However, a decrease in water flux with increasing surface concentration of the grafted PEG polymer was observed. Kang et al. coated PP membranes with allylamine and acrylic acid [149]. Even though the plasma-treated membranes had smaller micropore sizes than the untreated membrane, they had a greater flux due to their higher hydrophilicity, as shown in Fig. 12. Plasma treatment with acrylic acid reduced the fouling with bovine serum albumin (BSA) to less than half. Deposition of acrylic acid followed by the grafting of amino-PEG onto PP membranes also leads to a reduced protein adsorption [150]. Kull et al. used nitrogen-based plasmas to modify polyethersulfone membranes [151]. After plasma treatment, the water flux through the membranes was increased and the protein fouling was reduced by 51–73 %.

The group of Timmons has developed antifouling coatings of ethylene oxide (EO) by pulsed plasma polymerization [152, 153]. They found that ultra short chain length PEO modified surfaces are biologically non-fouling. Baydal et al. has done research on bactericidal and antifouling surfaces [154–156], some of the developed coatings are being commercially used.

For blood contacting materials, non-fouling properties and minimal interaction with the biological environment are necessary to achieve a good hemocompatibility and decrease the possibility of thrombosis. In [157], an overview is given of various plasmachemical processes of fluoropolymer (like polytetrafluoroethelyne (PTFE)) modification for improved hemocompatible materials. PTFE is used in ophthalmology, endoscopy, orthcatheopedics and in cardiac surgery. For synthetic vessels, drainage tubes, vascular prostheses and other catheters, a good hemocompatibility is crucial. Plasma treatment with O_2, Ar, N_2 and NH_3 of PTFE could significantly reduce platelet adhesion, while for Ar and N_2 plasmas can even reduce the platelet activation (spreading) [158]. A combination of plasma polymerization of acetylene to deposit diamond-like carbon (DLC), followed by an ammonia plasma treatment, and deposition of heparin could increase the blood coagulation time by a factor of 10 [159] (see Fig. 13). The amount of immobilized heparin on the surface was clearly correlated to the coagulation time.

Some authors have studied the improvement of hemocompatibility of PET by plasma modification [160–162]. Both helium plasma [160] and acetylene plasma treatment [161]

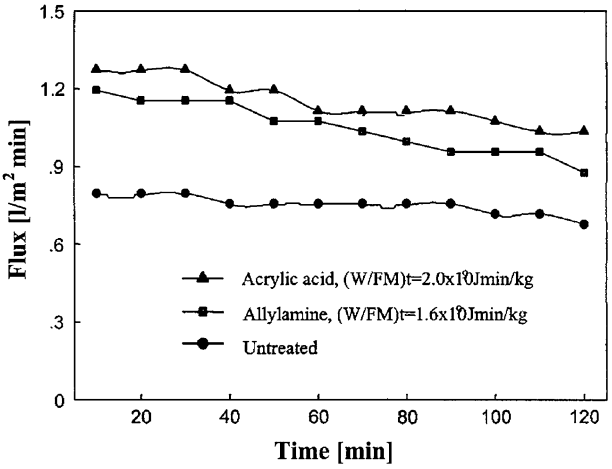

Fig. 12 Comparison of pure water fluxes through the membranes before and after the plasma treatment at 5 W and 5.332 Pa for 10 min [149]

