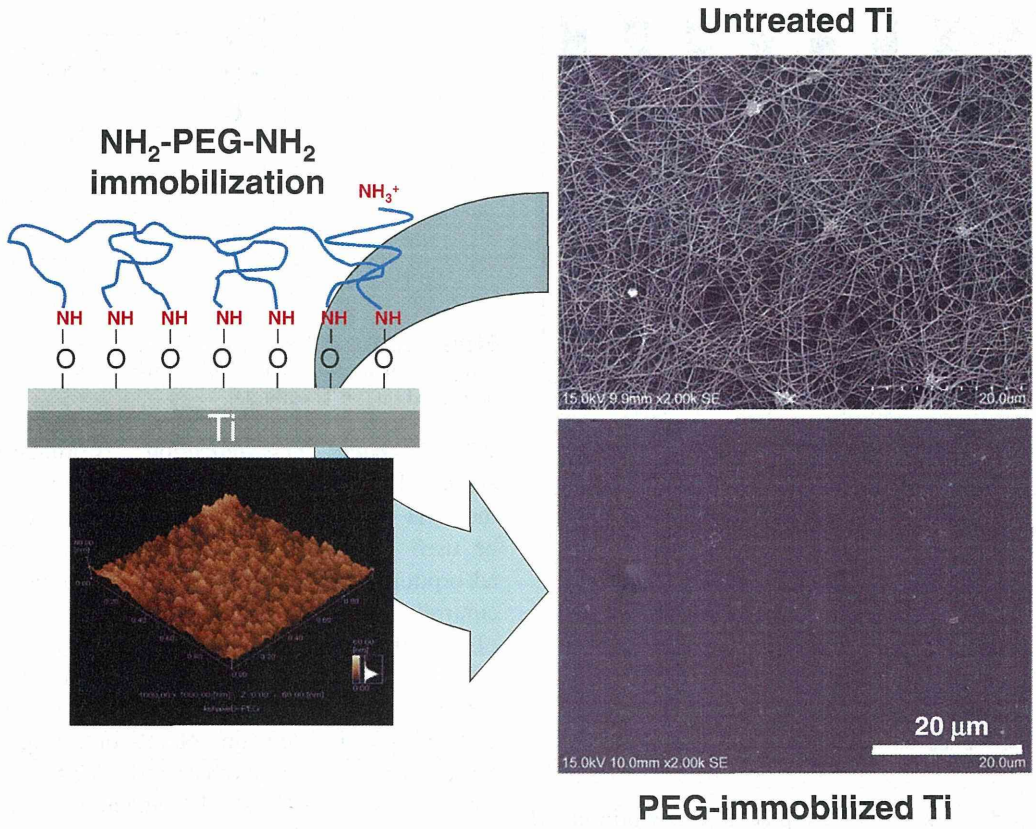

Figure 19. PEG immobilization by electrodeposition on the Ti surface and inhibition of platelet adhesion by immobilization [100].

indicating that this electrodeposition technique is useful for the biofunctionalization of metal surfaces. It can be applied to all electrically conductive materials and materials having complex surface topography.

9.3. Biomolecules

9.3.1. Concept. Since the natural environment around the implant is aqueous, while the surface of the implant is either bare or oxidized metal, specific demands are imposed on the coating to mediate between these different structural entities. The purpose of these demands is to obtain the native conformation of all proteins and cells that are in contact with the coating and to avoid all forms of aggregation and other conformational changes that might lead to protein denaturalization or cell death.

One approach is the immobilization of biological molecules (growth factors, adhesive proteins) on the implant surface to induce a specific cellular response and promote osseointegration. The application of large extracellular matrix proteins, however, can be impractical due to their low chemical stability, solubility in biological fluids, and high cost. In addition, entire extracellular matrix molecules are usually of allogenetic or xenogenetic origin and, thus, are associated with the risk of immune reaction and pathogen transfer.

Self-assembled monolayers provide chemically and structurally well-defined surfaces that can often be manipulated using standard synthetic methodologies [78]. Thiols on self-assembled monolayers [79, 80] and siloxane-anchored self-assembled monolayers [81] have been thoroughly studied. A problem related to the application of immobilized biomolecules via silanization techniques is the hydrolysis of siloxane films when exposed to aqueous (physiological) conditions [82]. More recently, alkyl phosphate films that remain robust under physiological conditions [83] have been used to provide an ordered monolayer on tantalum oxide surfaces [84, 85], and alkaliphosphonic acids have been applied to coat the native oxide surfaces of metals and their alloys including iron [86], steel [87] and Ti [88].