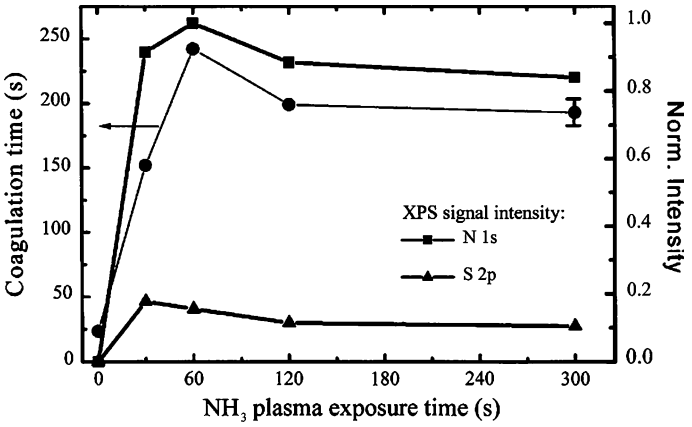

Fig. 13 Comparison between the normalized XPS signal intensities (S 2p an N 1 s) and thrombin time until blood coagulation in dependence on the exposure time in an ammonia plasma beam for heparinised DLC films on PTFE vascular grafts. The data are connected by lines to guide the eye. Note the correspondence between heparin coverage and antithrombogenic activity [159]

increased the clotting time and decreased platelets adhesion and activation. Plasma polymerization of PEG also leads to a surface which is less thrombogenic due to a reduced adhesion and aggregation of platelets [162]. Ar plasma treatment and subsequent graft polymerization of glycidyl methacrylate onto polyethylene (PE) films followed by immobilization of heparin decreased the amount of adhered platelets [163], while the preirradiation grafting technique of epoxypropyl methacrylate on PP followed by heparin immobilization reduced the amount of thrombi formed on the surface [164]. Also nitrogen RF plasma treatment of polyetherurethane (PEU) could reduce clotting time [165], whereas the surface of poly(dimethyl siloxane) activated with argon plasma and grafted with poly(ethylene glycol) methyl methacrylate showed no improved blood compatibility [166].

Conclusions

During the last decades, the more demanding needs of the growing and ageing population have stated more challenging requirements to health care. Especially in the field of tissue engineering: more people than ever need an implant or an organ transplantation. To be able to supply the growing demands, extensive efforts have been made to lead the emerging interdisciplinary field of tissue engineering to a promising, fast developing, yet challenging research topic. A better understanding of cell biology, biomaterial science and cell-material interaction, have led to some hopeful advances. In this context the surface modification of biocompatible polymers is of interest for many research groups. The last decade extensive efforts have been made to optimize the surface properties of biocompatible polymers to make them suitable candidates for implants and for tissue engineering scaffolds. To be able to develop environmentally friendly technologies and to avoid the use of toxic chemicals which might cause problems towards cell viability, plasma surface modification is becoming more and more prominent. Plasma surface modification of traditional polymers has proven its possibilities, and modification of biocompatible polymers is showing promising results. However, tissue engineering remains an interdisciplinary field, and still

some crucial information on and a good understanding of cell-polymer interaction is missing. As we gain more insight into this fundamental phenomena, researchers will be able to fine-tune the surface modification to the specific needs of cell adhesion, proliferation and differentiation.

We hope this review has given a comprehensive literature overview of plasma surface modification of biocompatible polymers to change the cell-material interactions. Traditional plasma treatment is most commonly used, however other plasma technologies, like plasma polymerization and plasma grafting, are emerging. These technologies all have shown to improve the cell-material interaction of various biomedical polymers. Besides better cell adhesion and growth on the surface of an implant or scaffold, also the prevention of bacterial adhesion is crucial. Although less investigated, the use of plasma modification to prohibit bacteria to adhere onto polymer surfaces has proven to be valuable. The challenge lies in being able to prevent bacterial adhesion without compromising the cell attachment. Also non-fouling surfaces to prevent blood cloth formation, are an important aspect, for example for heart valves. Due to the various possible applications of biomedical polymers, with even more divers requirements, it is evident that different specialized plasma modifying procedures and technologies will have to be developed to meet the various needs. Two of these specialized procedures are the treatment of 3D structures and the spatial control of cell adhesion. Together, these can be used to create and design new, complete artificially grown organs. If different cells types can be grown on different locations of 3D structures, one should be able to create tissue engineered products and even organs like kidneys, livers and hearts. To achieve this ambitious goal, still many research has to be done, and interdisciplinary collaborations should be undertaken. The development and (plasma) treatment of porous structures, the first steps in this process, are still the subject of many studies. It is expected that this research topic will become more and more important in the near future.

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