9.3.2. Peptides. In a living tissue, the most important role played by the extracellular matrix has been highlighted to favor cell adhesion [89]. Interactions occur between cell membrane receptors and adhesion proteins (or synthetic peptides) derived from the bone matrix, such as type I collagen or fibronectin [90]. These proteins contain the RGD (Arg–Gly–Asp) motif which specially connects transmembrane between the actin cytoskeleton and the RGD motif, and the whole system can activate several intracellular signaling pathways modulating cell behavior (e.g. proliferation, apoptosis, shape, mobility, gene expression and differentiation) [91].

Owing to the main role of the RGD sequence in cell adhesion, several research groups developed biofunctionalized surfaces by immobilization of RGD peptides. Grafting of RGD peptides has been performed

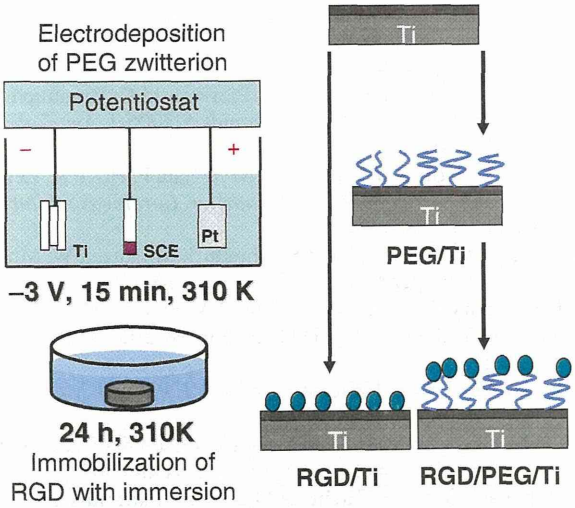

Figure 20. Schematic of the immobilization of RGD on PEG electrodeposited on Ti surface. To immobilize RGD, PEG with an $-NH_2$ group and a –COOH group (NH_2–PEG–COOH) must be employed. The $-NH_2$ group is required to bind with the metal oxide on the metal surface, whereas the –COOH group binds RGD.

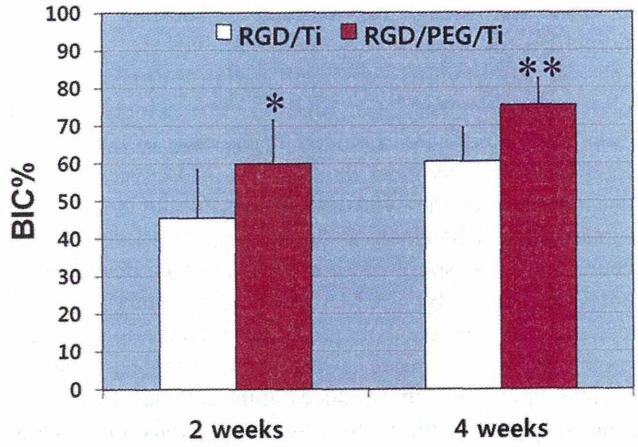

Figure 21. Mean percentage of the bone-to-implant contact (BIC%) over all threads of implants 2 and 4 weeks after implantation ($*p < 0.05$, $**p < 0.01$) [102]. RGD/PEG/Ti implants displayed significantly higher BIC% values in all threads and in the total lateral length compared with RGD/Ti implants at 2 and 4 weeks of healing.

on different biomaterials, such as Ti [92–94], and has been shown to improve osteoconduction *in vitro*. Methodologies differ by the conformation of RGD (cyclic or linear) and by the technique used for the immobilization [89, 90, 93–95]. Since the graft of an RGD peptide is known to be efficient in bone reconstruction [96], the challenge is to develop simple and cheap methods to favor cell attachment to biomaterial surfaces [94, 95].

Self-assembled molecular monolayers bearing RGD moieties have been grafted to various surfaces using either silanes [97], phosphonates on oxidized surfaces [94], or thiols on Au [95], but have revealed some application problems for large-scale production. Phosphonates are known to adsorb on Ti. To be mechanically and physiologically stable, phosphonate layers have to be covalently bound to the material surface by using drastic conditions [88, 98], such as anhydrous organic solvents or high temperature, which are not compatible with bimolecular stability. Monolayers of RGD phosphonates have been formed using a complex multistep process that requires tethering a primer onto a Ti surface, then a linker, and finally the peptide [99]. To immobilize RGD to the electrodeposited PEG on Ti, PEG with an $-NH_2$ group and a –COOH group (NH_2–PEG–COOH) must be employed. One terminal group, $-NH_2$, is required to bind stably with a surface oxide on a metal. The other terminal group, –COOH, is useful to bind biofunctional molecules such as RGD, as shown in figure 20 [100]. This RGD/PEG/Ti surface accelerates calcification by the MC3T3-E1 cell [101]. The calcification and bone formation are most pronounced on the RGD/PEG/Ti surface (figure 21) [102].

The glycine (G)-arginine (R)-glycine (G)-asparaginic acid (D)-serine (S) sequence peptide, the GRGDS peptide, is coated using a chloride activation technique to enhance the adhesion and migration of osteoblastic cells [103]. The expression levels of many genes in MC3T3-E1 cells are altered.

9.3.3. Protein and collagen. Among the relevant molecules involved in biochemical modification of bone-contacting surfaces, growth factors, such as bone morphogenetic protein-2 (BMP-2), are of primary interest. BMP-2 has been known to play an important role in bone healing processes and to enhance therapeutic efficiency. Ectopic bone formation by BMP-2 in animals has been well established following the first reports of BMP-2 [104–106]. A synthetic receptor-binding motif mimicking BMP-2 is covalently linked to Ti surfaces through a chemical conjunction process [107]. A complete and homogeneous peptide layer covers the Ti surfaces; the content is further measured by gamma counting. Biological evaluations show that the biochemically modified Ti was active in terms of cell attachment behavior. The rate of bone healing is higher on treated than untreated Ti surfaces. BMP-4 is immobilized on a Ti–6Al–4V alloy through lysozyme to improve the hard tissue response [108]. Proteins are silane-coupled to the oxidized surfaces of the Co–Cr–Mo alloy, the Ti–6Al–4V alloy, Ti and the Ni–Ti alloy to improve tissue compatibility [109].

Type I collagen is immobilized by immersion in a collagen solution [110]. The production of type I collagen increases with modification by ethane-1,1,2-triphosphonic acid and methylenediphosphonic acid grafted onto Ti [111]. Type I collagen is grafted through glutaraldehyde as a crosslinking agent [112]. For electrodeposition, the current alternating at 1 Hz between −1 V and +1 V versus SCE is effective to immobilize type I collagen on Ti, and the durability in water is high [113].

Fibronectin was immobilized directly on Ti using the tresyl chloride activation technique [114]. L-threonine and O-phospho-L-threonine were immobilized on an acid-etched Ti surface [115].

9.3.4. Hydrogel. Immobilization or coating of hydrogel on the metal surface is currently used in an attempt to add a drug delivery ability to orthopedic

implants and stents or fluorescent sensing ability to microchips. Currently, synthetic polymeric hydrogels, such as poly(hydroxyethylmethacrylate) (pHEMA) and poly(hydroxyethylacrylate) (pHEA), are widely used as compliant materials, particularly in the case of contact with blood or other biological fluids [116]. Moreover, when the adhesion between the hydrogel coating and the metal surface is inadequate, a breakage at the coating-steel interface may occur [117]. A spray-coating method was developed to control the coating by pHEMA of complex surfaces of a 316L steel stent for percutaneous coronary intervention [118]. A promising synthetic route is represented by electrochemical polymerization, which produces thin coatings directly on metal substrates with interesting applications in corrosion protection and development of bioactive films [119–122]. As far as the field of orthopedics is concerned, in recent years, many procedures based on surface modification have been suggested to improve the biocompatibility and biofunctionality of Ti-based implants [123]. HEMA, a macromer poly(ethylene-glycol diacrylate) (PEGDE), and PEGDE copolymerized with acrylic acid were used to obtain hydrogels. A model protein and a model drug were entrapped in the hydrogel and released according to the pH change [124].

10. Conclusions

Metallic materials are widely used in medicine for not only orthopedic implants but also cardiovascular devices and other purposes. Their physical properties, such as mechanical, biodegradable and magnetic properties, have been improved by redesigning alloys and manufacturing processes. On the other hand, the metal surface may be biofunctionalized by various techniques, such as dry and wet processes, the immobilization of biofunctional molecules, and the creation of metal-polymer composites. In particular, the electrodeposition technique is useful for all electroconductive and morphological materials. These techniques make it possible to apply metals to scaffolds in tissue engineering.

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